Abstract Publication

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* TH = Thursday, FR = Friday, SA = Saturday
** OR = Oral, PO = Poster, PUB = Publication Only

The presenting author’s name is underlined.

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- Basic/Clinical Science Sessions
- Clinical Practice Sessions
- Translational Sessions
- Special Sessions
- Educational Symposia
- Oral Abstract Sessions
- Poster Sessions

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Abstract Supplement

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TH-OR01

The Relationship Between Intravenous Fluid Administration and Renal Outcomes After Angiography
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Background: Contrast associated AKI (CA-AKI) may result in prolonged hospital stay and increased mortality. Fluids remain the mainstay for prevention. There is a lack of consensus on the optimal fluid rate and amount. Using the PRESERVE dataset, we studied the effect of peri-procedural fluid administration strategies on CA-AKI and 90-day need for dialysis, dialysis, or a 50% increase in serum creatinine.

Methods: We conducted a secondary analysis of 4993 of PRESERVE participants who received either IV saline or IV bicarbonate prophylaxis. Although fluid type was randomized, strategy of administration was at the discretion of the clinician. We divided the study group into quartiles by total fluid volume. Multivariable analysis was performed using logistic regression adjusting for age, history of heart failure, diabetes mellitus, left ventricular end-diastolic pressure, baseline glomerular filtration rate, procedure type, inpatient vs. outpatient status, and duration. We also tested for the interaction between fluid volume and duration of fluid administration categorized as ≤6 or ≥6 hours.

Results: Compared to the highest quartile (Q4) of fluid volume, there was a significantly increased risk of the primary 90 day end point in quartile 1. There were no differences between quartiles 2 and 3 compared to quartile 4. There was no significant difference in the incidence of CA-AKI across the groups. The interaction between volume and duration of fluid administration was not significant.

Conclusions: We found that fluid volumes <646 ml may be associated with an increased risk for the primary outcome although residual confounding cannot be excluded, and that administering higher volumes over a total duration of <6 hours seems to be equally protective. The utility of high volume, short duration fluid administration protocols will facilitate the safe performance of out-patient procedures.

TH-OR02

AKI in Patients Treated with Immune Checkpoint Inhibitors
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Background: Data on immune checkpoint inhibitor-associated acute kidney injury (ICPI-AKI) are largely limited to single-center case series. We performed a multicenter study, the largest to date, to investigate risk factors, clinicopathologic features, outcomes, and survival in patients with ICPI-AKI.

Methods: We collected detailed data on 429 patients with ICPI-AKI and 429 controls who received ICPIs contemporaneously but did not develop ICPI-AKI from 30 randomized, strategy of administration was at the discretion of the clinician. We divided the study group into quartiles by total fluid volume. Multivariable logistic regression was used to identify predictors of ICPI-AKI at diagnosis and recovery.

Results: ICPI-AKI occurred at a median of 16 weeks (IQR, 8-32) following ICPI initiation. Lower baseline eGFR, proton pump inhibitor (PPI) use, and prior or concomitant extrarenal immune-related adverse events (irAEs) were associated with a higher risk of ICPI-AKI (Figure A). Acute tubulointerstitial nephritis was the most common lesion on biopsy (125/151 biopsied patients [82.7%]). Hematuria, pyuria, and proteinuria were present in only 30-60% of patients with ICPI-AKI, and were more common in patients with greater severity of AKI. Renal recovery occurred in 276 patients (64.3%) at a median of 7 weeks (IQR, 3-10) following ICPI-AKI. Treatment with steroids was associated with higher odds of renal recovery (adjusted OR, 1.81; 95% CI, 1.03-3.13) (Figure B), particularly when initiated within 3 days of ICPI-AKI diagnosis (adjusted OR, 1.77; 95% CI, 1.01-3.13). Steroid use was also associated with a lower risk of death (adjusted HR, 0.52; 95% CI 0.36-0.75). Of 121 patients rechallenged, only 20 (16.5%) developed recurrent ICPI-AKI.

Conclusions: Lower baseline eGFR, PPI use, and extrarenal irAEs are each independent risk factors for ICPI-AKI. Two thirds of patients have renal recovery following ICPI-AKI. Early treatment with steroids is associated with renal recovery and better overall survival.

TH-OR03

The Incidence and Risk Factors of AKI Among People with HIV on Antiretroviral Treatment
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Background: The epidemiology of hospitalized acute kidney injury (AKI) among people with HIV (PWH) in the era of modern antiretroviral therapy for all PWH is not well-characterized.

Methods: We evaluated the incidence and risk factors for hospitalized AKI from 2005-2015 in a prospective study of PWH from the Johns Hopkins HIV Clinical Cohort. We defined hospitalized AKI as ≥3 mg/dL rise in serum creatinine (SCr) within any 48-hour period or 50% increase in SCr from baseline and assessed associations of risk factors with incident AKI using multivariable Cox regression models.

Results: Most participants (75%) were Black, 34% were female, mean age was 43 years and mean eGFR 106 mL/min/1.73 m2. The incidence of AKI fluctuated annually, peaking at 40 per 1,000 person-years (PY) (95% CI: 22-69) in 2007, and reached a nadir of 20 per 1,000 PY (95% CI: 11-34) in 2010 (Figure). After multivariable adjustment, characteristics independently associated with AKI included Black race (HR=2.4; 95% CI: 1.4-2.40), hypertension (HR=1.16; 95% CI: 1.09-2.38), diastolic proteinuria >1+ (HR=1.78; 95% CI: 1.06-2.97), history of AIDS (HR=1.82; 95% CI: 1.29-2.56), and lower serum albumin (HR=2.87 per 0.1 mg/dL; 95% CI: 2.78-2.97).

Conclusions: In this contemporary cohort of PWH, the annual incidence of first AKI fluctuated during the study period. Attention to modifiable AKI risk factors and social determinants of health may further reduce AKI incidence among PWH.

Funding: NIDDK Support
TH-OR04
Nephrotoxin Exposure and AKI: A Magnitude Assessment Using NINJA Methodology in the Adult Population
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Background: The Nephrotoxic Injury Negated by Just-in-Time Action (NINJA) program was designed to identify pediatric patients with high exposure to nephrotoxic medications and to predict and prevent AKI from these exposures. We extend the NINJA program to adults to assess the magnitude of nephrotoxin exposure and AKI: Pathways, Predictors, and Prevention in the adult population.

Methods: The NINJA program was designed to identify pediatric patients with high exposure to nephrotoxic medications and to predict and prevent AKI from these exposures. We extend the NINJA program to adults to assess the magnitude of nephrotoxin exposure and AKI: Pathways, Predictors, and Prevention in the adult population.

Results: Of 241,680 patients with prior AKI, 30,807 (12.7%) patients met our criteria for high nephrotoxin exposure.

Conclusions: The high NINJA score was associated with significantly increased risk of AKI and NTMx-AKI in adults.

TH-OR05
Proton Pump Inhibitor Exposure and Risk of AKI after Cardiac Surgery
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Background: Proton pump inhibitors (PPIs) are widely used in patients undergoing cardiac surgery. PPI use has been associated with increased risk of acute kidney injury (AKI) and nephrotoxicity. The objective of this study was to evaluate the association between preoperative PPI exposure and risk of AKI in patients undergoing cardiac surgery.

Methods: We conducted a population-based study of patients aged ≥ 66 years old undergoing cardiac surgery at the University of Iowa Hospitals and Clinics (UIHC) between January 1, 2019 and December 31, 2019, which was included in this retrospective analysis.

Results: Of 2,939 patients, 2,787 patients (94.8%) had complete data and were included in the analysis. Preoperative PPI exposure was defined as a PPI prescription record within 3 weeks of admission. The rate of AKI requiring dialysis was significantly higher in the PPI exposure group compared to the non-exposure group (14.0% vs. 11.0%, p<0.001).

Conclusions: Preoperative PPI exposure was associated with increased risk of AKI in patients undergoing cardiac surgery.

TH-OR06
Readmission and Mortality After AKI Hospitalization
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Background: Patients who survive an episode of AKI are at increased risk of cardiovascular mortality and morbidity but may receive fewer cardioprotective drugs than patients without AKI. We conducted a population-based study of patients aged ≥ 66 years old undergoing cardiac surgery at the University of Iowa Hospitals and Clinics (UIHC) between January 1, 2019 and December 31, 2019, which was included in this retrospective analysis.

Methods: We conducted a population-based study of patients aged ≥ 66 years old undergoing cardiac surgery at the University of Iowa Hospitals and Clinics (UIHC) between January 1, 2019 and December 31, 2019, which was included in this retrospective analysis.

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Conclusions: Preoperative PPI exposure was associated with increased risk of AKI in patients undergoing cardiac surgery.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: In patients with a history of myocardial infarction, survivors of AKI were less likely to receive prescriptions for all 3 cardiovascular drug classes with strong evidence (ACE/ARB, beta-blocker, and statin) and more likely to receive loop diuretics and mineralocorticoid receptor antagonists within one year of hospital discharge. Most medication changes stabilized at 3 months, indicating a critical timeframe to provide follow-up care.

TH-OR08

IMPROVE AKI: A Cluster-Randomized Trial of Team-Based Coaching Interventions to Improve AKI

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Background: Over 2 million people in the U.S. undergo cardiac catheterization procedures each year with acute kidney injury (AKI) occurring in up to 4% of all patients. However, orders are often not standardized to ensure adequate oral and intravenous fluids, reduced NPO time, and limited contrast dye dose across or within hospitals to prevent AKI. Therefore, we hypothesized that providing team-based coaching in a Virtual Learning Collaborative (VLC) would reduce post-procedural AKI incidence compared to Technical Assistance (TA), both with and without Automated Surveillance Reporting (ISR).

Methods: We conducted a 2x2 factorial cluster-randomized trial that randomized 20 hospitals to receive TA, TA+ASR, VLC, or VLC+ASR for 18 months. All sites received an AKI Prevention Toolkit that included AKI preventive strategies. We fit multilevel logistic models for AKI with site-level random effects to account for the clustered design.

Results: Across 20 randomized Veterans Administration medical centers, there were 4,517 patients including 1,153 patients with pre-existing chronic kidney disease (CKD) during the 18-month intervention phase of the trial. There were 510 AKI events (214 among CKD patients). In all patients, the VLC+ASR intervention cluster had a substantial reduction in AKI when compared to TA alone (aOR=0.55; 0.36, 0.84) mirrored by a strong yet non-significant effect among CKD patients (aOR=0.76; 0.46, 1.24).

Conclusions: This implementation trial estimates that the combination of VLC with ASR reduces a highly significant 45% at an institution and is suggestive of a reduction among CKD patients. Therefore, the combined VLC with ASR team-based coaching intervention is an effective, scalable framework to establish aggressive prevention protocols to prevent AKI.

Funding: NIDDK Support

Figure 1: Multilevel logistic models for acute kidney disease with site-level random effects for all cardiac catheterization patients and those patients with chronic kidney disease.

TH-OR09

Properties of Proenkephalin (penKid) in Septic AKI

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Background: Acute kidney injury (AKI) remains a serious complication in critically ill patients. The current definition of AKI continues to be based on changes in serum creatinine (SCr) and diuresis. However, neither SCr nor changes in diuresis provide an accurate assessment of renal function. Proenkephalin (penKid) is a small and stable peptide derived from the same precursor molecule as encephalins. Recent evidence suggests that plasma PenKid concentrations more accurately reflect the true glomerular filtration rate than SCr. We therefore investigated the kinetic and diagnostic properties of penKid in critically ill patients with septic AKI.

Methods: In a secondary analysis of a prospective observational study, penKid levels were measured in intensive care unit patients with positive Sepsis-3 criteria. Plasma penKid levels were analyzed in relation to the severity and course of AKI and under renal replacement therapy. Area under the receiver-operating characteristic curve (AUC-ROC) analyses were performed.

Results: Sixty-two patients had no or mild AKI, 96 patients developed moderate or severe AKI without requiring RRT, and 42 patients developed RRT criteria or died within seven days after inclusion. Thirty-nine patients had transient AKI and 92 patients experienced persistent AKI or required RRT. Overall, penKid kinetics were more dynamic than SCr and penKid courses preceded corresponding SCr courses by 48 h to 72 h. In patients without AKI, penKid levels generally remained below 50 pmol/L. Moreover, penKid levels discriminated well between transient and persistent AKI or the need for RRT. After 24 hours of sepsis therapy, the combination of SCr and penKid showed a higher AUC of 0.82 (95% CI 0.76-0.88) for predicting RRT or death compared with SCr or penKid alone (SCr: AUC 0.78, 95% CI 0.70-0.86; penKid: AUC 0.80, 95% CI 0.73-0.87). Interestingly, penKid courses were hardly affected by RRT and in some cases even increased under RRT.

Conclusions: Plasma penKid appears to indicate changes in renal function more dynamically than SCr and seems to provide additional diagnostic information on renal function. Remarkably, RRT appears to have little effect on plasma concentrations of penKid. Thus, penKid could allow assessment of renal function under RRT. Further research is needed to verify these results.

TH-OR10

Renal Outcomes After Chimeric Antigen Receptor T Cell (CAR-T) Therapy: A Single-Center Perspective

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Background: Recently chimeric antigen receptor T-cell immunotherapy (CAR-T) has shown promise for refractory non Hodgkin lymphoma. While involving genetically engineered T cells to express chimeric antigen receptors (CAR) the most significant concern is the development of cytokine release syndrome (CRS). The release of cytokines can lead to vasodilation, decreased cardiac output, and intravascular volume depletion which may potentiate renal injury. Unfortunately a paucity of data exists of renal outcomes in patients treated with CAR-T, especially with chronic kidney disease (CKD). We aim to further elucidate renal outcomes in patients treated with CAR-T at our institution.

Methods: We reviewed the course of 39 adults who received CAR-T at our institution between July 2018 and May 2021. Baseline demographics (age, gender, comorbidities), and laboratory values were obtained. Primary outcomes compared the incidence of acute kidney injury (AKI), death and CRS between patients with and without CKD as defined by KDIGO (kidney disease improving global outcomes). Fisher’s exact tests were used to calculate associations of univariate risk ratios. Multivariate survival analysis (COX model) was conducted for all outcomes, adjusting age, gender and death between patients with and without CKD.

Results: With an average age of 58.7 years (SD=10.5), 24 males and 15 females, 14/39 had mild CKD (i.e., less than 60 ml/min/1.73 m<sup>2</sup> ) and 4/39 had moderate CKD (GFR 30-60 ml/min/1.73 m<sup>2</sup> ). Of the 9 AKI cases (6 class 1, 1 class 2, 2 class 3), 5 resolved, 2 progressed and 2 patients expired. There were a total of 10 deaths (8-678 days after CAR-T). Univariate, there was a correlation between underlying hypertension and AKI and death (RR (95% CI) = 3.4 (1.2, 9.8), p=0.04), i.e., RR (95% CI) = 5.0 (1.8, 13.9), p=0.008) and death (RR (95% CI) = 4.4 (1.6, 11.8), p=0.02), but there was no association between CRS and the development of AKI. Multivariate survival analysis didn’t find any difference between patients with and without CKD.

Conclusions: Our findings did not show an increased risk of AKI or death in CKD patients treated with CAR-T. This supports the use of CAR-T in CKD patients, but with our small sample size, and lack of diverse ethnicities, more studies are needed to determine the safety of CAR-T therapy.

TH-OR11

Treatment of Osteoporosis in CKD5D Patients Based on Bone Turnover: A Randomized Controlled Trial Showing Better Survival in Patients with Non-High Turnover

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Background: Bone turnover in osteoporotic CKD5D patients (pts.) may be elevated due to the bone disease or low (Non-high Turnover, NHTO). There is no information on a tailored approach based on bone turnover. In HT0, characterized by excessive resorption, it makes sense to use antiresorbers, while they should be avoided in NHTO.

Methods: 119 adult CKD-5D pts. with DXA t-scores < -1.0 were randomized (1:1) to receive treatment (Txs) with teriparatide or standard of care (Ctrl) on 182 pts. into treatment with Alendronate or Ctrl. Demographic and clinical data, lab values, DXA and QCT total hip BMD, and MSQCT measurements of aortic calcium were obtained at baseline and 12 months. Outcomes were changes in BMD and aortic calcification (AAC). Declaration of Helsinki was followed. There were 48 NHTO and 71 HT0 pts. The median total PTH was 183 (IQR 138-337) in the NHTO group and 669 (IQR 502-1068) in the HT0 group. Treatment groups and turnover arms were well balanced relative to patient race (34% AA), sex (57% m), age (61 ±9 ±12.5 y), duration of disease (4.7 ± 4.0 y) and DXA DXA T-score (-2.9 ± 6.7). Throughout the study, 37 pts. withdrew due to transplantation and personal reasons.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Results: Bone loss was improved in treated NHTO pts. (Trx: +3.5 g/cm² ±SE 4.7 vs. Ctrl: –5.7 ±SE 4.7, p<.019) but not significantly in HTO pts. (Trx: +0.2 g/cm² ±SE 5.7 vs. Ctrl: –3.5 ±SE 3.4, p=.377). DAC was higher in the HTO arm (NHTO: 4.5 ±SE 1.6 vs. HTO: 8.7 ±SE 1.4, p=.049) and lower in African Americans (AA: 3.6 ±SE 1.7 vs. White: 8.8 ±SE 1.4, p=.017). The multivar. DAC regression coefficient for HTO vs. NHTO was 5.0 (95% CI 9.9–0.2, p=.019) and for AA vs. Whites was –5.4 (95% CI –9.6–1.1, p=.013). In the NHTO group there were 0 deaths compared to 18% deaths in the HTO group (11 deaths, p = .005).

Conclusions: We demonstrate a benefit to teriparatide for management of osteoporosis in CKD pts. with PTH between 138-337 pg/mL. These same pts. had a significant survival benefit relative to the HTO pts. and had less progression of aortic calcification. African American CKD5D pts. experienced less progression of aortic calcification regardless of turnover status or treatment modality.

Funding: NIDDK Support, Private Foundation Support

TH-OR12

The Calcified Vasculature in CKD Secretes Signal Proteins That Inhibit Bone Mineralization

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Background: Our group has recently demonstrated that CKD-induced vascular calcification impairs bone formation & mineralization in an in vivo model by transplanting calcified aortas from CKD rats into healthy recipients. Aim was to confirm our hypothesis of a direct crosstalk between the vasculature & bone in in vitro experiments.

Methods: Vascular calcification was induced in uremic Wistar rats. Normal aortas (NA) & uremic calcified aortas (CA) were incubated ex vivo or co-incubated with UMR-106 cell line (UMR). Media was measured for Wnt inhibitors sclerostin (Scl), Dkk1, SFRP4 & activin A (Act A). UMR-106 cell mineralization stained with Alizarin Red.

Results: CA completely inhibited mineralization in UMR-106 cells (Figure 1).

Mineralization inhibitor osteopontin (OPN) mRNA & protein were highly upregulated in UMR-CA (OPN mRNA UMR-CA 23.50 [5.53-51.06], UMR-NA 2.78 [1.20-7.85], UMR 0.80 [0.39-5.49], p<.001). Induction of OPN was abolished by LiCl. ANKH was upregulated in UMR-CA (5.94 [0.61-2.83] vs. UMR-NA 1.58 [1.18-2.29], p<.001). The CA secreted large amounts of Scl (1936 [495-4400] vs. NA 31 [7-83] pg/ml, p=0.002), Dkk1 (353 [110-686] pg/ml vs. none in NA), and Act A (12158 [4712-18000] vs. NA 1838 [250-4146] pg/ml, p=0.002).

Conclusions: The present study confirms our hypothesis on a direct crosstalk between vasculature and bone. The uremic calcified aorta secretes signal molecules that inhibit bone mineralization.

Funding: Private Foundation Support

TH-OR13

HIF-PHI Have Direct Actions in Osteocytes: Implications for Anemia Treatment in CKD

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Background: Patients with CKD manifest overlapping oxygen sensing/endoctrine dysfunction as osteocyte-produced FGF23 is highly elevated under prevailing anemia, however the cellular mechanisms driving FGF23 production are not understood. Our goal was to test the molecular context of osteocyte oxygen sensing, and the roles of these systems in FGF23 induction which can have severe effects on CKD bone disease.

Methods: A hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI; FG-4592, ‘Roxadustat’) was used to test parent undifferentiated MSCs (‘MPC2’, mesenchymal progenitor cell clone 2) and 3-week differentiated osteocytes (Ocy), to mimic changes in cellular oxygen status in vivo, followed by ATACseq and RNAseq. Conditional Fgf23 KO mice were treated with FG-4592 in vivo.

Results: Following FG-4592 (50µM) treatment of MSCs and Ocy, unbiased RNAseq and Gene Ontology analysis validated Ocy enrichment for bone ossification/mineralization processes as well as revealed unforeseen pathways critical for oxygen and iron utilization. ATACseq showed that FG-4592 acutely (48 h) increased genome-wide chromatin accessibility, with HOMER motif analysis identifying highly significant enrichment in Ocy HIF-1α/β and -2α transcription factor binding motif accessibility (p<1e-33). In contrast, HIF motif accessibility in FG-treated MSC was unchanged, revealing a predisposition of Ocy to mediate oxygen responses. RNAseq (confirmed by qPCR) also showed significant upregulation of Fgf23 in FG-4592-treated Ocy cultures (logFC 5.8; FDR<0.001) but not in MSCs (logFC 0.08; FDR NS), and HIF1α inhibition completely suppressed Ocy Fgf23. Further, the iron chelator DFO increased Fgf23 (80-fold), which was dose-dependently reduced by holo-transferrin (p<0.001), underscoring direct effects of oxygen/iron on Ocy. In normal mice, FG-4592 injections induced plasma iFGF23 (450-900 pg/ml, p<0.001). In contrast, conditional Fgf23 deletion from Ocy (flox-Fgf23/Dmp1-cre) completely abolished this response despite similarly elevated plasma EPO (8,000-77,000 pg/ml, p<0.001) in both genotypes.

Conclusions: These data show Ocy are poised to respond to oxygen/iron via rapid genomic accessibility and transcriptional mechanisms, which together may drive Ocy biomineralization potential through FGF23 and thus have important implications for CKD-MBD.

Funding: NIDDK Support, Other NIH Support - NHLBI, NIAMS
TH-OR14

Association of Genetically Predicted FGF23 with Heart Failure: A Mendelian Randomization Study
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Background: Multiple observational studies provide evidence of the role of FGF23 in the pathophysiology of heart failure, among individuals with CKD and in the general population. However, these studies suffer from many potential biases, e.g.confounding and reverse causation, limiting their ability to robustly identify causal associations. Mendelian randomization (MR) has emerged as a powerful study design to provide evidence supporting or refuting causality.

Methods: We performed a two-sample MR study to assess the causal association of FGF23 with overall heart failure and heart failure subtypes. Instrumental variables were defined as independent SNPs associated with FGF23 genome-wide: rs17479566, rs11741640, rs9925837, rs17216707, and rs2760971. Summary-level data from the HERMES consortium and individual-level data from BioVU, was used to examine associations of the 5 SNPs with incident heart failure and subtype. We additionally developed an eFGFR polygenic risk score based on CKD-GEN summary statistics, composed of SNPs associated with eFGFR at p<5 x 10^-8, and dichotomized the eFGFR PRS at one SD below the mean.

Results: We found that genetically increased circulating FGF23 was significantly associated with higher risk of heart failure overall and with heart failure with preserved ejection fraction among individuals with genetically-predicted low eFGFR. Elevated FGF23 was not associated with reduced ejection fraction heart failure or preserved ejection fraction in individuals with genetically predicted low eFGFR.

Conclusions: Our results provide evidence supporting a causal association between FGF23 and heart failure, particularly preserved ejection fraction heart failure, among individuals with low eFGFR.

Funding: NIDDK Support

TH-OR15

The Spatial-Temporal Heterogeneity Dictating Kidney FGF23 Bioactivity as Identified by Single-Cell RNA Sequencing
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Background: FGF23 is critical for maintaining phosphate balance via interactions with vitamin D and Klotho (KL), and its effects on gene expression have been described at tissue levels. However, KL is expressed in multiple nephron cell types thus the full spectrum and spatial-temporal mechanisms dictating FGF23 bioactivity remain undefined.

Methods: A single cell RNA-seq approach was used to identify the dynamics of FGF23-mediated bioactivity. Kidneys were isolated from FGF23 (400ng/g)-injected mice at one SD below the mean.

Results: From libraries of 10,000 male/female kidney cells, 21 UMAP cluster were defined as independent SNPs associated with FGF23 genome-wide: rs17479566, rs11741640, rs9925837, rs17216707, and rs2760971. Summary-level data from the HERMES consortium and individual-level data from BioVU, was used to examine associations of the 5 SNPs with incident heart failure and subtype. We additionally developed an eFGFR polygenic risk score based on CKD-GEN summary statistics, composed of SNPs associated with eFGFR at p<5 x 10^-8, and dichotomized the eFGFR PRS at one SD below the mean.

Results: We found that genetically increased circulating FGF23 was significantly associated with higher risk of heart failure overall and with heart failure with preserved ejection fraction among individuals with genetically-predicted low eFGFR. Elevated FGF23 was not associated with reduced ejection fraction heart failure or preserved ejection fraction in individuals with genetically predicted low eFGFR.

Conclusions: Our results provide evidence supporting a causal association between FGF23 and heart failure, particularly preserved ejection fraction heart failure, among individuals with low eFGFR.

Funding: NIDDK Support

TH-OR16

Distinct Effects of FGF23, Iron and Phosphate on Mineral Metabolism and Kidney Function in Mice with CKD
Guillaume Courbon, Marta Martinez-Calle, Jadeah J. Spindler, Aline Martin, Valentin David. Northwestern University, Chicago, IL.

Background: Elevated levels of fibroblast growth factor 23 (FGF23), hyperphosphatemia and iron deficiency are common complications of chronic kidney disease (CKD) and strong predictors of disease progression and death. We have previously found that administration of ferric citrate (FeC) an iron-based, oral phosphate binder, to mice with CKD reduced dietary phosphate absorption and FGF23, increased iron stores, slowed CKD progression and prolonged survival. This suggests that FGF23, phosphate and/or iron play a major role in CKD progression.

Methods: To distinguish between the individual and combined effects of FGF23, phosphate and iron in CKD, we fed WT and Col4a3KO mice (model CKD) from 4-10wks either control (Ctrl), low iron (LI), low phosphate (LP), 1% carboron (Ci) or ferric citrate (FeC) diets. To further study the role of iron in CKD, we compared the effects of these diets in mice receiving iv ferric deriomaloside (FD) using biochemical, histological and RNAseq analyzes.

Results: CKD mice showed higher serum FGF23, PTH, phosphate and low calcium levels and administration of Li diet further accentuated these differences. Surprisingly, phosphate restriction in LP-CKD mice minimally reduced hyperphosphatemia and PTH levels and had no effect on FGF23. In sharp contrast, all iron containing diets reduced PTH and FGF23 levels. Surprisingly, similar effects were observed in mice receiving iv iron, suggesting that iron deficiency is a stronger predictor of FGF23 excess in CKD than hyperphosphatemia. Compared to Ctrl-CKD mice, FC enriched diets showed the strongest potential to reduce FGF23 (~68%), and serum phosphate (~37%) and the only treatment to increase calciocrit (~220%). Biochemical, histological and RNAseq analyses also showed that only the combined reductions of phosphate and FGF23, and iron repletion, achieved by FeC treatment, improved kidney function and slowed CKD progression. These benefits were fully reversed when FeC-treated mice received a daily dose of 30ng/g of rFGF23 during 28 days. FGF23 administration increased renal inflammatory signaling and further accentuated CKD progression.

Conclusions: Our results suggest that combined corrections of FGF23, phosphate and iron slows CKD progression and suggest that FGF23 plays a major role in CKD progression independently of other disease modifiers.

Funding: NIDDK Support, Commercial Support - Akebia, Private Foundation Support

TH-OR17

Critical Role of Osteopontin in Maintaining Urinary Phosphate Solubility in CKD
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Background: The loss of functional nephrons dramatically increases tubular phosphate concentrations in residual nephrons to levels that exceed supersaturation. Osteopontin (OPN), a SIBLING protein expressed by epithelial cells of the distal nephron, is known to enhance calcium-phosphate solubility in vitro; however, the role of OPN in maintaining tubular mineral solubility in CKD remains undefined.

Methods: We used CKD mouse models to determine: (1) the expression and timing of kidney/urine OPN changes in relation to mineral metabolism and kidney function markers, (2) the differential effects of tubular injury and acute nephron reduction on OPN expression, (3) how OPN deficiency alters kidney mineral deposition in CKD, and (4) how neutralization of the mineral-binding (ASARM) motif of OPN alters mineralization and injury in phosphaturic mice.

Results: OPN protein expression is markedly increased in all tubular segments in mouse models of cystic kidney disease (pck/pck, glomerulonephritis (Col4a3KO)), and chronic tubulointerstitial injury (aristolochic acid). In Col4a3KO mice with slowly progressive CKD, kidney OPN expression and urinary OPN-Cr increased before gross histologic changes in the kidney or a rise in BUN, serum Cr, FGF23 and PTH. Unilateral nephrectomy studies in wild-type mice proved that nephron reduction alone was sufficient to increase tubular OPN production. Induction of CKD in OPN-null mice fed a high phosphate diet led to severe nephrocalcinosis (Figure 1). Lastly, pharmacologic neutralization of the ASARM motif of OPN in phosphaturic mice reduced mineralization and injury in phosphaturic mice.

Conclusion: Tubular OPN expression is increased in very early CKD and nephron loss alone is sufficient to induce these changes. OPN serves a key biological function to maintain tubular phosphate solubility in CKD.

Funding: NIDDK Support, Other NIH Support - NHLBI

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
TH-OR18
Tenanapor Controls Serum Phosphorus and Reduces PTH and FGF-23 in Patients with Dialysis with Severe Secondary Hyperparathyroidism
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Background: Secondary hyperparathyroidism (SHPT) is common in patients with chronic kidney failure, and most nephrologists treat parathyroid hormone (PTH) values >600 pg/mL. Hyperphosphatemia may directly contribute to SHPT, making the glands less responsive to therapy. Tenanapor is a first-in-class phosphate absorption inhibitor (PAI) that targets the paracellular pathway, the primary pathway of phosphate absorption.

Methods: The phase 3 PHREEDOM trial evaluated the safety and efficacy of tenanapor in patients on dialysis with hyperphosphatemia. Following washout from binders, patients whose serum phosphorus (sP) was increased by 1.5 to 6.0 mg/dL were randomized. Those randomized to the tenanapor arm received tenanapor 30 mg PO BID for 26 weeks. Serum calcium (sCa), sP, PTH, and FGF23 were measured at baseline, midway, and at the end of the treatment period. The magnitude of the median reductions was similar in the medication change and non-change subgroups (0 mg/dL and 0.3 mg/dL, respectively). With similar changes in medication change and non-change subgroups (1.9 mg/dL ± 1.5 mg/dL at baseline), median FGF23 was 15.275 ± 21.79 mg/dL with a median reduction of 316.35 ± 156.27 mg/dL (40.7%) at the end of the treatment period. The magnitude of the median reductions was similar in the medication change and non-change subgroups (42.78 mg/dL [40.9%] and 273.0 mg/dL [38.7%], respectively). On average, sP decreased by 1.8 mg/dL (from 8.0 to 6.1 mg/dL at baseline), with similar changes in medication change and non-change subgroups (1.9 mg/dL and 1.8 mg/dL, respectively). sCa remained unchanged overall (0.2 mg/dL) and in the medication change and non-change subgroups (0.0 mg/dL and 0.3 mg/dL, respectively).

Conclusions: Tenanapor effectively lowers sP in patients on maintenance dialysis with severe SHPT and demonstrates that effective sP control with tenanapor improves both PTH and FGF23 concentrations.

Funding: Commercial Support - Ardelyx, Inc.

TH-OR19
Initial Evaluation of High-Dose Extended-Release Calcifediol (ERC) in Patients with Stage 5 CKD on Hemodialysis (HD)
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Background: ERC has been approved since 2016 for treatment of secondary hyperparathyroidism (SHPT) in adults with stage 3-4 CKD and vitamin D insufficiency at weekly doses of 210 or 420 mgc (30 or 60 mcg/day). Conversion of calcifediol to calcitriol by CYP27B1 is thought to occur primarily in the kidney despite expression elsewhere, supporting a belief that normal serum levels of 1,25-dihydroxyvitamin D (1,25D) cannot be maintained with advancing CKD. A phase 2a study explored treatment of end-stage renal disease patients with SHPT requiring regular HD with high strength ERC (300 mcg thrice weekly during HD) or matching placebo. Serum 25D, 1,25D, calcium (Ca) and phosphorus (P) were measured at baseline, midway and at the end of the treatment period. The magnitude of the median reductions was similar in the medication change and non-change subgroups (0 mg/dL and 0.3 mg/dL, respectively). With similar changes in medication change and non-change subgroups (1.9 mg/dL ± 1.5 mg/dL at baseline), median PTH reduction was 300 pg/mL (35.4%). Median change. Among those with medication changes, median PTH reduction was 231 pg/mL (26.9%); among those without changes, PTH reduction was 300 pg/mL (35.4%). Median

Conclusions: Tenanapor effectively lowers sP in patients on maintenance dialysis with severe SHPT and demonstrates that effective sP control with tenanapor improves both PTH and FGF23 concentrations.

Funding: Commercial Support - OPKO Health

TH-OR20
Parathyroid-Specific Knockout of Core Circadian Clock Gene Bmal1 Increases Proliferation of the Parathyroid Gland in CKD
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Background: Proper rhythms in metabolism, hormone secretion and cell cycle are maintained by a molecular circadian clock (CC) in the CNS as well as in peripheral tissues. The transcription factor Bmal1 is a major component of the CC. We have previously shown that an internal CC operates in the parathyroid gland (PTG) and that it is disturbed in uremia. We constructed a PTG-specific Bmal1 knockout mouse to investigate the function of the PTG clock in health and in CKD.

Methods: PTG-specific knockout of Bmal1 was generated by crossing PTHerce mice with Bmal1fl/fl mice (WT) giving rise to PTHerce; Bmal1fl/fl (KO). Blood samples and PTGs were harvested at 4h interval. CKD was induced by feeding mice an adenine diet for 3 weeks. Gene expression was examined by qPCR, protein expression by western blot and proliferation by Ki-67 labeling. Circadian rhythmicity was assessed by cosinor analysis.

Results: Bmal1 protein was reduced by 77% in the PTGs of KO mice and circadian rhythmicity of Bmal1 gene expression was abolished along with abolishment of rhythmic expression of clock genes Cry1/Cry2 (p<0.0001). Expression of clock genes Per2 (p<0.001), Cry1 (p<0.0001) and Cry2 (p<0.0001) was compared to WT. The disturbed clock in KO resulted in abrogated rhythmicity of clock-controlled cell cycle regulator Wee1 (KO p<0.16, WT p<0.0016) and of regulators of parathyroid proliferation Gcm2 (KO p<0.03, WT p<0.03) and Gata3 (KO p<0.84, WT p<0.01). Gata3 was upregulated compared to WT (p<0.01). Plasma PTH was significantly rhythmic in both KO and WT mice. In a basal condition the phenotype of KO mice was similar to WT, regarding weight, femur length, basal PTH levels and secretory response to hypocalcemia. Uremia significantly increased the PTG Ki-67 labeling index in KO compared with WT (7.0% vs. 2.4%, p=0.036).

Conclusions: Bmal1 knockout in the PTG resulted in disrupted rhythm of CC genes and a clock-controlled cell cycle regulator. The significant rhythms of regulators of parathyroid proliferation Gcm2 and Gata3 found in PTGs of WT mice was absent in KO mice. Diabetogenic CK regimen (6.67 mg/dL) expression was found when PTGs of KO mice were challenged by CKD as compared to WT mice, indicating a key role of the CC in regulating the proliferation in the PTGs.
Results:

Genetic investigations revealed four mtDNA variants in 12 families: m.T3286C (n=1), m.4977A>G (n=2), m.8344A>G (n=1), and m.16369C>T (n=3, in MT-TI). Variants segregated with the phenotype and were near homoplasmic in affected individuals. Importantly, affected members of six families with an MT-TI variant additionally suffered from progressive chronic kidney disease (KoD). Kidney biopsies in two affected individuals showed abnormal mitochondria, especially in the distal tubule. Maximal mitochondrial respiratory chain capacity was reduced in patient fibroblasts, caused by dysfunction of oxidative phosphorylation complex IV. In vitro pharmacological inhibition of complex IV, mimicking the effect of the mtDNA variants, demonstrated an inhibitory effect on NCC activity and NCC-mediated sodium uptake. Furthermore, this effect was accompanied by greater association of SGK1 with both mTORC2 and WT and (MT-TI) deletion and the recovery of NCC expression, had similar effects to loss of WT on SGK1 phosphorylation and ENaC current.

Conclusions: Genetic data support a scaffolding role for WNK1 and 4 that promotes mTORC2-SGK1 interaction and hence phosphorylation through a mechanism that does not require its kinase activity. Extracellular K+, which has a well-established role to inhibit WNK-dependent ENaC phosphorylation, stimulates WNK1/4-SGK1 interaction, and may lead to an mTORC2-SGK1-NCC complex, resulting in enhanced SGK1 activity and ENaC activation in PCs.

Funding: NIDDK Support, Private Foundation Support

TH-OR24

Role of WNK1 and NK4 in Sensing Extraskeletal Potassium in Principal Cells to Modulate mTORC2-Dependent Activation of Epithelial Sodium Channel

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Background: mTORC2 phosphorylation of SGK1 and consequent activation of ENaC is essential in the regulation of ion transport by principal cells (PCs) of the distal tubular system. We recently demonstrated that local K+ concentration could be sensed by PCs to activate ENaC through mTORC2-SGK1 signaling, and suggested a role for WNK1 in this mechanism. However, the mechanistic basis of this regulation has not yet been explored. In DCT, WKYMUP modulates NCC activity in response to extracellular K+ in a kinase-dependent manner. Here we have explored the role of WNK1 and K+ in local sensing of extracellular K+ and ENaC regulation in the mpkCCD cultured PC model.

Methods: We used CRISPR to generate WNK1-/- and WNK4-/- mpkCCD cells. WT and KO cells were grown on Transwell filters and adapted to 1 or 3 mM KCl on the basolateral side, followed by raising [K+] to 5 mM in the presence or absence of WKYMUP.

Results: In WT mpkCCD cells, extracellular K+ stimulated ENaC phosphorylation and current through mTORC2-dependent SGK1 phosphorylation, and ENaC phosphorylation and current. Transfection of WNK1 and WNK4 mpkCCD cells with either WT or kinase-dead WNK1 restored K+-stimulated ENaC phosphorylation, and ENaC activity. Furthermore, this effect was accompanied by a greater association of SGK1 with both mTORC2 and WT (K+ or kinase-dead). WNK4 deletion and the recovery of NCC expression, had similar effects to WNK1 on SGK1 phosphorylation and ENaC current.

Conclusions: Our data support a scaffolding role for WNK1 and 4 that promotes mTORC2-SGK1 interaction and hence phosphorylation through a mechanism that does not require its kinase activity. Extracellular K+, which has a well-established role to inhibit WNK-dependent ENaC phosphorylation, stimulates WNK1/4-SGK1 interaction, and may lead to an mTORC2-SGK1-NCC complex, resulting in enhanced SGK1 activity and ENaC activation in PCs.

Funding: NIDDK Support, Private Foundation Support

TH-OR25

Comparative Effectiveness of Patiromer and RAAS Inhibitor Continuation vs. No Potassium Binder and Discontinued RAAS Inhibitors on Healthcare Resource Utilization and Cost Outcomes in Hyperkalemia

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Background: Patiromer (PAT) is a sodium-free, non-absorbed potassium (K+) binder approved for treatment of hyperkalemia (HK). The objective of this study was to estimate relative cost of treating Medicare Advantage patients (pts) with HK with different therapeutic strategies.

Methods: This retrospective, propensity score–matched cohort study utilized the de-identified Optum Clinformatics® Data Mart (from 2016 to 2019). Two HK cohorts were identified: 1) pts exposed to PAT+RAASi vs DC RAASi and 2) pts who discontinued RAASi therapy (DC RAASi). All pts had serum K+ ≥5.0 mEq/L, HK diagnosis, and a6 ms insurance enrollment. Pts were propensity score matched on baseline characteristics. Relative healthcare spending rate (exposure contrast: PAT+RAASi vs DC RAASi) was estimated.

Results: Three hundred and sixty-five patients were included (187 in PAT+RAASi and 178 in DC RAASi). Overall, mean age was 74 yrs, 59% male, and 31% Hispanic. Pts had a mean of 5 comorbidities: CKD (95%), diabetes mellitus (73%), chronic heart failure (32%), cardiac arrhythmias (33%), and coronary artery disease (39%). At 3 mos, 168 pts (84 matched pairs) remained uncensored and were included in the analysis. Total healthcare spending rate for DC RAASi cohort was $15,344 vs $9135 (95% confidence interval, $6303, $13,241) for PAT+RAASi cohort over 3 mos (P<0.01; Figure) and was driven by marked reductions in outpatient and ED costs.
**TH-OR26**

**Dietary Anion Prioritizes Pendrin Activation over Aldosterone**

Seyedmohammadebrahim Tahaei,1 Susan M. Wall,2 Paul A. Welling,1 Julus Hopkins Medicine, Baltimore, MD; 1 Emory University School of Medicine, Atlanta, GA.

**Background:** Ectopic activation of the sodium–chloride cotransporter and increased intracellular sodium and chloride have been associated with kidney disease. Pendrin, a transmembrane protein, is expressed on the basolateral membrane of the collecting duct, and its activation increases sodium and chloride excretion. In the present study, we investigated the role of dietary anions in modulating pendrin expression.

**Methods:** C57/Bl6J male mice (2 month old) were randomized to matched control diet (2% KCl), high potassium bicarbonate (13.4% KHCO3), or high potassium chloride (4 days), and the response to changing the anion in the context of high potassium, high sodium potassium salt to control acid-base balance rather than to maintain K+ homeostasis. An alkaline-rich, high potassium diet drives pendrin expression to prevent metabolic alkalosis, while pendrin is rapidly downregulated to limit hyperchloremic acidosis with aldosterone to the same extent but had opposite effects on pendrin abundance. KHCO3 measured by standard methods. Kidney Pendrin mRNA and protein abundance were measured by qRT-PCR and western blot, respectively.

**Results:** Dietary KCl and KHCO3 loading increased plasma potassium and aldosterone to the same extent but had opposite effects on pendrin abundance. KHCO3 loading increased pendrin, while dietary KCl loading inhibited it. Pendrin protein and transcript abundance decreased within 24 hours of switching the high KHCO3 diet to high KCl, and the response was coincident with an increase in plasma chloride and a decrease in bicarbonate. Switching the high KCl diet to high KHCO3 had the opposite response, increasing pendrin protein and transcript as plasma bicarbonate increased and chloride decreased. Neither anion switch protocol changed the extent of hyperaldosteronism or hyperkalemia.

**Conclusions:** Pendrin regulation is prioritized by the dietary anion. Ingestion of an alkaline-rich, high potassium diet drives pendrin expression to prevent metabolic alkalosis, while pendrin is rapidly downregulated to limit hyperchloremic acidosis with aldosterone to the same extent but had opposite effects on pendrin abundance. KHCO3 loading increased pendrin, while dietary KCl loading inhibited it. Pendrin protein and transcript abundance decreased within 24 hours of switching the high KHCO3 diet to high KCl, and the response was coincident with an increase in plasma chloride and a decrease in bicarbonate. Switching the high KCl diet to high KHCO3 had the opposite response, increasing pendrin protein and transcript as plasma bicarbonate increased and chloride decreased. Neither anion switch protocol changed the extent of hyperaldosteronism or hyperkalemia.

**Funding:** NIDDK Support, Private Foundation Support

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**TH-OR27**

**Intracellular Water Shift and Disturbed Osmoregulatory Responses to High Sodium in Patients with Hereditary Multiple Exostosis**


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**Background:** Tissue Na+ accumulation plays an important role in Na+ homeostasis. During high Na+ diet, negatively charged glycosaminoglycans (GAGs) facilitate extracellular Na+ accumulation in various tissues. Patients with Hereditary Multiple Exostosis (HME) have a heterozygous loss of function mutation in a gene involved in heparan sulfate (HS) synthesis. HME patients may therefore respond differently to high Na+ conditions with regard to Na+ and water homeostasis.

**Methods:** We performed a randomized cross-over study in 7 male HME patients and 12 healthy controls, matched for age, body mass index, blood pressure and eGFR. All subjects followed randomized both an 8-day low Na+ diet (LSD, <50mmol/d) and high Na+ diet (HSD, >200mmol/d). After each diet, blood and urine samples were collected. Also, body fluid compartments measurements were performed by using the distribution curve of inulin and 131-I-albumin.

**Results:** After LSD, body fluid volume distribution over total body water (TBW) was equal (Fig 1A). HSD resulted in a different distribution between groups (Fig 1B), while absolute TBW increase was not different (1.4% vs 1.5%, p=0.9). HME patients showed 3.9% ICFV expansion without concurrent changes in plasma effective osmolality (p=0.18). Whereas, in healthy controls, 23.0% IFV expansion was accompanied by increased plasma effective osmolality (p=0.01). HSD-induced changes in HS were associated with ICFV change in healthy controls (Fig 1C).

**Conclusions:** HME patients, characterized by defective HS, show distinct body fluid composition and altered osmoregulation after HSD when compared to controls. The incapacity to expand IFV may reflect reduced extracellular Na+ accumulation with reduced osmotic driving force. As a consequence, water shifts to the ICFV at a hypotonic stress, indicating disturbed maintenance of a stable milieu intérieur. Our results underscore that intact HS synthesis is crucial for Na+ homeostasis and fluid balance.

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**TH-OR28**

**Renal Lymphatic Pumping Involves Interstitial Sodium Regulation of NKCC1 Transporter**

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**Background:** Sodium-potassium-chloride cotransporter 1 (NKCC1) is regulated by extracellular sodium and has recently been shown to modulate vascular dynamics contributing to hypertension. Previously, we showed that NKCC1 is expressed in renal lymphatic vessels of rats and in cultured human lymphatic endothelial cells (LECs). Since interstitial sodium retention is a hallmark of proteinuric injury and nephrotic syndrome, we examined whether high interstitial sodium environment affects expression of the NKCC1 transporter and alters pumping dynamic function of renal lymphatic vessels.

**Methods:** Porcine aortic endothelial cells injected rats (PAN) served as a model of nephrotic syndrome and saline-injected rats served as control. In vivo, MRI was used to assess the renal sodium and water content. Renal lymph, which reflects the interstitial composition, was collected and sodium concentration analyzed. Ex vivo, contractile dynamics of isolated renal collection lymphatic vessels were studied in a perfusion chamber. Blunted LECs were used to identify the role of high sodium on NKCC1.

**Results:** MRI revealed a significant elevation in the renal sodium and water content in PAN vs control rats. The renal lymph of PAN contained significantly higher sodium vs controls although the plasma sodium concentration was not different between the groups. Ex vivo studies revealed that high sodium environment decreased contractility of renal collecting lymphatic vessels. Immunostaining and PCR studies showed PAN injury increased NKCC1 expression in renal lymphatic vessels vs control. In cultured LECs, high sodium concentration increased mRNA and reduced phosphorylated NKCC1 protein expression suggesting a protective mechanism of NKCC1 and NKCC1’s downregulation may be a part in renin-angiotensin-aldosterone system (RAAS) to manage HK in matched Medicare Advantage pts. Study Limitation: Potential Exostosis (HME) have a heterozygous loss of function mutation in a gene involved in homeostasis and fluid balance.

**Funding:** NIDDK Support

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**TH-OR29**

**A Novel Model of Hyperuricemia via Inducible Uricase Knock-Out**

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**Background:** Hyperuricemia contributes to the development of kidney stones, chronic kidney disease, cardiovascular disease, metabolic syndrome, and gout. Classically, hyperuricemia was viewed as caused by an overproduction of urate (UA), underexcretion, or a combination of the two. Creating genetic animal models for overproduction type hyperuricemia is complicated because, unlike humans, mice express the enzyme uricase (Uox), which metabolizes UA. Previous models using germline Uox knock out resulted in significant juvenile mortality related to crystal induced nephropathy making longitudinal and transcriptional investigations difficult. Here we describe a novel inducible model of Uox inactivation (UOX-iKO) that surmounts previous challenges to begin to elucidate renal consequences of overproduction type hyperuricemia.
Methods: CRISP-RCas9 was used to insert LoxP sites into the Uox gene of C57BL/6J mice with tamoxifen induced Cre (Gt(Rosa)26Sor(cre)1Bve/1Bve). Male (M) and female (F) mice were induced at 9 weeks with tamoxifen or vehicle control and sacrificed after 2 weeks or followed longitudinally. RNA-Seq was performed on kidneys of 2 weeks induced and control mice, followed by DESeq2 and pathway analysis.

Results: Induced animals of both sexes showed significant increases in serum UA and urinary UA excretion 2 weeks after induction, increases that persisted for 10 weeks with no increase in mortality. RNA-Seq analysis revealed both sexes showed differential expression of urinary biomarkers and other immune associated genes including renal immune markers Lcn2 and Sic1, indicating subtle acute renal injury, even without changes in BUN. M mice demonstrated significant decreases in expression of UA transporter Slc17a1 and Slc17a3, while F mice showed a significant increase in UA associated transcription factors Hfha. M but not F mice also had differential expression of genes involved in metabolic processes, while F but not M mice showed differential expression in signal transduction pathways including phospholipase C and toll-like receptor signaling. Conclusions: The UOX-iKO mice cannot metabolize UA, and thus are an excellent model for overproduction of UA. These mice provide significant insights into the acute transcriptional changes occurring after UA increases, mechanisms of renal UA homeostasis in vivo, and new insights into hyperuricemia treatment.

Funding: NIDDK Support

TH-OR30
Factors Associated with Sex Differences in the Risk of Kidney Stones
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Background: Kidney stone disease is a highly prevalent condition. Men are at higher risk of developing stones compared with women, however recent data suggest a changing epidemiology with women being relatively more affected than in the past. The reasons for such differences and changes over time are not clear.

Methods: We analyzed the association between sex and incident kidney stones using data from three large cohorts. Kidney stone incidence rates for men and women overall and across categories of age and calendar time were computed and hazard ratios (HRs) and 95% confidence intervals (CIs) generated with age-adjusted Cox proportional hazards regression models. Mediation analysis was performed to estimate the amount of excess risk for men explained by established risk factors, including waist circumference, history of high blood pressure, history of diabetes, use of thiazides, dietary intakes. Twenty-four hour urine composition was also examined.

Results: The analysis included data from 268,553 participants, contributing 5,872,249 person-years of follow-up, during which 10,302 incident stone events were confirmed. The incidence rate of kidney stones was 271 and 159 per 100,000 person-years for men and women, respectively. The age-adjusted HR for men compared with women was 2.32 (95% CI 2.20, 2.45). Part of the difference in rates was explained by the risk factors included in the analysis, mainly waist circumference and fluid intake. The risk of stones was consistently higher across categories of age among men compared with women (HRs ranging from 2.02 to 2.76). Regarding calendar time, the risk remained higher among men, but tended to decrease over time while it increased among women, resulting in a 48.1% decrease for after 2009 compared with before 1990. Supersaturations for calcium oxalate and uric acid were higher among men, primarily because of 26.3% higher urine oxalate, 16.3% higher urine uric acid, 23.5% higher urine phosphate and more acidic urine. Urine volume, citrate, oxalate and pH contributed significantly toward an increased risk among men.

Conclusions: The risk of kidney stones is higher among men compared with women. This difference is only partly explained by modifiable lifestyle risk factors; however, differences in urine chemistries explain a substantial fraction of the excess risk. Differences in urine chemistries explain a substantial fraction of the excess risk.

Funding: Other NIH Support - DK049410, DK01417, CA186107, CA176726, and CA167552

TH-OR31
Deconvolution of Genetic Variation Using High-Quality cis-Regulatory Elements Map of Kidney Cells
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Background: Genome-wide association studies (GWAS) have facilitated the discovery of disease- or trait-associated genetic variants that can ultimately lead to improved precision of clinical diagnosis and/or molecular pathogenesis in a translational medicine framework. However, identifying specific cell types within organs in which the GWAS signals exist and how these signals are exerted remains a significant challenge, especially for the complex and heterogeneous kidney.

Methods: To tackle this, we constructed high-quality maps of cis-regulatory elements (CREs) for kidney cells to deconvolute GWAS variants for kidney-relevant phenotypes. Specifically, we devised a computational framework using a sequence-based predictive model that maximally detects CREs by identifying open-chromatin regions with marginal read-mappings but harboring CRE sequence features. We applied this method to kidney ATAC-seq data.

Results: Our high-quality CRE maps have enabled us to detect >100,000 CREs for podocytes, a key (~1%) cell type involved in kidney filtration function. Newly found CREs explained the significant proportion of SNP-heritability for a major kidney trait (Urinary Albumin-to-Creatinine Ratio (UACR)); Pr[0.93]. Heritability analysis using these CRE maps uncovered the differential contribution of specific cell types to two major functional traits, major kidney functional traits, UACR and estimated glomerular filtration rate (eGFR). As would be predicted from physiologically understanding, CREs for podocytes and proximal tubule cells (PT) had enriched proportion of SNP-heritability for UACR and eGFR, respectively (UACR; Pr[0.68] for podocyte, 2.3 for PT, eGFR; Pr[0.71] for PT). Moreover, we found the podocyte relevance of a known GWAS variant (rs7183125; OR=2.25, P=4.7x10^-10) on PLAU1 associated with Membranous Nephropathy. Our CRE map showed strong podocyte-unique CRE that overlaps with the index variant, suggesting that the index SNP is potentially the causal variant perturbing podocyte-specific transcriptional regulation of PLAU1.

Conclusions: Taken together, we expect that the deconvolution of GWAS variants using the high-quality kidney CRE maps will provide cell-type relevant of GWAS variants on genetic effects not captured by single-cell RNA-seq alone.

Funding: NIDDK Support, Private Foundation Support

TH-OR32
Epistatic Interactions of APOL1 Modify the Association Between APOL1 and CKD in African and Hispanic Americans
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Background: Chronic kidney disease (CKD) is a major public health problem, and African and Hispanic minorities are at increased risk than white individuals. APOL1 (Apolipoprotein L1) (APOL1) locus has been identified as a significant genetic contributor to the disparities, only a minority of individuals with APOL1 high-risk genotype develop kidney disease suggesting a major role for genetic and environmental modifiers. Prior genetic association studies studying gene/gene variants interacting with APOL1 were limited by small sample sizes and detected very few significant interactions.

Methods: In this study, we conducted a genome-wide single nucleotide polymorphism (SNP)xAPOL1 interaction analysis to identify SNPs that modify the association of APOL1 high-risk genotypes with CKD in the largest minority cohort to date. Interaction analyses were conducted separately for four independent cohorts, 12,145 African Americans (AAs) and 16,580 Hispanic Americans (HAs) from the Population Architecture through Genomics and Environment (PAGE) Study and 6,827 AA and 10,314 HAs from the BioMe Biobank, followed by sample size based meta-analysis.

Results: Among the four cohorts, CKD cases and APOL1 high-risk genotypes were observed with higher frequencies in AA (8.40% CKD and 11.95% APOL1 in PAGE; 18.21% CKD and 13.90% APOL1 in BioMe) than in HA (3.40% CKD and 0.45% APOL1 in PAGE; 14.14% CKD and 1.69% APOL1 in BioMe). We tested about 28 million SNPs in our interaction analyses and identified 51 significant SNPs (P value < 1.0 x 10^-8) interacting with the APOL1 locus across the genome (Figure 1). Of these, 28 SNPs were within a gene, and 14 out of the 28 SNPs were within the gene PHIP2B which has been showed to be involved in controlling translation and glucose homoeostasis.

Conclusions: Although further biological validation is needed, our results provide early insights on the impact of genetic interaction on the association between APOL1 and kidney disease.

TH-OR33
Phenotypic Spectrum of COL4A3 Variants: The Geisinger Mycode/DiscoEHR Study
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Background: Patients with heterozygous COL4A3 variants have been shown to be at increased risk of kidney disease, ranging from microscopic hematuria to focal segmental glomerulosclerosis (FSGS) and end-stage kidney disease (ESKD). Most studies of patients with COL4A3 variants have focused on individuals presenting with more severe manifestations, and thus the full phenotypic spectrum remains unclear. Methods: We used data from 174,416 participants in the Geisinger MyCode/DiscoEHR study, an unselected health system-based cohort with whole exome sequencing and EHR data. We identified participants with COL4A3 variants listed as pathogenic or likely pathogenic (P/LP) in ClinVar at minor allele frequency <0.01. Phenotypes were assessed using ICD diagnostic codes, linkage to the US Renal Data System, blood and urine laboratory data, and targeted chart review. Associations between
COL4A3 P/LP variants and Alport syndrome-related phenotypic features were assessed using logistic regression. Additional analyses were done comparing carriers and non-carriers for the most common variant (p.Gly695Arg) observed in our cohort.

**Results:** There were 329 (0.2%) participants with a previously reported P/LP rare COL4A3 variant. Individuals with a COL4A3 variant (mean age 58.8 years) were at increased risk of ESKD (OR 3.79, 95% CI: 2.36-6.08), hematuria (OR 1.99, 95% CI: 1.37-2.88), FSGS/renal sclerosis (OR 7.46, 95% CI: 3.31-16.84), and eGFR <60 ml/min/1.73m² (OR 1.46, 95% CI: 1.07-1.99) but not hearing loss. The most common P/LP variant was p.Gly695Arg with 161 heterozygous individuals in 58 families (Table). Compared to those without the p.Gly695Arg variant, those with the p.Gly695Arg variant were at increased risk of hematuria (OR 3.44, 95% CI: 1.38-8.86), and ESKD (OR 12.39 (1.59-96.33; P=0.02). Two patients had a known family history of Alport Syndrome, and only 1 patient had been diagnosed using clinical genetic testing.

**Conclusions:** In an unselected health system cohort, we demonstrate that rare P/LP variants in COL4A3 increase risks of hematuria, FSGS, and ESKD, and are undiagnosed in the vast majority of individuals.

**Funding:** NIDDK Support

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**TH-OR34**

The Genetic and Clinical Spectrum of Tubulointerstitial Kidney Disease and Associated Syndromes Revealed Through Whole-Genome Sequencing in the UK 100,000 Genomes Project

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**Background:** Tubulointerstitial kidney disease (TKD) is a heterogeneous group of monogenic disorders with progressive chronic kidney disease characterised by interstitial fibrosis, tubular atrophy and variable clinical manifestations. TKD includes recessive ciliopathies, autosomal dominant tubulointerstitial kidney diseases (ADTKD) and mitochondrial diseases. The Genomics England (GEL) project offered a unique opportunity to apply a novel discovery approach, synthesizing the effect of common and rare variants using a whole-gene-based pathogenicity score (GenePy). This scoring system results in per gene-per person pathogenicity scores, with higher scores representing a higher mutational burden.

**Methods:** We applied the GenePy scoring system integrating patient zygosity, allele frequency, and deleteriousness metrics. We identified unrelated Europeans for a phenotype-genotype approach of 232 cases with TKD and 8,282 controls with no documented kidney phenotype. GenePy scores were generated for a discrete set of candidate genes for each individual. The highest decile GenePy scores were compared to a random-tailed Mann-Whitney U-test. We then used an unbiased genotype-phenotype approach by calculating GenePy scores for all 78,050 germline genomes. Individuals were ranked by gene score, and individuals with the highest scores were assessed for their phenotype.

**Results:** The difference in top decile scores between cases and the same proportion of controls was statistically significant for PKD2 (p=2.81x10^-10), DNAB11 (p=3.56x10^-10), XPNPEP3 (p=0.0083), UMOD (p=0.0015) and CEP290 (p=0.034). Novel variants consistent with TKD were identified. The unbiased genotype-phenotype approach additionally revealed variants consistent with monogenic TKD in participants recruited for diverse reasons, including cancer.

**Conclusions:** Using a novel gene-level scoring system, we describe new gene variants associated with TKD and associated phenotypes. Patients were identified in non-kidney disease recruits demonstrating the benefit of an unbiased ‘gene first’ approach in large scale datasets such as the 100,000 Genomes Project.

**Funding:** NIDDK Support

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**TH-OR35**

A Glomerular Transcriptional Landscape of APOL1 in Black Patients with Focal Segments Glomerulosclerosis

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**Background:** Apolipoprotein L1 (APOL1)-associated focal segmental glomerulosclerosis (FSGS) is the dominant form of FSGS in Black people. There are no targeted therapies for this condition, in part because the molecular mechanisms underlying APOL1’s pathogenic contribution to FSGS are incompletely understood. Studying the transcriptional landscape of APOL1 FSGS in patient kidneys is an important way to discover genes and molecular behaviors that are unique or most relevant to the human disease.

**Methods:** With the hypothesis that the pathology driven by the high-risk (HR) APOL1 genotype is reflected in alteration of gene expression across the glomerular transcriptome, we compared expression and co-expression profiles of 15,703 genes in 16 Black FSGS patients with a HR vs 14 with a low-risk (“LR”) APOL1 genotype. Expression data from APOL1-inducible HEK293 cells and normal human glomeruli were used to pursue genes and molecular pathways illuminated in these studies.

**Results:** We discovered (1) increased expression of APOL1 in HR and nine other significant differentially expressed genes, including stanniocalcin (STC1), which has a role in mitochondrial and calcium-related processes, (2) differential correlations between HR and LR APOL1 and metabolism pathway genes, but similar correlations with extracellular matrix- and immune-related genes, (3) significant loss of co-expression of mitochondrial genes in HR FSGS, and (4) an NF-kB-down-regulating gene, NKIRAS1, as the most significant hub gene with strong differential correlations with NDUF family and immune-related genes.

**Conclusions:** Overall, differences in mitochondrial gene regulation appear to underlie many differences observed between HR and LR FSGS. All data are available for secondary analysis through the “APOL1 Portal” (http://APOL1portal.org).

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
TH-OR38

The C-Terminal Tail of Polycystin 1 Rescues Cystic Phenotype in a Mitochondrial Enzyme-Dependent Fashion

Laura Onuchic,1 Valeria Padovano,2 Giorgia Schena,1 Vanathy Rajendran,1 Nikolay P. Gresko,1 Ke Dong,1 Xiaojuan Shi,1 Hongying Shen,2 Stefan Somlo,1 Michael J. Caplan,1 1Yale University School of Medicine, New Haven, CT; 2Broad Institute, Cambridge, MA.

Background: Approximately 85% of Autosomal Dominant Polycystic Kidney Disease (ADPKD) cases are caused by mutations in PKD1, which encodes polycystin-1 (PC1). PC1 is a large transmembrane protein that underlies C-terminal cleavage, generating fragments (PC1-CTT) that translocate to mitochondria and nucleus. We find that PC1-CTT expression in an inducible PC1 KO ADPKD mouse model substantially rescues cystic phenotype and we elucidate mechanisms involved in this effect.

Methods: We generated BAC transgenic mice expressing a Flex-Stop 2HA-PC1-CTT inserted in the Rosa26 locus and crossed it with the inducible Pax6rT/Ta: TetO-Cre; Pkd1fl/fl ADPKD mouse model. Doxycycline induction of these mice (PC1-CTT; Pax6rT/Ta; TetO-Cre; Pkd1fl/fl on the C57BL/6J background) leads to PC1-CTT expression in renal epithelial cells that lack full-length PC1. We applied MS-based proteomics and Co-IP techniques to identify PC1-CTT interactors and used MS-based metabolomics to identify mitochondrial differences associated with the observed phenotype.

Results: Compared to PC1 KO mice, PC1 KO expressing PC1-CTT have 3-fold lower kidney weight/body weight ratio (5.10% vs 14.85%, p<0.0001) and 3.6-fold lower BUN (32.7mg/dL vs 120.7mg/dL, p<0.0008), with both groups presenting comparable gender distributions. BUN levels in PC1-CTT-expressing ADPKD mice are comparable to those in WT controls. We show that PC1-CTT interacts with mitochondrial enzyme Nicotinamide Nucleotide Transhydrogenase (NNT) and confirm the importance of this interaction by crossing the same PC1-CTT-expressing PC1 KO mice with NNT-deficient C57BL/6J mice. These mice do not exhibit an improved cystic phenotype. Both in vivo and in vitro, PC1-CTT re-expression in the presence of NNT leads to increased mitochondrial mass, altered redox modulation, increased assembly of ATP synthase at a “per mitochondria” level as well as decreased tubular proliferation, suggesting potential mechanisms for the observed rescue. Finally, unbiased metabolomics reveals that PC1-CTT’s ability to rescue the ADPKD metabolic profile is tied to the presence of NNT.

Conclusions: Expression of PC1-CTT and its interaction with NNT significantly rescues ADPKD renal phenotype. Considering its small size, PC1-CTT could be explored as a gene therapy approach for ADPKD.

Funding: NIDDK Support, Private Foundation Support

TH-OR39

Read-Through Therapeutics Reduce Cystogenesis in a Novel Cohort of CRISPR Base Edited ADPKD Organoids

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Background: In autosomal dominant polycystic kidney disease (ADPKD), truncating nonsense mutations are responsible for 40-50% of cases, with increased disease severity and limited treatment options. Eukaryotic ribosomal selective glycosides (ERSGs) allow read-through of premature stop codons to restore full-length proteins as a novel therapeutic approach. However, existing animal and kidney organoid models of ADPKD lack mutations amenable to read-through.

Methods: Human pluripotent stem cells were CRISPR base edited to introduce four specific nonsense mutations previously documented in ADPKD patients – PKD1 R186X and R872X and PKD2 R186X and R872X. Mutations were confirmed by sequencing and protein changes by immunoblot. Mutant and isogenic control stem cells were differentiated into kidney organoids to determine if nonsense mutations conferred a cystic phenotype. Premature stop codon read-through potential was evaluated for impact on cyst formation and toxicity (live/dead staining and LDH release) over a period of two weeks using two unique ERSGs.

Results: Nonsense mutant clones of each targeted genotype were obtained with the desired single base pair mutation and lacked expression of full-length protein. Fewer than 5% of isogenic control organoids formed cysts compared to > 80% in untreated mutant control. Treatment of mutant organoids with ERSGs reduced cystogenesis to < 20% and slowed the rate of cyst expansion in a dose-dependent manner. Treatment associated toxicity was not significantly detected at efficacious doses.

Conclusions: CRISPR base editing enabled rapid generation of an ADPKD organoid cohort with patient targeted nonsense mutations. The data suggest that read-through by ERSGs is a viable therapeutic approach for reducing cystic burden in a large subpopulation of patients with ADPKD, supporting the advancement of ERSGs in human clinical trials.

Funding: NIDDK Support, Commercial Support - Elixir Pharmaceuticals

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Whole-Genome Sequencing Reveals the Genetic Architecture of Posterior Urethral Valves

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Background: Posterior urethral valves (PUV) are the commonest cause of childhood kidney failure and a major unmet clinical problem in pediatric nephrology. While usually sporadic, familial clustering and twin studies suggest a genetic component that is as yet unidentified. Using large-scale whole genome sequencing (WGS) we sought to understand the genetic architecture of PUV and identify key contributing genes.

Methods: We analysed WGS data from 132 unrelated PUV patients and 23,727 ancestry-matched unaffected controls from the 100,000 Genomes Project, seeking enrichment of common and rare single-nucleotide and structural variation (SV) on a genome-wide, per-gene, and cis-regulatory element basis.

Results: Exome-wide there was no significant enrichment of rare coding variation in any one gene. SV analysis identified an increased burden of rare inversions affecting under 0.001 revealed significant (P = 7.8x10-12, OR 4.4; MAF 0.007), both of which are replication in an independent cohort of 398 European PUV patients. Bayesian fine mapping and functional annotation mapped these loci to the transcription factor TBX5, which replicated in an independent cohort of 398 European PUV patients. Controlling for time-varying BP and BP meds significantly attenuated these hazard ratios (Fig. 1). Results were similarly attenuated using baseline BP and BP meds (incident HR 1.06 (95% CI 1.00-1.02); admission HR 1.63 (95% CI 1.52-1.74); admission HR 2.28 (95% CI 2.05-2.53)) or with addition of comorbidities and atherosclerotic risk factors (Fig. 1). Controlling for time-varying BP and BP meds significantly attenuated the risk of HF observed in patients with CKD. Interventional trials targeting BP are needed to establish whether intensive BP control can reduce the risk of HF in CKD.

Funding: NIDDK Support, Other NIH Support - NHLBI, Veterans Affairs Support

Conclusions: Adjusting for HTN to a large degree attenuates the increased risk of HF in patients with CKD. Interventional trials targeting BP are needed to establish whether intensive BP control can reduce the risk of HF in CKD.

Hazard of HF incidence and admissions in CKD

Role of Hypertension in the Risk of Heart Failure in CKD

Sydney E. Hartsell,1 Guo Wei,1 Robert E. Boucher,1 Adhish Agarwal,1 James C. Fang,1 Adam Bress,1 Alfred K. Cheung,2,3 Srinivasan Beddhu,1,2 The University of Utah School of Medicine, Salt Lake City, UT; 1VA Salt Lake City Health Care System, Salt Lake City, UT.

Background: Chronic kidney disease (CKD) is a risk factor for heart failure (HF), but the extent to which hypertension (HTN) contributes to development of HF in CKD is unclear.

Methods: We used the VA Informatics and Computing Infrastructure (VINCI) platform to identify a national cohort of veterans with prevalent CKD (two or more outpatient CKD-EPI eGFR <60 mL/min/1.73m2) taken 60 days apart from January 2010 to December 2015. We used inpatient and outpatient ICD 9/10 codes to define HF admissions and incident HF through August 2018. We first related CKD stages at baseline with the time to HF hospitalizations and incident HF with adjustment for demographics and baseline comorbidity in a multivariable Cox regression. Next, we adjusted for baseline blood pressure (BP) and BP-lowering medications (BP meds). Finally, we conducted a time varying Cox regression model with 3-month averages of BP values and BP meds.

Results: Of the 915,038 veterans with prevalent CKD, we included 632,872 (69%) without known HF at baseline. Over about 3.5 million patient-years of follow up, 111,549 (18%) patients developed HF and 29,597 (5%) were hospitalized for HF. Compared to stage 3A CKD, more advanced CKD stages were significantly associated with HF incidence and admissions (Fig. 1). Results were similar when adjusted for demographics only (incident HR 1.63 (95% CI 1.52-1.74); admission HR 2.28 (95% CI 2.05-2.53)) or with addition of comorbidities and atherosclerotic risk factors (Fig. 1). Controlling for time-varying BP and BP meds significantly attenuated these hazard ratios (Fig. 1). Results were similarly attenuated using baseline BP and BP meds (incident HR 1.06 (95% CI 0.99-1.13); admission HR 1.24 (95% CI 1.12-1.38).

Conclusions: Whether intensive BP control can reduce the risk of HF in CKD.

Funding: NIDDK Support, Other NIH Support - NHLBI, Veterans Affairs Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Background: Several studies have shown associations between childhood hypertension (HTN) and subclinical-cardiovascular outcomes (SCOs) such as left ventricular hypertrophy (LVH), increased pulse wave velocity (PWV) and increased carotid intima media thickness (cIMT). These data support the effect of elevated blood pressure (BP) in children leading to cardiovascular risk in adults; however, the association is not consistent in all studies. In this review, we investigate the prevalence of SCOs in children with HTN, diagnosed by ambulatory blood pressure monitor (ABPM).

Methods: A systematic literature search was conducted on four electronic databases to include relevant full-length publications in English language, published abstracts and conference proceedings from Jan 1974 to Mar 2020. Article screening, data extraction and quality assessment were independently completed and verified by two reviewers. Primary outcomes included SCO outcomes such as LVH, left ventricular mass index (LVMI), PWV and cIMT as per standard definitions. Meta-regression was done to adjust for the effect of body mass index (BMI) on LVMI.

Results: Of 8996 studies, 38 were included for analysis. SCO indices were significantly greater in those with HTN than those with normotension (NTN). Mean difference between the HTN and NTN group was 0.03mm (95% CI: 0.01, 0.05) for cIMT, 0.42 m/sec (95% CI: 0.25-0.6) for PWV, and 5.02gm^-2 (95% CI: 3.66-6.39) for LVMI. HTN group had 3-times higher odds of LVH (3.10 [95% CI: 1.65-5.82]). Meta-regression showed that BMI had a significant impact on the mean differences in LVMI, with the mean difference in LVMI increasing by 0.81gm^-2 (95% CI [0.42, 1.19], p < 0.001) per unit increase in BMI.

Conclusions: Children with ambulatory HTN have a greater risk of SCOs. These findings emphasize the importance for children to have their BP within normal values.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: Mean (SD) age and eGFR (SD) by the CKD-Epi equation of the 3753 participants were 58 years (11), and 44 mL/min/1.73m² (15), respectively. Baseline cognitive impairment was present in 10.1% of overall participants (n = 365), and 5.4%, 9.5%, and 16.4% of participants with baseline SBP <120, 120-140, and ≥140 mm Hg, respectively (p < 0.01). There were 314 individuals who developed cognitive impairment during a median 6 years of follow-up. After multivariable adjustment, participants with higher baseline SBP were more likely to have incident cognitive impairment (hazard ratio (HR) [95%CI] = 1.09 [1.03, 1.16] per 10 mmHg higher SBP); this relationship was attenuated when using time-updated SBP (HR [95%CI] = 1.04 [0.99, 1.10]) (Table 1).

Conclusions: Among patients with CKD, elevated baseline SBP but not time-updated SBP was associated with incident cognitive impairment.

Funding: NIDDK Support

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Table 2: Compliance at Baseline and Endpoint

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<td>Control group, mean (SD) mHg</td>
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Table 1: Baseline demographics and BP
TH-OR48

Regulation of Sodium Excretion and Blood Pressure by the Nuclear Factor of Activated T Cells 5 (NFCI5) in Renal Tubular Cells

Akiko Hiramatsu, Yuichiro Izumi, Yutaka Kakizoe, Masataka Adachi, Hiroshi Nonoguchi, Takashige Kuwabara, Masashi Mukoyama. Department of Nephrology, Kumamoto University, Graduate School of Medical Sciences, Kumamoto, Japan.

Background: NFCI5 is an osmoreceptive transcription factor, which is crucial for cell survival under hypertensive conditions such as those encountered in the renal medulla. Physiological role of NFCI5 in the kidney, however, is still obscure. We investigated the role of NFCI5 in renal tubules using renal tubal cell-specific NFCI5-knockout (KO) mice.

Methods: We crossed NFCI5 floxed mice with Pax8-flox/–/– mice to obtain mice with inducible and specific deletion of NFCI5 in renal tubular cells. To characterize the mice, urine and blood parameters and blood pressure of wild type (WT) and KO mice were examined at basal condition. Then, WT mice and KO mice were fed either a high-salt diet (HSD) or a regular-salt diet (RSD) for 4 weeks. The mRNA expression of sodium transporter-related genes in the kidney was examined by real-time PCR. Protein expression of the epithelial sodium channel (ENaC) in the membrane fraction was examined by Western blotting. Concentrations of urea and sodium in the renal medulla were measured.

Results: Compared to WT mice, KO mice exhibited polyuria (WT vs. KO: 2.0 ± 0.09 vs. 5.2 ± 0.18 m/dlay) at basal condition. The serum sodium level was increased (151.8 ± 0.78 vs. 156.6 ± 0.45 mEq/L) and the urinary sodium excretion was decreased (498.7 ± 25 vs. 368.9 ± 15 mEq/gCr) in KO mice. Interestingly, the systolic blood pressure (SBP) was significantly increased in KO mice (97.4 ± 2.4 vs. 114.9 ± 1.1 mmHg). mRNA expressions of AQP2 and UT-A1, a water channel and a urea transporter, respectively, were significantly decreased in KO mice, suggesting that increased delivery of sodium to the medulla increased the blood pressure in KO mice (97.4 ± 2.4 vs. 114.9 ± 1.1 mmHg). mRNA expressions of AQP2 and UT-A1, a water channel and a urea transporter, respectively, were significantly decreased in KO mice, suggesting that increased delivery of sodium to the medulla increased the blood pressure in KO mice (97.4 ± 2.4 vs. 114.9 ± 1.1 mmHg).

Conclusions: These results suggest that NFCI5 can regulate the urine concentration and sodium reabsorption in renal tubules, which could be important for body fluid homeostasis and blood pressure regulation.

Funding: Government Support - Non-U.S.

TH-OR49

Fluid Overload, 24-Hour Blood Pressure Patterns, and Their Association with Cardiorenal and Kidney Outcomes in CKD

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Background: Fluid overload is well-known risk factor for adverse cardiovascular and kidney outcomes in chronic kidney disease (CKD) patients. However, it is unclear whether fluid overload is associated with blood pressure (BP) patterns and their relationship to adverse clinical outcomes in CKD patients.

Methods: A total of 1,147 CKD (stage 1 to 5) patients were enrolled from the prospective observational cohort of CMERC-III (Cardiovascular and Metabolic Disease Etiology Research Center High Risk). The patients were classified into tertile based on fluid status defined as the extracellular water to total body water ratio (ECW/TBW) measured by bioelectrical impedance analysis; hypovolemic, euvolemic, and hypervolemic groups. BP patterns were assessed by 24-h BP measurements; dipper (nighttime BP fall 10-20%), extreme dipper (nighttime BP fall >20%), non-dipper (nighttime BP fall 0-10%), and reverse dippers (nighttime BP fall >0%) Primary outcome was composite of nonfatal myocardial infarction, nonfatal stroke, and all-cause mortality. The secondary outcome was progression of CKD (composite of at least 50% decrease in eGFR >50% from baseline or eGFR <60 ml/min/1.73 m², or end-stage kidney disease).

Results: The mean age of study subjects was 59±12.2 years and 615 (53.6%) were male. The hypertensive group was associated with increased risk of reverse-dipping pattern (OR, 2.46; 95% CI, 1.30-4.64; P=0.001). During a median follow-up of 42.1 (41.3-42.9) months, the composite of cardiovascular events and CKD progression occurred in 42 (3.7%) and 345 (30.1%), respectively. The Kaplan-Meier analysis showed that reverse dippers were associated with increased risk of cardiovascular events and CKD progression compared to hypovolemic group. In multivariable Cox analyses, hypoalbuminemia group was associated with increased risk of cardiovascular events (HR, 4.44; 95% CI, 1.16-17.0; P=0.03). Moreover, hypertensive group was associated with increased risk of CKD progression (HR, 2.47; 95% CI, 1.77-5.45; P=0.001). This increased risks of cardiovascular events and CKD progression with hypoalbuminemic status were still consistent in patients with reverse-dipping pattern.

Conclusions: The increased risk of cardiovascular events and kidney disease progression in CKD patients with fluid overload can be explained by an association with a reverse-dipping BP pattern.

TH-OR50

Galec tin 3 and Air Pollution in Hypertensive Patients with and Without CKD

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Background: Air pollution is a major contributor to cardiovascular and kidney complications. The mechanisms linking air pollution with cardio renal events are not well understood. We sought to assess whether Galec tin 3 level, a marker of myocardial fibrosis and remodeling is associated with air pollution exposure in hypertensive patients with and without chronic kidney disease.

Methods: Satellite-derived PM2.5 measurements were linked with participants in the Systolic Blood Pressure Intervention Trial (SPRINT, Clinicaltrials.gov NCT0120602). A total of 1019 SPRINT participants with available Galec tin 3 levels at study baseline and 24 months follow-up were included in these analyses. Multivariable linear regression models, adjusted for age, sex, race, eGFR, Framingham risk score, body mass index, and random assignment with weights to assess the association between air pollution and Galec tin 3 at baseline and longitudinal change at 2 years.

Results: The mean PM2.5 was 9.6 μg/m³, and the median (IQR) Galecin 3 level was 14.4 (11.5-18.0) ng/mL. In multivariable models, we found no association between PM2.5 and baseline (β=0.02, P=0.46) or longitudinal change (β=0.05, P=0.12) in Galec tin 3. In the subgroup of participants with CKD (n=201), PM2.5 was associated with change in Galec tin 3 (β=0.21, P=0.002), which remained statistically significant after multivariable adjustments (β=0.23, P=0.003). In the overall cohort (n=1019), there was a significant association between PM2.5 and eGFR with change in Galec tin 3 (P-value for interaction=0.02).

Conclusions: Air pollution may be associated with worsening myocardial fibrosis as evidenced by increasing levels of Galec tin 3 in individuals with preexisting CKD. Further studies are needed to corroborate these findings with rigorous cardiac imaging studies.

Funding: Other NIH Support - MD is supported by R01HL141846

TH-OR51

Diagnostic Application of NanoString Gene Scores in Transplant Biopsies with Suspicious Features of Antibody-Mediated Rejection


Background: Antibody-mediated rejection (AMR) is the leading cause of renal allograft loss, a diagnosis which is reached using the Banff Classification for Allograft Pathology. Biopsies that only partially fulfil the histological criteria for AMR, those with immunohistochemistry features of AMR but without chronic kidney disease. Further studies needed to corroborate these findings with rigorous cardiac imaging studies.

Methods: A total of 1019 SPRINT participants with available Galectin 3 levels at study baseline were male. The hypertensive group was associated with increased risk of reverse-dipping pattern (OR, 2.46; 95% CI, 1.30-4.64; P=0.001). During a median follow-up of 42.1 (41.3-42.9) months, the composite of cardiovascular events and CKD progression occurred in 42 (3.7%) and 345 (30.1%), respectively. The Kaplan-Meier analysis showed that reverse dippers were associated with increased risk of cardiovascular events and CKD progression compared to hypovolemic group. In multivariable Cox analyses, hypoalbuminemia group was associated with increased risk of cardiovascular events (HR, 4.44; 95% CI, 1.16-17.0; P=0.03). Moreover, hypertensive group was associated with increased risk of CKD progression (HR, 2.47; 95% CI, 1.77-5.45; P=0.001). This increased risks of cardiovascular events and CKD progression with hypoalbuminemic status were still consistent in patients with reverse-dipping pattern.

Conclusions: The increased risk of cardiovascular events and kidney disease progression in CKD patients with fluid overload can be explained by an association with a reverse-dipping BP pattern.

Change in Galec tin 3 and PM2.5 exposure by eGFR

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
between AMR and No AMR Cases (AUC 0.8742, 95% CI 0.8095-0.9388, p<0.0001) and we developed a gene score cut-off, maximising sensitivity and specificity. In biopsies suspicious for AMR, but which did not complete the full diagnostic criteria, a high Gene Score was predictive of allograft loss, compared to biopsies with a low gene score (p=0.0065).

Conclusions: Non-string analysis of gene expression in FFPE biopsy samples can be used to identify biopsies suspicious for AMR that are at higher risk of allograft loss, and may have a role in characterising cases that represent AMR, even in the absence of full diagnostic criteria.

TH-OR52
Proteomics Reveals Extracellular Matrix Injury in the Glomeruli and Tubulointerstitium of Kidney Allografts with Early Antibody-Mediated Rejection
Serpi Clotet Freixas, Caitriona M. McEvoy, Chiara Pantrello, Max Kotlyar, Madhurangi Arambewela, Alexander Boshart, Sofia Farkona, Yun Niu, Yanhong Li, Andrzej Chruscinski, Rohan John, Ana Konvalinka. University Health Network, Toronto, ON, Canada.

Background: Antibody-mediated rejection (AMR) accounts for ~50% of allograft losses. AMR is caused by donor-specific antibodies (DSA) against HLA and non-HLA antigens in the glomeruli and the tubulointerstitium, which together with interferon gamma and tumor necrosis factor-alpha (TNFalpha), trigger graft injury. The reasons behind cell-specific injury in AMR remain unclear. Identifying compartment-specific proteome alterations may help uncover mechanisms of early antibody-mediated injury.

Methods: We studied 30 for-cause kidney biopsies with early AMR, acute cellular rejection (ACR) or acute tubular necrosis (ATN). We laser-captured microdissected glomeruli and tubulointerstitium and subjected them to unbiased proteome analysis.

Results: We found 107 glomerular and 112 tubulointerstitial proteins significantly differentially expressed in AMR vs. ACR. Similarly, 112 (glomeruli) and 124 (tubulointerstitium) proteins were regulated in AMR vs. ATN. Basemembrane and extracellular matrix (ECM) proteins were decreased in both compartments in AMR, compared with ACR and ATN. We verified decreased glomerular and tubulointerstitial LAMC1 expression, and decreased glomerular NPHS1 and PTTPR expression in AMR. Cathepsin-V (CTSV) was predicted to cleave ECM-proteins in the AMR glomeruli. We identified galectin-1 expression, and galectin-1 expression and secretion, in human glomerular endothelial cells. We also studied glutathione S-transferase omega-1 (GSTO1), an ECM-modifying enzyme, increased, the ECM in the AMR tubulointerstitium. GSTO1 expression was significantly increased in TfnR-treated proximal tubular epithelial cells.

Conclusions: Basement membranes are often remodeled in chronic AMR, and we demonstrated that this remodeling begins early in glomeruli and tubulointerstitium. Targeting ECM-remodeling in AMR may represent a new therapeutic avenue.

TH-OR53
Single-Cell Profiling Reveals Sex-Based Transcriptomic Programs in Healthy Human Kidney
Caitriona M. McEvoy,1,2 Julia M. Murphy,1,2 Lin Zhang,1 Jessica A. Mathews,1 Sergi Clotet Freixas,1 James An,1 Mehran Karimizadeh,1 Delaram Posyabahar,1 Shenghui Su,1 Bo Wang,2 Gary Bader,2 Sarah Q. Crome,1,2 Ana Konvalinka,1,2 University Health Network, Toronto, ON, Canada; 1University Health Network, Toronto, ON, Canada; 2Vactor Institute, Toronto, ON, Canada.

Background: Single-cell transcriptomics provide unprecedented insight into disease states in the kidney, yet our understanding of the transcriptomic programs of human kidney cells at homeostasis is limited by difficulty accessing healthy, fresh tissue. Sex-based dichotomy in human kidney cells remains unexplored, but may underpin acute and chronic kidney diseases e.g. progressive diabetic kidney disease and IRI which exhibit a male preponderance.

Methods: We sequenced single-cell suspensions of 19 pre-implantation living donor biopsies (9 male, 10 female) (FGenomics). Analyses were performed with Cellranger and Seurat R. Sex-based transcriptomic differences were examined using varimax rotated principal component analysis, machine learning approaches and differential expression analysis.

Results: 27677 high-quality cells forming 23 clusters were identified with several immune populations and all anticipated parenchymal populations. Individual kidney populations were examined for separation due to donor sex, with clear separation observed for the PT population alone using varimax-rotated principal component analysis (Fig1a). Machine learning identified the most discriminant subset of genes (Model:100 genes) that could correctly classify cell sex (AUC 0.98). 75 genes were differentially expressed between males and females (p<0.05, LogFC>0.25). Anti-oxidant metalloproteinase genes were increased in females. Pathway analysis revealed metalloproteinase-related processes (oxidative phosphorylation, and the TCA cycle) as increased in males (Fig1B).

Conclusions: We report striking sex-based transcriptomic differences in PT cells, suggesting higher baseline metabolic activity in males, and increased anti-oxidant metalloproteinase genes in females. These sex-based differences in PT gene expression may provide insights into the well-recognized, but previously unexplained sexual dimorphism observed in kidney diseases.

TH-OR54
Vaccination with Class-Ib MHIC Binding Synthetic Superagonist and Adoptive Transfer of Antibody-Specific CD8 Tregs Prolong Cardiac Allograft Survival in Alloantigen-Sensitized Hosts
John Y. Choi,1,2 Hye-jung Kim,2,3 Harvey Cantor,2,3 Jamil R. Azzi,1,2 Brigham and Women’s Hospital Department of Medicine, Boston, MA; 2Harvard Medical School, Boston, MA; 3Dana Farber Cancer Institute, Boston, MA.

Background: Previously, we showed Qa-1 (HLA-E in human) restricted CD8+ T cells (CD8 Tregs) are highly suppressive of follicular helper T cells (Tfh), and play a critical role in suppressing donor-specific antibody-mediated rejection (AMR). Allreactive CD4 T cells upregulate Qa-1 in association with stress peptides such as FL9 which are recognized by CD8 Tregs. Therefore, we hypothesized that vaccinating hosts with a superagonist that mobilizes CD8 Treg and adaptive transfer of antigen-specific CD8 Treg may protect heart allografts from antibody-mediated rejection (AMR). Allreactive CD4 T cells upregulate Qa-1 in association with stress peptides such as FL9 which are recognized by CD8 Tregs.

Methods: We sequenced a tetramer to sort FL9-Qa-1 specific CD8 T cells and sequenced their T cell receptors (TCR). We screened over 100 peptides synthesized with FL9 backbone and identified a superagonist that induces the strongest CD8 T cell response. We then sensitized and transferred Qa-1 specific CD8 T cell populations to recipients of cardiac allografts. We observed significant prolongation of allograft survival in sensitized and Qa-1 specific CD8 T cell recipients compared with untransplanted hosts. We extended these observations to searching for additional stress peptides, and we identified an additional stress peptide, FL9-MV. We also investigated the human equivalent of FL9 peptide, and examined the potential unwanted toxicity of FL9-Qa-1 specific CD8 T cell allografts.

Results: The superagonist induced a strong CD8 Treg response that suppresses Tfh, activated B cells, plasma cells and DSA in vivo. Allograft retrieval from the treatment group showed less C4d deposit and attenuated graft injury. The treatment group also showed prolonged allo graft survival; the superagonist and the adaptive transfer showed a synergistic effect.

Conclusions: Allo-sensitized, cardiac transplantation is a stringent model in which allografts undergo a robust process of AMR. While antibody-mediated graft injury in clinical transplantation is a major barrier to long-term kidney allograft survival, we believe the graft protection using the superagonist and antigen-specific CD8 Treg is biologically significant with a high translational potential. Further investigation is needed to maximize the efficacy of CD8 Treg therapy, such as co-administration of CD8 Treg-specific co-stimulatory molecules. In addition, we are investigating the human equivalent of FL9-Qa-1 specific CD8 T cells on allografts.

Funding: Other NIH Support - NIAID

TH-OR55
Sodium-Glucose Cotransporter 2 Inhibitors in Kidney Transplant Recipients
Jeong-Hoon Lim,1 Soie Kwon,1 Hee Won Noh,1 Soojeen Jee,1 Hee-Yeon Jung,1 Ji-Young Choi,1 Sun-Hee Park,1 Chan-Duck Kim,1 Yong-Lim Kim,1 Jung Pyo Lee,1 Jung-Hee Cho,1 Kyungpook National University School of Medicine, Daegu, Daegu, Republic of Korea; 2Seoul National University College of Medicine, Seoul, Republic of Korea.

Background: The effect and safety of sodium-glucose cotransporter 2 inhibitors (SGLT2i) have not been investigated in kidney transplant recipients (KTRs) with diabetes. We evaluated the impact of SGLT2i in a multicenter cohort of diabetic KTRs.

Methods: A total of 2083 KTRs with diabetes were enrolled from six transplant centers in Korea. Among them, 226 (10.8%) patients prescribed with SGLT2i for more than 90 days. The primary outcome was a composite of all-cause mortality, death-censored graft failure, and serum creatinine doubling. An acute dip in estimated glomerular filtration rate (eGFR) over 10% was surveyed after SGLT2i use. A minority (15.6%) of the SGLT2i users showed a synergistic effect.

Conclusions: Allo-sensitized, cardiac transplantation is a stringent model in which allografts undergo a robust process of AMR. While antibody-mediated graft injury in clinical transplantation is a major barrier to long-term kidney allograft survival, we believe the graft protection using the superagonist and antigen-specific CD8 Treg is biologically significant with a high translational potential. Further investigation is needed to maximize the efficacy of CD8 Treg therapy, such as co-administration of CD8 Treg-specific co-stimulatory molecules. In addition, we are investigating the human equivalent of FL9 peptide, and examining the potential unwanted toxicity of FL9-Qa-1 specific CD8 T cell allografts.

Funding: Other NIH Support - NIAID
acute eGFR dip during the first month, but the eGFR recovered thereafter (Figure 2). The risk factors for the eGFR dip were time from transplantation to SGLT2i usage and mean tacrolimus trough level.

Conclusions: SGLT2i improved a composite of all-cause mortality, death-censored graft failure, or serum creatinine doubling in KTRs. SGLT2i can be used safely and have beneficial effects on preserving graft function in diabetic KTRs.

Figure 1. Kaplan–Meier curves for the outcomes

Figure 2. Temporal changes in the eGFR of SGLT2i users due to eGFR dip.

TH-OR56
The Role of Combined Gene Expression Profiling and Donor-Derived Cell-Free DNA to Diagnose Acute Rejection in Patients with Acute Allograft Dysfunction
Sookhyeon Park, Kexin Guo, Lihui Zhao, John J. Friedewald. Northwestern University Feinberg School of Medicine, Chicago, IL.

Background: Gene expression profiling (GEP) has been used to monitor for subclinical acute rejection. Conversely, the majority of data with donor-derived cell-free DNA (dd-cfDNA) has been in patients with allograft dysfunction. We hypothesized that combining GEP and dd-cfDNA could improve the diagnostic performance to detect acute rejection in patients with acute allograft dysfunction.

Methods: We analyzed a total of 131 blood samples paired with kidney biopsies from patients (n=96) with biopsy-proven acute rejection. Blood samples were analyzed with the GEP and the dd-cfDNA assay. The area under the receiver operating curve (AUC) for dd-cfDNA was 0.72 (p=0.69) and for GEP was 0.54 (p=0.14). Tables 1 and 2 show the performance of GEP and dd-cfDNA separately based on their continuous output variables, and for combining two assays with logistic regression.

Results: Of 131 blood samples, 50 and 81 cases were biopsy-proven clinical acute rejection and acute allograft dysfunction without rejection, respectively. In binary analysis, GEP showed a lower positive predictive value (PPV) at 0.54 to 0.64 from dd-cfDNA, but a higher negative predictive value (NPV) at 0.70 to 0.79. When both assays were positive, PPV increased to 0.68 (95% CI, 0.50-0.88). In cases when both tests were negative, NPV increased to 0.88 (95% CI 0.78-0.96) (Table 1). Performance of GEP and dd-cfDNA on detection of antibody-mediated rejection and acute cellular rejection shown in Figure 1. The combined use of two assays showed similar AUROC, to 0.75 than GEP (0.74, p-value = 0.26) and dd-cfDNA (0.72, p-value = 0.69). A very high, 2 Emily Aimee Blumberg, 3 Abdolreza Haririan, 4 Jingyang Wu, 5 Aimee K. Sundberg. 1 University of Utah Health Care, Salt Lake City, UT; 2 Johns Hopkins University Division of Infectious Diseases, Baltimore, MD; 3 University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; 4 University of Maryland, Baltimore, MD; 5Shire Human Genetic Therapies, Inc., a Takeda company, Lexington, MA.

Background: Risk of nephrotoxicity limits antiviral use for treatment (tx) of transplant recipients with CMV infection. We report efficacy (including sub-analysis of kidney recipients) and renal safety data from a phase 3 study of MBV vs IAT in patients (pts) with R/R CMV infection (NCT02931539).

Methods: Transplant recipients (n=127) with CMV infection (screening plasma DNA<910IU/mL) R/R to prior tx (failure to achieve>1log 10 decrease in CMV DNA after 14days+genotyped resistance) were randomized 2:1 MBV (400mg BID):IAT (valganciclovir, foscarine[FOS], cidofovir) for 8wks. Primary endpoint:confirmed CMV clearance at end of Wk8 (plasma DNA<137IU/mL in 2 consecutive tests±5days apart). Key secondary endpoint:CMV clearance and symptom control at end of Wk8 maintained through Wk16. Group differences were adjusted for baseline CMV DNA level+solid organ/hematopoietic cell transplant where applicable. Subgroup analysis of kidney recipients was conducted. Tx-emergent adverse events (TEAEs) were assessed (safety set).

Results: More MBV (randomized set: 235 MBV, 117 IAT[47 FOS]) pts achieved the primary (55.7% vs 29.9% IAT; adjusted difference[AD] 32.8%, 95% CI 22.8–42.7; p=<0.001) and key secondary endpoint (18.7% vs 10.3% IAT; AD 9.5%, 95%CI 2.0—16.9; p=0.013). For kidney recipients (74 MBV, 32 IAT), 59.5% MBV vs 34.4% IAT pts achieved CMV clearance (AD 26.7%, 95%CI 7.5–45.9). Rates of TEAEs were similar between MBV and IAT (Table). Dysgeusia was the most frequent TEAE with MBV (37.2%, IAT 3.4% pts). Tx-related TEAE of increased immunosuppressant drug level was reported in 6% pts treated with MBV (IAT 0% pts). Renal and urinary TEAE rates were lower for MBV (17.1% pts than IAT (26.7% pts[FOS 44.7% pts]). A lower proportion of pts had tx-related acute kidney injury (AKI) with MBV (1.7% than IAT (7.8%[FOS 19.1%]). Pts in the IAT arm discontinued tx due to AKI (5.2% [FOS 12.8%]); no pts treated with MBV discontinued tx due to renal TEAEs.

Conclusions: Maribavir was superior to IAT for achievement of clearance of R/R CMV infection among transplant recipients, with consistent benefit in kidney recipients. Rates of renal TEAEs were lower with MBV than IAT.

Funding: Commercial Support - Funding: Shire ViroPharma, Incorporated, a Takeda company

Figure 1. GEP and dd-cfDNA performance by rejection types

Table 1 Diagnostic performance of a gene expression profiling and donor-derived cell-free DNA for acute rejection

<table>
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<tr>
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<th>GEP alone</th>
<th>dd-cfDNA alone</th>
<th>GEP+dd-cfDNA</th>
<th>Positive + or dd-cfDNA</th>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>0.76</td>
<td>0.42</td>
<td>0.88</td>
<td>0.43</td>
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<tr>
<td>Specificity</td>
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<td>0.29</td>
<td>0.70</td>
<td>0.52</td>
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<tr>
<td>PPV</td>
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<td>0.63</td>
<td>0.64</td>
<td>0.51</td>
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<tr>
<td>NPV</td>
<td>0.80</td>
<td>0.70</td>
<td>0.81</td>
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Table 2 Subclinical acute rejection diagnostic performance of GEP and dd-cfDNA

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TH-OR57
Phase 3 Study of Maribavir (MBV) vs. Investigator-Assigned Therapy (IAT) for Refractory/Resistant (R/R) Cytomegalovirus (CMV) Infection Post-Transplant: Analysis of Kidney Recipients and Renal Safety
Fuad S. Shihab, Robin K. Avery, Emily Blumberg, Abdolreza Haririan, Jingyang Wu, Aimee K. Sundberg. 1 University of Utah Health Care, Salt Lake City, UT; 2 Johns Hopkins University Division of Infectious Diseases, Baltimore, MD; 3 University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; 4 University of Maryland, Baltimore, MD; 5Shire Human Genetic Therapies, Inc., a Takeda company, Lexington, MA.

Background: Risk of nephrotoxicity limits antiviral use for treatment (tx) of transplant recipients with CMV infection. We report efficacy (including sub-analysis of kidney recipients) and renal safety data from a phase 3 study of MBV vs IAT in patients (pts) with R/R CMV infection (NCT02931539).

Methods: Transplant recipients (n=127) with CMV infection (screening plasma DNA<910IU/mL) R/R to prior tx (failure to achieve>1log 10 decrease in CMV DNA after 14days+genotyped resistance) were randomized 2:1 MBV (400mg BID):IAT (valganciclovir, foscarine[FOS], cidofovir) for 8wks. Primary endpoint:confirmed CMV clearance at end of Wk8 (plasma DNA<137IU/mL in 2 consecutive tests±5days apart). Key secondary endpoint:CMV clearance and symptom control at end of Wk8 maintained through Wk16. Group differences were adjusted for baseline CMV DNA level+solid organ/hematopoietic cell transplant where applicable. Subgroup analysis of kidney recipients was conducted. Tx-emergent adverse events (TEAEs) were assessed (safety set).

Results: More MBV (randomized set: 235 MBV, 117 IAT[47 FOS]) pts achieved the primary (55.7% vs 29.9% IAT; adjusted difference[AD] 32.8%, 95% CI 22.8–42.7; p=<0.001) and key secondary endpoint (18.7% vs 10.3% IAT; AD 9.5%, 95%CI 2.0—16.9; p=0.013). For kidney recipients (74 MBV, 32 IAT), 59.5% MBV vs 34.4% IAT pts achieved CMV clearance (AD 26.7%, 95%CI 7.5–45.9). Rates of TEAEs were similar between MBV and IAT (Table). Dysgeusia was the most frequent TEAE with MBV (37.2%, IAT 3.4% pts). Tx-related TEAE of increased immunosuppressant drug level was reported in 6% pts treated with MBV (IAT 0% pts). Renal and urinary TEAE rates were lower for MBV (17.1% pts than IAT (26.7% pts[FOS 44.7% pts]). A lower proportion of pts had tx-related acute kidney injury (AKI) with MBV (1.7% than IAT (7.8%[FOS 19.1%]). Pts in the IAT arm discontinued tx due to AKI (5.2% [FOS 12.8%]); no pts treated with MBV discontinued tx due to renal TEAEs.

Conclusions: Maribavir was superior to IAT for achievement of clearance of R/R CMV infection among transplant recipients, with consistent benefit in kidney recipients. Rates of renal TEAEs were lower with MBV than IAT.

Funding: Commercial Support - Funding: Shire ViroPharma, Incorporated, a Takeda company

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
TH-OR58
LIVING IN HIGH MINORITY, LESS ENGLISH-PROFICIENT COMMUNITIES MAY FACILITATE LIVING DONOR KIDNEY TRANSPLANTATION AMONG ASIAN AMERICANS AND PACIFIC ISLANDERS
Alixa C. Kilian,1 Brittany A. Shelton,1 Paul A. Maclean,1 Marshall C. Mcleod,1 Alexis J. Carter,1 Rhiannon D. Reed,1 Haiyan Qu,1 Babak Orandi,1 Vinay Kuma11, Deirdre L. Sawinski,1 Jayme E. Locey11,1 University of Alabama at Birmingham, Birmingham, AL; 2University of Pennsylvania, Philadelphia, PA.
Background: Living donor kidney transplantation (LDKT) racial disparities have increased. Living in linguistically isolated communities or areas with large minority populations has been associated with decreased access to transplant, but LDKT recipient-donor pairs are 95% racially concordant. The contemporary relationship between LDKT access and living in high minority, less English proficient communities is unknown.
Methods: The Scientific Registry of Transplant Recipients Utilized was identified to adult, kidney-only transplant recipients (1/1/2018-12/31/2018). The Minority Status and Language Theme of the Centers for Disease Control and Prevention 2018 Social Vulnerability Index was linked to recipients zip codes. Modified Poisson regression was utilized to evaluate likelihood of LDKT.
Results: Of the 18,950 kidney transplant recipients included in this study, 32% achieved LDKT. Black (adjusted relative risk (aRR): 0.60, 95% confidence interval (CI): 0.49-0.74) and Asian American and Pacific Islander (AAPI) recipients (aRR: 0.52, 95% CI: 0.39-0.70) were less likely to receive LDKT compared to White recipients. Overall, community minority status and language proficiency was not associated with LDKT (aRR: 1.01, 95% CI: 1.00-1.02), but the effect of this vulnerability measure varied by race. Among AAPI recipients only, living in higher minority, less English proficient communities was associated with increased likelihood of LDKT (ratio of aRR: 1.66, 95% CI: 1.12-2.47; Figure 1).
Conclusions: While all minority recipients had lower likelihood of LDKT, living in higher minority, less English proficient communities may be paradoxically advantageous for AAPI patients. Given LDKT racial concordance, living in areas with shared culture or language may facilitate LDKT access among AAPI.
Funding: NIDDK Support

TH-OR59
MODIFIABLE RISK FACTORS FOR NEW-ONSET HYPERTENSION AFTER LIVE DONOR KIDNEY DONATION
Yae Rim Kim,1 Junjeong Kang,2 Seehoon Park,1 Yong Chul Kim,1 Yong Su Kim,1 Hajeong Lee,4 Keimyung University School of Medicine, Daegu, Daegu, Republic of Korea; 2Ewha Women’s University College of Medicine and Graduate School of Medicine, Seoul, Republic of Korea; 3Seoul National University College of Medicine, Seoul, Republic of Korea; 4Seoul National University Hospital, Jongo-gu, Seoul, Republic of Korea.
Background: Hypertension is a common comorbidity and also a risk factor for the development of end-stage kidney disease in living kidney donors. Herein, we aimed to evaluate the impact of exposure to overweight after donation on the development of new-onset hypertension.
Methods: A total of 6,581 donors and 13,350 controls were extracted from the national health insurance database between 2001 and 2018. Subjects took national health check-up 2 times and more were included. Controls were randomly extracted after matching with age, sex, date of donation, underlying hypertension and diabetes in the general population. Exposure to overweight and obesity was defined by body mass index (BMI) ≥23 kg/m² and ≥25 kg/m² during follow-up period. Overweight/obesity status was divided into 4 groups: 1) persistently no exposure, 2) exposure at only last health check-up, 3) persistently exposure in two times of health check-up, and 4) recovered from exposure at last health check-up. We used a multivariable logistic regression model to identify risk factors for new-onset hypertension.
Results: A total of 1,642 donors and 3,655 controls were finally included in the study. During 7.3±3.2 years, there were 142 (8.6%) and 253 (6.9%) subjects newly diagnosed with hypertension, respectively. After adjusted such variables showed significance in univariate analysis, kidney donation significantly increased risk for the development of hypertension (adjusted odds ratio (aOR): 1.53, 95% confidence interval (CI) 1.21-1.93). Persistent overweight significantly increased risk for the development of hypertension (aOR: 3.53, 95% CI 2.07-6.35 vs. aOR: 1.69, 95% CI 1.19-2.43), whereas recovered from overweight did not increase risk (aOR: 1.61, 95% CI 0.36-5.1 vs. aOR: 0.87, 95% CI 0.35-1.87) in kidney donor and controls, respectively. Exposure to persistent obesity significantly increased the risk for hypertension in both groups, but recovered from obesity still increased the risk in kidney donors (aOR: 2.51, 95% CI 1.03-5.45) in contrary to the control (aOR: 1.60, 95% CI 0.88-2.76).
Conclusions: Both exposures to overweight or obesity increased the risk for new-onset hypertension, but recovered from overweight or obesity showed different results in donors. Physicians need to be focused on counseling for reducing the modifiable risk factor such as for overweight during the follow-up period.

TH-OR60
A MATE KIDNEY ANALYSIS TO DETERMINE THE IMPACT OF PREEMPTIVE TRANSPLANTATION ON OUTCOMES OF HIGH KIDNEY DONOR PROFILE
Deceased Donor Transplants
Justin Gill,1 Matthew J. Kadatz,1,2 James H. Lan,1,2 Doris Tung Chang,1 John S. Gill,1 Jagbir Gill,1 1The University of British Columbia, Vancouver, BC, Canada; 2Vancouver Coastal Health Research Institute, Vancouver, BC, Canada; 3Providence Health Care, Vancouver, BC, Canada.
Background: There is no inadequate supply of kidneys for transplant. The kidney donor profile index (KDP1) combines donor factors into a percentile that summarizes the likelihood of deceased donor transplant failure. High KDP1 kidneys are frequently discarded. Pre-emptive transplantation is associated with improved patient and graft survival, but it is unknown if this benefit is preserved with high KDP1 kidneys.
Methods: Using the SRTR database, N = 7,232 deceased donor transplants were identified where one donor kidney was transplanted pre-emptively (before the recipient required dialysis) and the other was used non-pre-emptively (after the recipient had initiated dialysis). We compared all-cause graft loss (ACGL), death censored graft loss (DCGL), and death with function (DWF) between the pre-emptive and non-pre-emptive recipients using univariable and multivariable time to event analyses adjusted for differences in recipient factors.
Results: Pre-emptive transplantation was associated with improved outcomes of ACGL, DCGL, and DWF (Fig 1). These results were consistent in the subgroup where the donor KDP1 was >= 91%. Furthermore, the risk of ACGL with a pre-emptive transplant from a KDP1 >= 91% donor (HR: 1.65, CI: 1.51 – 1.81) was similar to the risk of ACGL from a non-pre-emptive transplant from a KDP1 51-80% donor (HR: 1.57 CI: 1.48 – 1.66) (Fig 2).
Conclusions: In this mate kidney analysis, outcomes after a pre-emptive transplant were superior compared to a non-pre-emptive transplant, even among kidneys from donors with very high KDP1. Pre-emptive transplantation of high KDP1 kidneys is an opportunity to safely increase the number of kidney transplants from the limited supply of deceased donor kidneys.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
TH-OR61
Quantifying Individual-Level Uncertainty in GFR Estimation
Xiaojian Zhu,1 Seth Lirette,1 Andrew D. Rule,1 Tom Mosley,1 Kenneth R. Butler,1 Javed Butler,1 Michael Hall,1 Pradeep Vaitla,1 James J. Wynn,1 Neville R. Dossabhoy,1 Eliseo Guallar,2 Tariq Shah,3 The University of Mississippi Medical Center, Jackson, MS; 2Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD; 3Mayo Clinic, Minnesota, Rochester, MN.

Background: Although the differences between estimated GFR (eGFR) and measured GFR (mGFR) are well-recognized, the magnitude and potential clinical implications of these differences at the individual level are not fully appreciated.

Methods: Using data from four US community-based cohorts with mGFR (total N=3,223), we calculated eGFR from serum creatinine alone (eGFRs) and cystatin and creatinine (eGFRc) using the CKD-EPI equations without race coefficients. Using quantile regression, we assessed eGFR’s individual-level reliability by calculating a 95% prediction interval (PI), defined as the distribution of 95% of the observed mGFR values at a given eGFR. We also assessed eGFR’s population-level reliability using standard metrics, including median difference (eGFR-mGFR). All GFR results are presented as ml/min/1.73m².

Results: The participants’ median age was 61 years, 32% were Black, and 55% were female. The median mGFR was 68 [IQR, 46 to 88]. At the population level, the median difference between eGFRs and mGFR was small (1.4; 95% CI: 0.9 to 1.9). In contrast, the individual-level 95% PI of the eGFRc was large, ranging from 53 to 120 at eGFRc ≥90 and from 19 to 55 at eGFRc ≥30 (Figure and Table). Substantial individual misclassification was also noted using eGFRs; 10% of individuals with eGFRc <60 and 28% of those with eGFRc ≥90 had mGFR above those thresholds. Results were similar for eGFRs.

Conclusions: A substantial individual-level discrepancy exists between eGFR and mGFR. The eGFR PI should be included with eGFR reporting. Some clinical decisions may need to be based on mGFR rather than eGFR.

Funding: Other NIH Support - NINR, NHLBI

Table 1

<table>
<thead>
<tr>
<th>eGFR, ml/min/1.73m²</th>
<th>10</th>
<th>30</th>
<th>50</th>
<th>60</th>
<th>90</th>
<th>100</th>
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<tbody>
<tr>
<td>95% CI</td>
<td>19.21 to 24.26</td>
<td>32.54 to 45.26</td>
<td>55.50 to 68.56</td>
<td>58.13 to 70.12</td>
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</tr>
<tr>
<td>95% PI (median of mGFR)</td>
<td>19.21</td>
<td>33.14</td>
<td>45.55</td>
<td>57.27</td>
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TH-OR62
Kidney Function Biomarkers Among American Indians (AI) and Hispanic Americans (HA)
Monica Moya Balasch, Christos Argyropoulos, Maria-Eleni Roumelioti. University of New Mexico School of Medicine, Albuquerque, NM.

Background: The NKF-ASN Task Force recommends that kidney function be measured GFR (mGFR) are well-recognized, the magnitude and potential clinical implications of these differences at the individual level are not fully appreciated.

Methods: Using data from four US community-based cohorts with mGFR (total N=3,223), we calculated eGFR from serum creatinine alone (eGFRs) and cystatin and creatinine (eGFRc) using the CKD-EPI equations without race coefficients. Using quantile regression, we assessed eGFR’s individual-level reliability by calculating a 95% prediction interval (PI), defined as the distribution of 95% of the observed mGFR values at a given eGFR. We also assessed eGFR’s population-level reliability using standard metrics, including median difference (eGFR-mGFR). All GFR results are presented as ml/min/1.73m².

Results: The participants’ median age was 61 years, 32% were Black, and 55% were female. The median mGFR was 68 [IQR, 46 to 88]. At the population level, the median difference between eGFRs and mGFR was small (1.4; 95% CI: 0.9 to 1.9). In contrast, the individual-level 95% PI of the eGFRc was large, ranging from 53 to 120 at eGFRc ≥90 and from 19 to 55 at eGFRc ≥30 (Figure and Table). Substantial individual misclassification was also noted using eGFRs; 10% of individuals with eGFRc <60 and 28% of those with eGFRc ≥90 had mGFR above those thresholds. Results were similar for eGFRs.

Conclusions: A substantial individual-level discrepancy exists between eGFR and mGFR. The eGFR PI should be included with eGFR reporting. Some clinical decisions may need to be based on mGFR rather than eGFR.

Funding: Other NIH Support - NINR, NHLBI

Table 1

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TH-OR63
Decline in Estimated Glomerular Filtration Rate (eGFR) Among Black Veterans After Removing the Race Coefficient: Results of the US Veterans Health Administration Electronic Health Records
Guofen Yang,1 Keith C. Norris,2 Robert Nee,3 Julia J. Scialla,2 Nan Hu,4 Wei Yu,4 Tom Greene,5 Alfred K. Cheung,6,7 University of Virginia School of Medicine, Charlottesville, VA; 2University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA; 3Walter Reed National Military Medical Center, Bethesda, MD; 7Florida International University, Miami, FL; 4University of Utah Health, Salt Lake City, UT; 5VA Salt Lake City Health Care System, Salt Lake City, UT.

Background: In the US, Black Americans with CKD have faster kidney function decline than White peers. We examined whether this faster decline was also observed when the race coefficient was removed from eGFR calculation among US veterans.

Methods: eGFRs were calculated from serum creatinine measurements (excluding acute care settings) using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) and the CKD-EPI without the race coefficient (CKD-EPI-RACEnot). We estimated eGFR slopes using quarterly averages of eGFRs for up to 8 years or until May 31, 2018 starting from the first quarter after CKD incidence (i.e., first eGFR<60 mL/min/1.73m² for ≥3 months). We used linear mixed-effects models with random intercept and slope, adjusting for age, sex, eGFR at CKD incidence, and CKD incidence year.

Results: From 2003-2017, 139,921 Black veterans had incident CKD defined by CKD-EPI-RACEnot and 100,510 by CKD-EPI; and 636,598 White veterans by CKD-EPI, with median number of quarterly averages of eGFRs per patient of 8, 8, and 7, respectively. Overall, eGFR decline was greater among Blacks defined by CKD-EPI than Whites (-1.37 vs -0.84 mL/min/1.73m² per year, Table), consistent with prior findings. eGFR decline among Blacks by CKD-EPI-RACEnot was attenuated (-1.07), but still greater than among Whites. In the two youngest groups, Blacks by CKD-EPI-RACEnot still had about 2-fold larger decline versus Whites (Table).

Conclusions: Black veterans with CKD defined by eGFR without race coefficient still had faster kidney function decline following CKD incidence compared to White veterans, but the difference was attenuated. Use of eGFR without race coefficient may pick up earlier, less aggressive cases of CKD among younger Blacks and promote earlier prevention.

Funding: NIDDK Support

Table 1

<table>
<thead>
<tr>
<th>Race</th>
<th>eGFR slope (mL/min/1.73m²/yr)</th>
</tr>
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<tbody>
<tr>
<td>Black</td>
<td>-1.37</td>
</tr>
<tr>
<td>White</td>
<td>-0.84</td>
</tr>
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</table>

p-values (ANOVA) from null-space kernel regression. DBP & hs-CRP were not predictive of any biomarker.
Slopes as eGFR decline per year (95% CI) with CKD-EPI with and without race coefficient

<table>
<thead>
<tr>
<th></th>
<th>Black, eGFR defined by CKD-EPI</th>
<th>Black, eGFR defined by CKD-EPI without race coefficient</th>
<th>White</th>
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<tbody>
<tr>
<td>Overall</td>
<td>1.02 (1.01-1.02)</td>
<td>1.01 (1.00-1.02)</td>
<td>1.00</td>
</tr>
<tr>
<td>Age 20-34</td>
<td>1.04 (1.02-1.05)</td>
<td>1.02 (1.00-1.03)</td>
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<tr>
<td>Age 35-44</td>
<td>1.04 (1.02-1.05)</td>
<td>1.02 (1.00-1.03)</td>
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<tr>
<td>Age 45-54</td>
<td>1.04 (1.02-1.05)</td>
<td>1.02 (1.00-1.03)</td>
<td>1.00</td>
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<tr>
<td>Age 55-64</td>
<td>1.04 (1.02-1.05)</td>
<td>1.02 (1.00-1.03)</td>
<td>1.00</td>
</tr>
<tr>
<td>Age 65-74</td>
<td>1.04 (1.02-1.05)</td>
<td>1.02 (1.00-1.03)</td>
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<tr>
<td>Age 75+</td>
<td>1.04 (1.02-1.05)</td>
<td>1.02 (1.00-1.03)</td>
<td>1.00</td>
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</tbody>
</table>

TH-OR64

Race, Genetic Ancestry, and GFR Estimation: Findings from the CRIC Study

Chi-yuan Hsu,1,4 Wei Yang,1 Rishi V. Parikh,4 Amanda H. Anderson,2 Teresa K. Chen,3 Debbie L. Cohen,4 Jiang He,2 Madhumita J. Mohanty,1 James P. Lash,6 Katherine T. Mills,7 Anthony N. Muriu,2 Ashfin Parsa,10 Mildr I. Saunders,10 Tarqi Shafi,10 Raymond R. Townsend,1 Shushrut S. Waikar,1 Jianqiao Wang,6 Myles Wolf,1 Thida C. Tan,10 Harold L. Feldman,1 Alan S. Go,6 CRIC 1University of California San Francisco, San Francisco, CA; 2Tulane University, New Orleans, LA; 3Johns Hopkins University School of Medicine, Baltimore, MD; 4Kaiser Permanente Northern California, Oakland, CA; 5University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; 6University of Illinois at Chicago, Chicago, IL; 7The University of Mississippi Medical Center, Jackson, MS; 8Boston University School of Medicine, Boston, MA; 9Wayne State University, Detroit, MI; 10National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD; 11The University of Chicago Medicine, Chicago, IL; 12Duke University, Durham, NC.

Background: Inclusion of race in GFR estimating equations is undesirable. Prior studies have not examined replacing race with genetic ancestry.

Methods: We studied 1248 Chronic Renal Insufficiency Cohort (CRIC) Study participants with urinary 125I-iothalamate clearance GFR (iGFR) measurements and complete data on self-reported race, genetic ancestry, serum creatinine (SCr) & cystatin C (CysC). Genotyping was conducted using the Illumina HumanOmni1-Quad v1.0 microarray. The cohort was split into development (2/3) and validation (1/3) samples. Using linear regression, we derived GFR estimating equations for iGFR using SCr or cystatin C, age, sex, and self-reported race or African ancestry. The derived equations were then applied to participants with urinary 125I-iothalamate clearance GFR (iGFR) measurements and 30% (P30) of iGFR.

Results: 539 participants were female and 458 self-identified as Black. Mean±SD age was 55±12.1 yr, iGFR 48±20 ml/min/1.73m², median [IQR] SCr was 1.5 [1.3-2.0] mg/dL, cystatin C 1.35 [1.09-1.71] mg/L. Median % African ancestry was 82.6% [74.5-88.3%] among those who self-identified as Black and 0.2% [0.1-0.2%] in those who did not. When using SCr to estimate GFR, incorporating vs omitting self-reported race yielded better performing estimates (Table). Incorporating genetic ancestry provided estimates of GFR similar to those incorporating self-reported race. Incorporation of race or ancestry was unnecessary when estimating GFR using cystatin C. A GFR estimating equation using cystatin C, age and sex performed comparably to an equation using SCr, age, sex, and race or ancestry.

Conclusions: Switching from SCr to cystatin C to estimate GFR yields comparably valid without needing to include either race or genetic ancestry.

Funding: NIDDK Support

TH-OR65

Comparison of Estimated Glomerular Filtration Rate with and Without Race Adjustment on Associations with ESRD: The CRIC Study

Joshua D. Bundy,1 Katherine T. Mills,1 Amanda H. Anderson,1 Wei Yang,1 L. Lee Hamm,2 Jing Chen,3 Jiang He,1,10 Tulane University School of Public Health and Tropical Medicine, New Orleans, LA; 2University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; 10Tulane University School of Medicine, New Orleans, LA.

Background: Lower estimated glomerular filtration rate (eGFR) is strongly associated with higher risk of end-stage renal disease (ESRD). eGFR equations typically include adjustment for Black race, but this practice is controversial and the impact of its removal on associations with ESRD are unknown.

Methods: We included 3786 participants (mean age 57.8 years; 45.2% women; 41.8% Black) from the CRIC Study. ESRD was defined as initiation of dialysis or transplantation. We evaluated five CKD-EPI equations for calculating eGFR based on serum creatinine (SCr), cystatin C (CysC), and with or without race adjustment. We estimated associations and predictions of 5-year ESRD risk using Cox proportional hazards regression and the 4-variable Kidney Failure Risk Equation (KFRE), which includes age, sex, eGFR, and urinary albumin-to-creatinine ratio. Models were evaluated using measures of discrimination (AUC) and calibration (Brier score).

Results: Within 5 years after baseline, 642 participants developed ESRD and the cumulative incidence among Black and white/others was 22.5% and 15.4%, respectively. Across all eGFR equations, the KFRE was superior for prediction of 5-year risk of ESRD compared with eGFR alone among all participants (AUC range, 0.899-0.915 vs. 0.816-0.837 for eGFR alone; P<0.001). Among Black participants, the KFRE using creatinine-based eGFR without race adjustment improved calibration compared with the other equations (Figure).

Conclusions: The KFRE has superior discrimination for 5-year risk of ESRD compared with eGFR alone, regardless of whether race adjustment is employed. Removing the race adjustment from the creatinine-based CKD-EPI equation may improve prediction of 5-year risk of ESRD.

Funding: NIDDK Support

TH-OR66

How Removing the Race Coefficient from eGFR Equations Impacts Racial Differences in CKD Progression Among People with HIV

Anthony N. Muriu,1 Erin Madden,2 Michael Shlipak,1 Michelle M. Estrella,1 NA-ACCORD 1University of California San Francisco, San Francisco, CA; 2Northern California Institute for Research and Education, San Francisco, CA.

Background: The impact of removing the race coefficient from eGFR equations on racial differences in CKD progression in people with HIV (PWH) is unknown.

Methods: We included 69,125 PWH enrolled in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) from Jan 1, 2005-Dec 31, 2014. Baseline date was defined as the date of enrollment in NA-ACCORD or beginning of cohort eGFR observation window, whichever came last. Reported race was categorized as Black, White, or Other. We defined CKD stages in 2 ways: 1) Serum creatinine-based CKD-EPI eGFR equation, which assigns higher eGFR for Black persons; and 2) CKD-EPI eGFR without the race coefficient. We created Markov models to estimate 5-year probabilities of transitioning from the initial stage to worse CKD stages, with death as a competing event; the associations of race (Black vs White) with progression across CKD stages were evaluated.

Results: 31,298 PWH were Black, in whom baseline antiretroviral use and HIV suppression were less prevalent and hepatitis C infection, hypertension and diabetes were more prevalent compared with White participants (N=27,542). eGFR without the race coefficient reclassified 25% of Black PWH into a worse CKD stage at baseline. Those reclassified had a higher prevalence of CKD risk factors compared with Black PWH who were not reclassified. When modeled with the race coefficient, Black PWH had 23% lower risk of progressing from CKD stage 1 to 2, similar risk of progressing from stages 2 to 3 and 3 to 4, increased risk of progressing from stage 4 to 5, and composite risk of ESRD or death compared with White PWH. When CKD progression was modeled using race-free eGFR, Black PWH consistently had a higher risk of CKD progression compared with White PWH (Table).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Conclusions: Prior studies suggesting that Black PWH have lower risk than White individuals for early CKD progression but higher risk at later stages were likely biased by the race coefficient. Assigning higher kidney function for all Black individuals based on race systematically masks a subgroup of Black PWH who are at higher risk of CKD progression.

Funding: NIDDK Support

TH-OR67
GFR in the Era of Precision Medicine: The Importance of a Measured GFR in Onco-Nephrology
Francesco Trevisani,1 Giulia Pegoraro,2 Daniele Pugno,2 Giulia Quattrini,3 Federico Di marco,2 Alessandra Cinque,1 Arianna Bettig,3 Umberto Capitanio,1 Andrea Salonia,1 Giorgio Pizzagalli,1 Francesco Montori,1 IRCCS Ospedale San Raffaele, Milano, Italy; 2Biorek S.R.L., Milano, Italy.

Background: An accurate assessment of renal function in nephrological patients (pts) is of paramount importance. Unfortunately, the most used method to measure GFR is represented by the estimated GFR(eGFR) which harbours a significant error in comparison to gold standard(mGFR). Aim of this study was to determine the extent of the error of eGFR compared to the mGFR in onco-nephrological pts.

Methods: A total consecutive cohort of 200 pts was collected to compare the eGFR formulas (MDRD, CKD-EPI 2012) with mGFR method(iohexol Plasma Clearance). Cohort composition: 116 oncological pts(cases) and 84 functional diseases pts(controls) matched for baseline variables. The agreement between eGFR and mGFR was evaluated using bias, precision, accuracy, and total deviation index. The differences between cohorts were evaluated with Fisher’s exact test and Chi-squared test and Wilcoxon rank sum test for continuous variables.

Results: Clinical data are reported in Table 1. The two matched cohorts displayed no statistical differences in term of clinical variables and agreement parameters(TDI, CCC and P30). Surprisingly, both groups harboured a non negligible errors in each CKD class with a huge discrepancy between the eGFR formulas and the gold standard method (Figure 1, 2), suggesting the great relevance of mGFR in the clinical decision making algorithm, both with two and one kidney.

Conclusions: The error in the classification of CKD stages using eGFR by formulas was too common in case and controls, with a poor agreement with mGFR in all CKD classes. The use of mGFR should be mandatory to obtain a tailored management in onco-nephrology.

Figure on the left represent the percentages of pts with four different intervals of error. Figure on the right represent the classification of pts in CKD stages by eGFR. True positive represent subjects that were correctly classified from eGFR and false positive represent the cases that were not classified in the corresponding class. Table shows the clinical data of the population divided in two cohorts: functional and oncological pts.

TH-OR68
The Effect of Age on Performance of the Kidney Failure Risk Equation in Advanced CKD
Gregory L. Hundemer,1 Navdeep Tangri,2 Manish M. Sood,1 Ayub Akbari,1 Ottawa Hospital Research Institute, Ottawa, ON, Canada; 1University of Ottawa, Ottawa, ON, Canada.

Background: The Kidney Failure Risk Equation (KFRE) is a validated clinical tool used to predict progression from CKD to kidney failure. Concerns over risk overestimation have been raised with prediction models, such as the KFRE, where death is not treated as a competing event. Herein, we evaluated the effect of age (with which the competing risk of death would be anticipated to increase) on KFRE performance in advanced CKD.

Methods: All patients referred to the advanced CKD clinic at the Ottawa Hospital from 2010-2018 were divided into age quartiles: <58, 58-67, 68-77, and >77 years. The follow-up. In additional analyses, we examined two eGFR measures < 60 ml/min/m² with up to 10 years follow-up. In additional analyses, we examined two eGFR measures < 60 ml/min/m² with up to 10 years follow-up. In additional analyses, we examined two eGFR measures < 60 ml/min/m² with up to 10 years follow-up.

Results: Among individuals (54.5% women, mean age 64 SD 7, mean baseline eGFR 82 SD 8, median ACR 1 IQR 1-3), an eGFR < 60 ml/min occurred in 37.2% during the follow-up. The final model including up to 6 variables (age, sex, baseline eGFR, hemoglobin, time from hypertension and diabetes mellitus diagnosis) yielded a 5-year c-statistics of 0.77 (no ACR) and 0.78 (with ACR) with excellent calibration. Model performance was similar in additional analyses and in an external validation.

Conclusions: An equation incorporating readily available and routinely collected administrative data variables can accurately predict the onset of CKD with or without ACR.

TH-OR69
A Prediction Equation for Incident CKD Using Routinely Collected Data: The Kidney Disease Risk Equation (KDRE)
Manish M. Sood,1 Stephanie Dixon,2 Emily Rhodes,1,2 Ottawa Hospital Research Institute, Ottawa, ON, Canada; 1Institute for clinical and evaluative sciences, London, ON, Canada.

Background: The identification of individuals at risk for incident CKD (eGFR ≤ 60 ml/min, stage 3a) is an important first step for disease surveillance, monitoring, education and allocation of key therapies to reduce CKD progression. Despite recommendations, albuminuria measurements in appropriate individuals remains poor. As such, we set out to develop and validate a prediction equation for new onset CKD with and without an albumin creatine ratio (ACR).

Methods: Population-level administrative data cohort of 1,109,905 adults (>66 years old) from Ontario, Canada April 1, 2008 and December 31, 2017 with a minimum of 2 eGFR measures (one for baseline ≥ 70 ml/min, one for outcome) were included. Prediction equations stratifying individuals with (n=191,690) and without (n=998,215) ACR were derived, internally validated by bootstrapping and externally validated in 122,149 (22,809 ACR, 99,335 non-ACR) individuals in Manitoba, Canada. The study outcome was a single eGFR measure < 60 ml/min/m² with up to 10 years follow-up. In additional analyses, we examined two eGFR measures < 60 ml/min/m² and a single eGFR < 65 ml/min/m² as study outcomes.

Results: Among individuals (54.5% women, mean age 64 SD 7, mean baseline eGFR 82 SD 8, median ACR 1 IQR 1-3), an eGFR < 60 ml/min occurred in 37.2% during the follow-up. The final model including up to 6 variables (age, sex, baseline eGFR, time from hypertension and diabetes mellitus diagnosis) yielded a 5-year c-statistics of 0.77 (no ACR) and 0.78 (with ACR) with excellent calibration. Model performance was similar in additional analyses and in an external validation.

Conclusions: An equation incorporating readily available and routinely collected administrative data variables can accurately predict the onset of CKD with or without ACR.

TH-OR70
Tubular Secretion of Creatinine and Clinical Outcomes: The AASK Trial
Pranay S. Garg,1 Kevin M. Cummins,2 Jennifer J. Gassman,2 Franziska K. Bubochi,2 Stefania Sacchini,2 Silvia M. H. Jolly,1 Jennifer J. Gassman,2 Alessandra Cinque,1 Arianna Bettig,3 Umberto Capitanio,1 Andrea Salonia,1 Giorgio Pizzagalli,1 Francesco Montori,1 IRCCS Ospedale San Raffaele, Milano, Italy; 2Biorek S.R.L., Milano, Italy.

Background: Tubular secretion is a critical kidney function that is not routinely assessed. We evaluated the association of tubular secretion of creatinine calculated using the difference between either measured glomerular filtration rate (mGFR) or estimated GFR (eGFR) and 24-hour urine creatinine clearance (CrCl) with long-term clinical outcomes.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: This prospective analysis of the African American Study of Kidney Disease (AASK), included 990 participants with baseline measures of systolic blood pressure, treatment, and achieved blood pressure. After a median follow-up of 13 years, a total of 137 participants developed AKI. Data were adjusted for age, sex, blood pressure, albuminuria, and other baseline characteristics.

Results: The overall incidence rate of AKI was 1.4 per 100 person-years. The incidence rate was highest in participants with the highest baseline blood pressure (HR 2.4, 95% CI 1.4-4.1) and lowest in those with the lowest baseline blood pressure (HR 0.4, 95% CI 0.2-0.9). The incidence rate was also higher in participants with albuminuria (HR 2.1, 95% CI 1.2-3.6) compared to those without.

Conclusions: This study highlights the importance of blood pressure control and albuminuria in the prevention of AKI. Further research is needed to understand the underlying mechanisms and develop effective interventions to reduce the risk of AKI.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Proximal Tubule Panxin1 Channel Regulates Mitochondrial Function and Cell Death During AKI
Nabin Poudel, Nataliya Skrypnyk, Shuqiu Zheng, Christopher B. Medina, Eibhim Goggin, Diane L. Rosin, Kodi S. Ravichandran, Mark D. Okusa. University of Virginia School of Medicine, Charlottesville, VA.

Background: Panxin1 (Panx1) channel serves as a conduit for release of small metabolites upon activation during cellular stress and injury. We have previously shown that pharmacological inhibition or genetic deletion of Panx1 in mice prior to injury is protective against renal ischemia-reperfusion injury (IRI). How Panx1 contributes to acute kidney injury (AKI) is unknown. We hypothesized that Panx1 induces cell death by mediating both intracellular and extracellular events.

Methods: We performed Panx1- or cisplatin-induced AKI in a novel human Panx1 overexpressing mouse (hPanx1-Tg) and in proximal tubule specific Panx1 overexpressing mice (hPanx1-Tg<sup>PROX1</sup>)) and assessed plasma creatinine, renal expression of neutrophil gelatin associated lipocalin (Ngal), and acute tubular necrosis score. We challenged hPanx1-Tg<sup>PROX1</sup> mice with cisplatin and assessed cell death and mitochondrial changes. We next assessed the changes in mitochondria of kidneys from cisplatin challenged hPanx1-Tg animals.

Results: hPanx1-Tg mice had significant rise in plasma creatinine and expression of Ngal in the kidneys in both models of AKI compared to their littermate controls. Proximal tubule specific overexpression of hPanx1 also resulted in overt injury following IRI or cisplatin-induced AKI compared to littermate controls. In vitro studies showed that overexpression of Panx1 in TKPTS cells resulted in significantly higher cell death compared to controls during cisplatin challenge, which was associated with reduced mitochondrial biogenesis, mitochondrial function, increased mitochondrial ROS production, and altered mitochondrial quality control. Assessment of mitochondria in kidneys showed a significant reduction in Drp1 levels in kidneys from hPanx1-Tg transgenic mice as compared to controls after cisplatin challenge.

Conclusions: Panx1 overexpression results in overt renal injury during AKI that is in part mediated by reduced mitochondrial function and quality control in proximal tubules that facilitates proximal tubule cell death. These results provide strong rationale for the development of selective inhibitors to inhibit Panx1 in the prevention or treatment of AKI.

Funding: NIDDK Support, Private Foundation Support

FR-OR05
The Long Noncoding RNA GSTM3P1 Is Induced to Exacerbate Ischemic AKI by Antagonizing MicroRNA-668
Qiongqiong Wei, Jiliang Zhou, Zheng Dong. Augusta University Medical College of Georgia, Augusta, GA.

Background: Long non-coding RNAs (lncRNAs) are a group of epigenetic regulators that may play important roles in kidney diseases, but the specific lncRNAs involved and the underlying mechanisms are poorly understood. We recently unveiled mir-668 as a potent protective microRNA in ischemic AKI (Wei Q et al. J Clin Invest 128:5448, 2018). By deep sequencing of mir-668-induced silencing complex, we have identified GSTM3P1, a lncRNA, as a potential inhibitor and regulator of mir-668.

Methods: The expression of GSTM3P1 and its mouse homologue gstm2-ps1 were examined in hypoxia-treated HK2 cells and in mouse kidneys after ischemic AKI. GSTM3P1 expression was overexpressed in renal cells for functional examination. Proximal tubule specific gstm2-ps1 knockout mouse model was established to test its role in ischemic AKI in vivo.

Results: GSTM3P1/gstm2-ps1 was markedly induced in the early phase of ischemic AKI in vitro and in vivo. HK2 cells, qPCR indicated a significant increase of GSTM3P1 at 3 hours after 1% O<sub>2</sub> treatment. In C57BL/6 mice, gstm2-ps1 was significantly induced in kidneys after 30 minutes of ischemia and 3 hours of reperfusion, which was also accompanied with the suppression of mir-668. In vitro, overexpression of GSTM3P1 led to more renal proximal tubular cell death after ATP depletion. GSTM3P1 overexpression in HEK cells caused significant decrease of the mature form of mir-668. A mir-668 binding site in GSTM3P1 was also confirmed by luciferase assay. We further generated kidney proximal tubule-specific gstm2-ps1 knockout (KO) mouse model. Compared to wild type littermates (WT), the conditional gstm2-ps1 KO mice were significantly protected from renal ischemia-reperfusion injury. Both blood urea nitrogen (BUN) and serum creatinine levels were significantly lower in gstm2-ps1 KO mice post ischemia-reperfusion injury.

Conclusions: These results indicate that GSTM3P1/gstm2-ps1 is induced in ischemic AKI, and following induction it mediates tubular cell death and injury by interacting and antagonizing mir-668.

Funding: NIDDK Support, Veterans Affairs Support

FR-OR06
Novel Immune Checkpoint Molecule TIGIT Is Upregulated on Kidney CD4 T Cells and Mediates AKI in Mice
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Background: T cells play important roles in acute kidney injury (AKI) but the molecular mechanisms are largely unknown. Our single-cell RNAseq analysis indicated that TIGIT knockout mice demonstrated increased mRNA expression of novel immune checkpoint molecule T cell immunoreceptor with Ig and ITIM domains (TIGIT) on kidney CD4 T cells after AKI. Here, we validated TIGIT expression on kidney T cells at protein level and investigated its effect on kidney T cell activation, function, and AKI outcome.

Methods: C57BL/6 wild type (WT) mice underwent bilateral ischemia reperfusion (IR). TIGIT expression and effect on kidney T cell activation and cytokine expression was assessed at baseline and after IR injury by flow cytometry in WT mice. TIGIT knockout (TIGIT KO) mice were used to assess effects on AKI. Human kidney at baseline and post ischemia for nephrectomy had CD4 TIGIT measured by flow cytometry.

Results: TIGIT expression increased significantly (p<0.001) on CD4 T cells in proximal tubule specific gstm2-ps1 KO mice compared to controls (15.0±1.5% vs 8.8±2.0%). Furthermore, TIGIT<sup>-</sup> vs CD4 T cells from WT kidneys showed a significantly increased expression of activation markers, CD25 (10.9±1.7% vs 2.4±0.2%, p<0.001), CD69 (14.5±1.4% vs 8.8±1.0%, p<0.01) and CD44 (93.9±1.5% vs 74.5±1.7%, p<0.001) compared to TIGIT<sup>+</sup> CD4 T cells. Intracellular cytokine analysis showed significantly increased IFNγ (50.4±3.3% vs 20.3±3.3%, p<0.001) and TNFα (55.7±0.5% vs 35.4±4.9%, p<0.02) expression by TIGIT<sup>-</sup> T cells compared to TIGIT<sup>+</sup> CD4 T cells after IR injury in WT mice. TIGIT KO mice showed significantly reduced SCR at 24 h (2.1±0.2 vs 2.6±0.1 mg/dL; p<0.03) and 72h (1.3±0.3 vs 2.7±0.4 mg/dL; p<0.02) post IR compared to WT mice. At baseline, treatment with TIGIT KO mice had significantly higher SCR (5.4±0.2 vs 2.7±0.4 mg/dL; p<0.05) compared to WT mice.

Conclusions: These data show that TIGIT expression increases on kidney CD4 T cells after ischemia and in mice. This correlates with increased CD4 activation and proinflammatory phenotype. Importantly, absence of TIGIT in mice reduced kidney dysfunction after AKI. TIGIT is a promising novel therapeutic target for AKI therapy and could also mediate other immune mediated kidney diseases.

FR-OR07
Compartment-Specific Role of Retinoic Acid Receptor Receptor Activation in AKI
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Background: Retinoic acid receptors (RARs) are activated in proximal tubules (PT), collecting ducts (CD), and renal macrophages (Møs) after ischemia-reperfusion AKI (IR-AKI), and systemic RAR inactivation increases Mn-dependent injury after IR-AKI. However, the functional roles of RAR activation in different cellular compartments are unknown.

Methods: RAR-LacZ (RAR reporter) PEPC-KCRE; R26R-Dominant Negative RAR (PT-DNRAR); AQ22-CRE; DNAR-Mø (DNAR-Mø) underwent bilateral IR- and/or rhabdomyolysis-AKI (rhabdo-AKI). Injury and RAR-LacZ localization were evaluated by BUN, LacZ staining and IF. Renal Mø activation determined by FACS; primary PTEC proliferation and metabolic activity using Seahorse.

Results: RARs are more widely activated after rhabdo- vs. IR-AKI: ~90% in LTL or Kim1<sup>+</sup> PTs<sup>−</sup> in 5% in AQ22<sup>−</sup> CD in F4/80<sup>−</sup> Møs; and <2% in THP1: ~10%<sup>1</sup> than in IR-AKI. However, the functional roles of RAR activation in different cellular compartments are unknown.

Conclusions: RAR-LacZ uses are greater specifically associated with IR-AKI. Increase RAR<sup>−</sup><sup>−</sup> Møs; and PTECs from PT-DNRAR CRE<sup>+</sup> mice were more metabolically active and proliferative compared to F4/80<sup>−</sup> Møs.

Funding: NIDDK Support

FR-OR08
Gasdemin D-Deficient Mice Are Hypersensitive to Necroptosis-Mediated AKI
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Background: Within the last decade, a central role for regulated necrosis (RN) in the pathophysiology of renal ischemia-reperfusion injury (IRI) has been established. RN is an umbrella term for several RN subtypes. With respect to the kidney, necroptosis and ferroptosis are the best studied pathways. However, the role of pyroptosis, a highly inflammatory RN type dependent on the protein GSDMD (gasdemin D), during IRI remains unclear.

Results: These studies indicate that RAR activation in different cellular compartments exert opposing effects on the severity AKI through distinct mechanisms, and provides the first evidence that differentiated and inflammatory PTECs, recently described molecular signatures of failed repair, may be protective in AKI.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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Results: We investigated gasdermin D- and gasdermin E-deficient mice in a well-established model of moderate IRI. Both strains showed more severe AKI than matched wildtypes as demonstrated by higher levels of serum creatinine and urea as well as more severe tubular damage. This effect was neither dependent on increased tubular cell death as measured by LDH release from freshly isolated murine tubules nor on increased infiltration by CD3+ or CD68+ cells. Based on previous studies, we speculated that pyroptosis-deficiency might promote necroptosis during AKI. To test this hypothesis, we generated MLKL/GSDMD-dKO. In IRI, co-deletion of MLKL ameliorated the effects of pyroptosis-deficiency and led to reduced levels of serum creatinine and urea as well as reduced tubular damage compared to both wildtype and pyroptosis-deficient mice. Furthermore, we investigated whether this interaction of pyroptosis and necroptosis is a general phenomenon to other forms of AKI by utilizing cisplatin-induced tubular injury as a second model. Again, pyroptosis-deficient mice were more sensitive to AKI and could be protected by co-deletion of MLKL.

Conclusions: In summary, Gasdermin D and E appear to have protective roles in murine AKI as they help to reduce MLKL-mediated necroptosis. Our data are in striking contrast to previously published data (Miao et al., Kidney International 2019).

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-OR11

Deep Learning Uncovers Clinical Subphenotypes of Diabetic Kidney Disease Driven by Genetic Variation in Rac1 Pathway

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Background: Although diabetic kidney disease (DKD) is a leading cause of end stage renal disease, therapeutic development targeting causal pathways has been limited by disease heterogeneity. Integration of clinical data and genomics may uncover hidden DKD subphenotypes.

Methods: DKD patients from the Mount Sinai BioMe Biobank were included. Using laboratory measurements, vitals, and clinical notes in a deep learning framework (Fig 1A) we performed unsupervised clustering, accounting for population structure. We then performed a genome wide association study comparing patients in each cluster with healthy controls.

Results: We identified two clusters (Fig 1C), M (mild, N = 972) and S (severe, N = 390). Cluster M had greater ESKD prevalence (36% vs 5%; p <0.001) and higher baseline serum creatinine (1.2 vs 1.1; p=0.001). Using exome sequencing, a missense variant in ARHGEF18, rs117824875, was significantly associated with DKD in cluster S, but not cluster M (OR = 7.7; p = 9.56x10^{-10}). This variant was also associated with DKD in an external cohort, UK Biobank (OR = 2.4, p = 0.044). ARHGEF18 knockdown in a diabetic zebrafish model induced whole body edema (Fig 1D). Stable overexpression of the rs117824875 mutant ARHGEF18 transcript in a human podocyte cell line led to decreased cell viability (Fig 1E), actin cytoskeleton reorganization (Fig 1F) and inhibited Rac1 activation (Fig 1G). Mutant ARHGEF18 transcripts exerted slower ubiquitin mediated degradation (Fig 1H).

Conclusions: Integration of electronic health records with exome sequencing using deep learning uncovering DKD heterogeneity driven by a gain of function variant in ARHGEF18. ARHGEF18 knockdown caused kidney failure in a zebrafish model. Mutant ARHGEF18 was resistant to degradation and activated the Rac1 pathway, suggesting pharmacological inhibition of ARHGEF18 may be a therapeutic target by preventing Rac-mediated podocyte damage (Fig 1I).
FR-OR12

Identifying Diabetic Kidney Disease Signatures in the Nuclei of the Tubular Epithelium Using a Novel Deep Learning Approach
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Background: Diabetic nephropathy (DN), a leading cause of end stage kidney disease (ESKD) is generally viewed as a glomerular disease. However, progression of DN towards ESKD correlates best with tubular pathology and fibrosis. Due to the spatial complexity of the human kidney, which includes many cell types, it is a challenge to capture the biology at the single cell level. While there is a growing body of information on the molecular phenotype of DN at the single cell level using omics approaches on diseased tissue, there is a lack of information on cellular changes in intact kidney tissue.

Methods: We used a 3D nuclei image-based deep learning approach to uncover spatially resolved single cell signatures of DN. 3D Imaging datasets were collected from fluorescence labeled human reference nephrectomy samples and biopsies from patients with DN. Using Volumetric Tissue Exploration and Analysis (VTEA) and cell-type markers, a 3D nuclei image dataset was generated from reference nephrectomy and used to train a custom Convolutional Neural Network (CNN). A second 3D nuclei image dataset was generated from images of biopsies taken from patients with DN and classified with CNN.

Results: We generated a 3D nuclei image library from DN tissue secured from the NIDDK/Kidney Precision Medicine Project. We used our nuclei-based CNN classification of renal cells to uncover unique classes of renal epithelial and identify novel single cell image-based signature in DN. Using VTEA, we were able to spatially localize these novel classes of renal epithelium and assess correlation with injury and renal structures for a spatially resolved 3D nuclei image-based signature of DN.

Conclusions: Our work demonstrates that 3D nuclei images from renal cells allows for differential identification of DN signatures. These data further suggest that in addition to glomeruli, the tubular epithelium plays a role in DN. Our work underlines the potential of using machine learning and deep learning approaches to automatically uncover new cell types which may emerge due to changes occurring in diabetes, while maintaining their spatial context. Thus, our work can provide insight into the cellular changes in intact kidney tissue during progression in DN.

Funding: NIDDK Support

FR-OR13

Multi-Omics Identifies CERS6 and C16:0 Ceramide in Podocytes as Novel Therapeutic Targets for Diabetic Kidney Disease
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Background: Dysregulated renal ceramide (Cer) sphingomyelin (SM) metabolism has been reported in human and animal models of diabetic kidney disease (DKD). However, there have been limited investigations in understanding the roles of Cer/SM in the pathogenesis of podocyte dysfunction. To understand the role of sphingolipid metabolism in normal and diabetic kidneys, we integrated matrix-assisted laser desorption/ionization-mass spectrometry imaging (MALDI-MSI) data to single nucleus Droplet-based sequencing (snDrop-Seq) and single-cell RNA sequencing (scRNA-Seq) data for a network analysis of a tabulated list of 48 Cer/SM metabolism-related gene/enzymes.

Methods: Two MALDI-MSI platforms (QE-HFX and FTICR) were employed to characterize the lipid profile in normal human kidney tissues (n=6; U. Michigan) in situ (spatial resolution: 20-30 µm). Same tissues were also processed by snDrop-Seq analysis for multi-omics data integration. To compare kidney scRNA-Seq profiles between DKD patients and healthy controls, patient kidney biopsies (n=44) from an early DKD cohort were collected and 18 living donor (LD) biopsies were used as reference healthy tissues. From these datasets, 30 different cell types identified by snDrop-seq were used to generate a comprehensive dataset of 48 Cer/SM metabolism-related gene/enzymes.

Conclusions: This highlights the value of kidney atlas for healthy and diseased kidneys on the single cell levels of genes and metabolites in the kidney precision medicine. Multi-omics techniques could help identify novel therapeutic targets for different types of kidney diseases.

Funding: NIDDK Support

FR-OR14

Integrated Multi-Omics Reveal the Complexity of TGF-β Signalling to Chromatin in Induced Pluripotent Stem Cell-Derived Kidney Organs
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Background: Critical pathological features of diabetic kidney disease are now accepted to include dysregulation of epigenetic processes as evidenced by the observed differential methylation in patients with or without progressive disease. TGFβ resides at the centre of therapeutic approaches for the treatment of renal fibrosis, but few intervention studies have demonstrated clinical efficacy. Recently, we demonstrated a novel direct interaction between Smad3 and EZH2, the enzymatic component of the polycomb repressive complex 2 (PRC2) during cell fate specification.

Methods: Using the 10X Genomics platform, we performed single cell RNA-seq and ATAC-seq on human iPSC-derived kidney organs treated with the EZH2 inhibitor, GSK343, for 1 hour prior to treatment with TGFβ1 for 48 hours.

Results: Single cell RNA-seq analysis revealed that TGFβ1 treated organs exhibited a similar fibrotic response to what is observed in human diabetic kidneys. Furthermore, TGFβ1 induced the differentiation of resident stromal cells into activated myofibroblasts, and this was accompanied by the upregulation of fibrogenic genes such as α-smooth muscle actin and transgelin, consistent to what is observed in vivo. Single cell ATAC-seq of iPSC-derived kidney organs treated with TGFβ1 revealed that TGFβ1 increases chromatin accessibility at all promoters, DNase1 hypersensitive, and transcription start sites in all cell types present within the organoid. Furthermore, TGFβ1 increased chromatin accessibility at some enhancers and this was cell-type dependent.

Conclusions: We propose that the enzymatic function of the polycomb repressive complex is necessary for TGFβ1 induced increase in chromatin accessibility and its subsequent gene regulatory functions. Understanding the exact nature of how TGFβ1 cooperates with epigenetic complexes at the chromatin level will allow for a more comprehensive understanding of how changes in cell fate occur in developmental and pathological contexts. Manipulation of the association between Smad3 and EZH2 may be a useful therapeutic strategy for the resolution of renal fibrosis.

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FR-OR15

Spatial Mapping of Murine Diabetic Kidney Disease (DKD) Transcriptomics at Single-Cell Resolution
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Background: DKD is the major cause of kidney failure in the USA, yet the molecular pathogenesis of DKD and the spatial distribution of the transcriptomic response to injury is poorly characterized. Single cell RNA sequencing and cell clustering has been used on a limited basis in DKD to explore distinct cell-type transcriptomic responses. Here we applied Multiplexed error-robust fluorescence in situ hybridization (MERICISH) to anatomically validate single cell RNAseq cell clustering in diabetic mouse kidney.

Methods: MERICISH was used to localize a panel of 260 cell-selective markers derived from single nuclear RNAseq clustering in frozen kidney sections from 3 murine models: C57BLKS db/m, db/db LacZ and db/db Renin-AA V. For each section contained ~100,000 cells. Single-cell gene expression profiling and cell identification by MERICISH allowed us to map the spatial organization of 11 major cell types: PT1, PT3, EC, DCT, Podo, LTAL, CTAL, and fibroblasts. Podocyte cluster transcripts Cdkn1c, Dendrin, Sema3g, and EphA6 were specifically expressed in glomeruli and EphA6 and Sema3g were significantly increased in diabetes. Top PT5 markers including Ppara, Slc7a9 and Slc5a2 exhibited superficial cortical localization whereas PT5 markers Slc22a19, Acox2 and Kcn3 were in the cortical/medullary region. Myh11 selectively labelled JGA while Nos1 marked the macula densa. Endothelial (EC) markers including Egfb7, Cdh5, Ehd3, Ptxad1, Ptds, Ephb4, exhibited distinct anatomic expression, with Ehd3 most highly expressed in glomeruli (figure), while Cdh5 and Ptpv were low to absent in glomeruli and rather predominated in peri-tubular interstitium.

Conclusions: This application of MERICISH single cell spatial transcriptomics to murine diabetic kidney identified neuron specific cell clusters and confirmed anatomically separate gene expression patterns in PT and EC subpopulations.

Funding: Commercial Support - Janssen R&D LLC

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underlines represent presenting author.
Results: PINK1−/− mice developed severer diabetic tubulopathy accompanied with much more albuminuria than STAK1−/− mice after induction of diabetes using STZ injection. More inflammatory and profibrotic cytokines were produced in the kidneys of diabetic PINK1−/− mice, eventually culminating in aggravated interstitial fibrosis. Dysmorphic and fissional mitochondria increased in the renal tubular cells of diabetic PINK1−/− mice and lower levels of mitochondrial ROS and increased mitophagy were observed in PINK1 OE HKC8. We found that upregulation of PINK1 reduced necroptosis of renal tubular cells under high glucose conditions and mitigated the expressions of profibrotic markers. However, PINK1 deficiency was associated with amplified mitochondrial ROS production, exacerbation of necroptosis related proteins expression, and profibrotic markers in HKC8. Inhibitor of necroptosis and antioxidant attenuated the expressions of profibrotic and inflammatory proteins in HKC8 during treatment with high glucose media.

Conclusions: Our data suggest that PINK1 has roles in suppression of tubular cell necroptosis under high glucose conditions and exerts a protective effect in diabetic tubulopathy.

Funding: Government Support - Non-U.S.

FR-OR18

RTN1A Mediates the Diabetic Kidney Disease Progression Through Endoplasmic Reticulum (ER) Mitochondrial Contacts in Renal Tubular Epithelial Cells

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Background: Renal tubular epithelial cell (RTEC) injury contributes to kidney fibrosis and the progression of diabetic kidney disease (DKD), but the major risk factors contributing to RTEC injury in early DKD remain unclear. We previously showed that specific transcriptome changes associated with ER–mitochondria (EMC) disruption, increases in RTEC in human and mice with DKD and contributes RTEC injury in vitro and in vivo through activation of ER stress. Here, we will further dissect the role and mechanism of RTN1A in RTEC injury in early DKD.

Methods: To assess the RTEC-specific role of RTN1A in the progression of DKD, we generated transgenic mice with tetracycline-inducible, RTEC-specific RTN1A overexpression (Pax8-rtTA;TRE-RTN1A). To assess the role of RTN1A in tubular injury in the setting of DKD, diabetes was induced in 6-week old transgenic mice with low-dose streptozotocin (STZ). Also, we also crossed the Pax8-RTN1A mice with diabetic OVE26. To delineate the molecular mechanisms of RTN1A-induced RTEC injury, we examined the RTN1A-interacting proteins by mass spectrometry. The role of RTN1A in regulation of ER-mitochondrial contacts (EMC) was assessed by measurement of both mitochondrial function and ER stress markers in the cultured RTEC and mice with RTN1A overexpression.

Results: We found that increased RTN1A expression in the RTEC induced significantly tubule-interstitial fibrosis and decline of renal function in both STZ and OVE26 diabetic mice with early DKD. We also demonstrated in vitro that RTN1A interacted with several mitochondrial proteins and RTN1A was enriched in the EMC. We showed that RTN1A overexpression in RTECs not only worsens ER stress but also induces mitochondrial dysfunction in RTEC in vitro and in vivo. As a novel mechanism, we demonstrated that RTN1A interacts with mitochondrial hexokinase-1 (HK1) and competing for its interaction with voltage-dependent anion channel-1 (VDAC1). Disengagement of VDAC1 from HK1 subsequently results in the activation of apoptosis and inflammasome pathways, leading to RTEC injury and loss.

Conclusions: Our findings highlight the previously unrecognized role of ER-mitochondrial crosstalk in RTEC injury and progression of DKD and the importance of RTN1A-mediated EMC regulation in DKD pathogenesis.

Funding: NIDDK Support

FR-OR19

Advanced Light Sheet Microscopy and 3D Image Analyses of Kidney Injury, Glomerulosclerosis, and Fibrosis in a Mouse Model of Diabetic Kidney Disease

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Background: Development of novel therapies for diabetic kidney disease (DKD) and other glomerulopathies is challenged by poor translatability of preclinical animal models. Novel models that capture the pathophysiological changes and advanced image analyses, we aimed to develop a method for quantification of kidney injury and fibrosis in a preclinical mouse model of progressive DKD.

Methods: Kidneys from hypertensive uninephrectomized db/db mice (reinIAV UNx Dbs), and healthy controls were fixed and processed for whole-mount immunohistochemistry and light sheet microscopy (LSM) to assess and quantify tubular injury by KIM-1, and fibrosis and glomerulosclerosis by tenascin in the intact kidney. Using 3D image analysis, the distribution and intensity of KIM-1 and tenascin were determined. To correlate 3D imaging endpoints with DKD severity, kidney fibrosis and injury was characterized using standard methodologies including 2D histology.

Results: In reinIAV UNx db/db mice, tenascin was present in glomeruli as showed by its overlap with podocin. A sub-population of glomeruli with augmented tenascin expression with no overlap of podocin was identified indicating that these glomeruli have global glomerulosclerosis and loss of podocytes. Tubulointerstitial tenascin was limited. These findings correlated with traditional histopathological assessment of glomerulosclerosis scoring and fibrosis quantification in PAS and collagen 3 stained kidney section, respectively. KIM-1 positive tubuli were also visualized in intact kidneys from reinIAV UNx db/db mice and showed a heterogeneous pattern across the kidney.

Conclusions: Novel models and advanced image analyses advanced image analyses, we aimed to develop a method for quantification of kidney injury and fibrosis in a preclinical mouse model of progressive DKD.

Funding: NIDDK Support
KIM-1 was clearly localized to the proximal tubules and was also present in parietal cells in a subpopulation of glomeruli. These observations correlated with 2D IHC staining of KIM-1. Kidneys from healthy controls were KIM-1 negative in both 3D and 2D.

**Conclusions:** Development of advanced microscopy and 3D imaging technologies allows for assessment of kidney fibrosis and injury in the intact mouse kidney. Thereby, this new imaging technique can be used to support functional and 2D histological readouts in mouse models to improve their translatability in the study of disease mechanisms and drug discovery for DKD.

**FR-OR20**

**Long Noncoding RNA IncMGC Mediates TGF-β-Induced Effects Related to Diabetic Kidney Disease via Nucleosome Remodeling Factors**

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**Background:** microRNAs (miRNAs) and long non coding RNAs (lncRNAs) play key roles in diabetic kidney disease (DKD). miR-379 megacrusel of miRNAs and its host transcript IncMGC (inc-megacrusel) are regulated by transforming growth factor-β (TGF-β), increased in glomeruli of diabetic mice and promote features of early DKD. However, biochemical functions of IncMGC are unknown. Here we screened IncMGC-interacting proteins by in vitro-transcribed IncMGC RNA pull down followed by mass spectrometry (MS). We also created IncMGC knockout (KO) mice by CRISPR-Cas9 editing and used mouse mesangial cells (MMC) from the KO mice to examine the effects of IncMGC on gene expression related to DKD, changes in promoter histone modifications and chromatin remodeling.

**Methods:** In vitro transcribed IncMGC RNA was mixed with lysates from HK2 cells (human kidney cell line). lncMGC interacting proteins were identified by MS and candidate proteins were confirmed by RNA immunoprecipitation (RIP) and qPCR. Cas9 and guide RNAs were injected into mouse eggs to create IncMGC-KO mice. Wild type (WT) and IncMGC-KO MMC were treated with TGF-β and RNA expression (by RNAseq and qPCR) was measured. Candidate IncMGC promoter region as well as many other loci including Col1a2, Col4a3, Col4a4 and CTGF were significantly lower in IncMGC-KO MMC than WT MMC.

**Conclusions:** IncMGC RNA interacts with several nucleosome remodeling factors to promote chromatin relaxation and enhance the expression of IncMGC itself and other genes including pro-fibrotic genes. Its epigenetic regulation in target kidney cells may contribute to DKD pathogenesis.

**Funding:** NIDDK Support

**FR-OR21**

**Impact of Medicare Bundled Payment System on Regional Racial Disparities in Home Dialysis Utilization**

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**Background:** The 2011 Medicare prospective payment system (PPS) for dialysis largely introduced bundled payment (PD) and home hemodialysis (HHD) treatment modalities. To examine whether racial disparities in home dialysis use (PD and HHDD) were affected, we compared regional changes in home dialysis use by White and non-White dialysis patients over time.

**Methods:** We conducted a retrospective cohort study of dialysis facilities offering home dialysis to 1,098,579 patients with end-stage kidney disease (ESKD) in 2006-2016. Health care region was defined as hospital referral regions (HRR). Patients of non-Hispanic Black/African American, Hispanic, non-Hispanic Asian or Pacific Islander, or other race/ethnicity were grouped into a general category of non-White due to small numbers of home dialysis patients and small samples in some HRRs. For each HRR-year, wecomputed home dialysis utilization rates for White patients by dividing counts of home dialysis users by White users of all dialysis modality. We repeated these procedure to compute rates for non-White patients, and compared these rates using a generalized estimating equation (GEE) model with a negative binomial distribution, adjusting for region (ESKD) provider and patient characteristics.

**Results:** The mean number of facilities offering home dialysis in each HRR increased from 15.6 in 2006 to 22.1 in 2016, with for-profit ownership (29.8% in 2006, 48.8% in 2016) and chain affiliation (82.3% in 2006, 91.7% in 2016) increasing over time. While average regional home dialysis utilization rates increased over time, disparities persisted with White patients consistently higher home dialysis utilization than non-White patients in every year (19.5% vs. 12.9% in 2006, 26.2% vs. 17.8% in 2016, on average across HRRs). In adjusted analysis, region-level home dialysis use was one-third lower among non-White patients compared to White patients. Home dialysis disparities did not change following the 2011 Medicare payment reform (incidence rate ratio (IRR)=0.97, 95% CI=0.92, 1.02; p=0.29).

**Conclusions:** Racial disparities in home dialysis use persist after Medicare payment reform despite modest increases in dialysis facility availability and patient utilization. Targeted policy efforts are needed to reduce disparities in the use of home dialysis.

**Funding:** Other U.S. Government Support

**FR-OR22**

**Real-World Analysis of Timing of Dialysis Transition and Mortality in a Nationally Representative Cohort of Advanced CKD Patients**

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**Background:** While there is still substantial variation in the timing of the dialysis initiation in advanced CKD patients transitioning to ESRD, large population-based studies have observed a trend towards earlier dialysis transition over time. We sought to conduct a real-world analysis of the impact of timing of dialysis transition on mortality rates in a nationally representative cohort of advanced CKD patients (≥2 eGFRs <25 separated by ≥90 days).

**Methods:** In advanced CKD patients transitioning to dialysis over 1/1/07-6/30/20, we examined the impact of timing of dialysis transition (defined by eGFR at the time of dialysis initiation) on mortality rates. Patients were identified from the OptumLabs® Data Warehouse (OLDW), which contains de-identified administrative claims, including medical and pharmacy claims and enrollment records for commercial and Medicare Advantage enrollees as well as electronic health record data. Patients were granularly categorized according to novel time-intervals of dialysis transition, defined as CKD stages 4B, 4C, 5A, 5B, and 5C (eGFRs <25, 15–20, 10–15, 5–10, and <5 at the time of dialysis transition, respectively). Poisson regression was used to compare mortality rates across exposure groups.

**Results:** Among 97,320 advanced CKD patients who transitioned to dialysis, 6%, 11%, 31%, 43%, and 9% initiated treatment at CKD stages 4B, 4C, 5A, 5B, and 5C. Patients who underwent incrementally earlier dialysis transition experienced increasingly higher raw mortality rates: 11K, 128, 141, 155, and 164 deaths per 1000 person-yrs for CKD stages 5C, 5B, 4C, and 4B. A similar trend was observed for Poisson model-based mortality rates in the overall cohort, as well as raw and model-based mortality rates stratified by age (<65 vs. ≥65 yrs).

**Conclusions:** In a real-world analysis of a nationally representative US cohort, incrementally earlier dialysis transitions demonstrated increasingly higher mortality rates. Further studies are needed to identify strategies optimizing survival in advanced CKD patients transitioning to dialysis.

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**FR-OR23**

**Associations of Local Area Deprivation Index with Outcomes During the First Year of Maintenance Dialysis**

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**Background:** Clinical outcomes among patients undergoing maintenance dialysis are typically ascribed to non-modifiable patient characteristics and treatments. However, outcomes may be highly influenced by local socioeconomic conditions. We assessed whether the Area Deprivation Index (ADI), a composite measure of income, education, employment, and housing quality within 9-digit ZIP Code areas, is associated with the incidence of death and kidney transplantation during the first year of maintenance dialysis.

**Methods:** We analyzed United States Renal Data System Standard Analysis Files. The cohort included patients who initiated outpatient dialysis in 2014-2017; we retained patients with a 9-digit ZIP Code of residence, according to the Medicare Enrollment Database, as that code facilitated linkage to the ADI. Patients were followed from the initiation of outpatient dialysis to the earlier of death or kidney transplantation; patients were censored after one year of follow-up. We fit Cox models of death and kidney transplantation, including ADI decile (higher = more disadvantaged) and adjustment for age, sex, race/ethnicity, primary cause of end stage kidney disease, comorbidity, and dialysis modality.

**Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.**
Results: The cohort included 381,623 patients. Over 14% of patients resided in 9-digit ZIP Codes in the highest ADI decile. ADI deciles were linearly associated with adjusted hazards of death and kidney transplantation (table). The highest versus lowest ADI decile was associated with 20% higher rate of death and 72% lower rate of transplantation.

Conclusions: Increasing socioeconomic disadvantage in the local area was associated with higher rates of death and markedly lower rates of transplantation during the first year of dialysis.

Funding: NIDDK Support

Abbreviations: ADI, area deprivation index; AHR, adjusted hazard ratio.

FR-OR24

Outcomes and Rate and Mortality in Hemodialysis: The Dialysis Outcomes and Practice Patterns Study (DOPPS)

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Background: Fluid management is an essential component of hemodialysis (HD) practice. Both insufficient fluid removal and rapid ultrafiltration rate (UFR) are associated with higher cardiovascular and all-cause mortality risk, particularly in US populations, but it is uncertain whether adhering to a single UFR limit will mitigate this risk.

Methods: This retrospective cohort study includes 47,640 adult in-center HD patients from phases 4-6 of DOPPS (2009-2018) from the US, Japan, Australia, New Zealand, Russia, 7 European and 6 GCC countries. Mean UFR was calculated over one week occurring during the first four-month DOPPS data collection interval. Follow-up for all-cause mortality began after this interval. Risk was estimated using Cox models adjusting for DOPPS phase, country, years on dialysis, age, sex, race, 7 comorbidities, body mass index (BMI), catheter use, 5 labs, Kt/V, residual urine volume, and pre-HD session systolic blood pressure.

Results: Mean UFR for the entire cohort was 83 (SD 3.8) ml/hr/kg and median follow-up time was 1.3 (IQR 0.7–2.3) years. In adjusted analyses, compared to patients with mean UFR of 7 to <10 ml/hr/kg, those with higher UFR had greater risk of mortality: HR 1.095 (95% CI 1.035–1.157) for UFR 10 to <13 ml/hr/kg, HR 1.21 (1.09–1.33) for UFR of 13 to <15 ml/hr/kg, and HR 1.38 (1.24–1.55) for UFR >15 ml/hr/kg. Higher UFR was associated with greater mortality risk for patients with higher weight or BMI (p-value <0.001 for both). DOPPS region did not modify the relationship between UFR and mortality despite differences in patient characteristics and HD practices across regions (p-value 0.67).

Conclusions: In a large international cohort, higher mean UFR, was associated with an increased risk of mortality. Patients with higher weight or BMI have a greater mortality risk from higher UFR, suggesting that a single UFR threshold to identify risk may not be equally beneficial for all patients.

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FR-OR25

Outcomes and Predictors Associated with Skin Sodium Concentration in Dialysis Patients

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Background: Sodium-23 magnetic resonance imaging (23Na MRI) allows the measurement of skin sodium concentration ([Na+]s). In patients requiring dialysis no data are available relating to the clinical outcomes associated with skin sodium accumulation or the determinants of increasing deposition.

Methods: This was an exploratory, observational study of adult hemodialysis (HD) and peritoneal dialysis (PD) patients. [Na+]s quantification with leg 23Na MRI at the study beginning. Outcomes of interest were all-cause mortality and composite all-cause mortality and major cardiovascular adverse events (MACE) and were assessed. Cumulative total and event-free survival were assessed using the Kaplan-Meier survival function after stratification into Skin [Na+] quartiles. Cox proportional hazards regression was used to model the association between Skin [Na+] and outcomes of interest. Multiple linear regression was used to model the predictors of Skin [Na+].

Results: 52 participants (42 HD, 10 PD) underwent the study procedures. Median follow-up was 423 days (IQR: 290–550). As shown in Figure 1, increasing Skin [Na+] quartiles were associated with significantly shorter composite event-free survival (log-rank χ2 (1) = 4.733, p <0.05). Skin [Na+] was significantly associated with all-cause mortality (univariate HR 1.059, 95% CI: 1.014–1.107; sex-adjusted HR: 1.063, 95% CI: 1.014–1.08; and composite all-cause mortality and MACE measured in univariate HR 1.054, 95% CI: 1.017–1.092; sex-adjusted HR: 1.055, 95% CI: 1.019–1.093). In multiple regression models, dialysate [Na+] serum albumin and congestive heart failure were significantly associated with Skin [Na+] in HD patients (R2 = 0.62).

Conclusions: Higher Skin [Na+] was associated with worse clinical outcomes in dialysis patients and may represent a direct therapeutic target.

Kaplan Meier curves for overall survival (A) and event-free survival as a composite of all-cause mortality and major adverse cardiovascular events (B), after skin [Na+] quartile stratification.

FR-OR26

Itch Reduction with Difelikefalin Correlates with Improved Sleep Quality in Hemodialysis Patients with Pruritus

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Background: CKD-associated pruritus (CKD-aP) may impair sleep of hemodialysis (HD) patients. This analysis of a Phase 3 open-label study evaluated if itch reduction in HD patients treated with the investigational, peripherally restricted kappa opioid receptor agonist, difelikefalin (DFK), correlated with improved sleep quality.

Methods: 222 patients with moderate-to-severe CKD-aP received intravenous DFK 0.5 mcg/kg thrice weekly for up to 12 weeks. Change in itch intensity from baseline to week 12 was evaluated by weekly mean of the 24-hour Worst Itching Intensity Numerical Rating Scale (WI-NRS) score (range 0 [no itch] to 10 [worst itch imaginable]). Impact of pruritus on sleep quality was evaluated by the change from baseline to week 12 in weekly mean of the 24-hour Sleep Questionnaire (SQQ) score (0 [did not interfere] to 10 [completely interfered]). Spearman’s correlation analysis was performed.

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Results: At week 12, most patients achieved a ≥3-point reduction in WI-NRS (74%) and SQQ score (66%). Patients with a ≥3-point (vs <3-point) reduction in WI-NRS had greater reductions in mean SQQ score (−5.22 vs −1.53) and 5-D Itch sleep question score (−1.83 vs −0.78) from baseline to week 12. There was a strong correlation between changes in WI-NRS and SQQ scores from baseline to week 12 (r=0.78) (Figure) and a moderate correlation between changes in WI-NRS and 5-D Itch sleep question scores during this period (r=0.48). Week 12 SQQ and 5-D Itch sleep disability question scores were strongly correlated (r=0.64).

Conclusions: Itch reduction with DFK correlated with improvements in sleep quality as evaluated by the SQQ and 5-D Itch sleep disability question.

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FR-OR27
Fluid-Related Risk Factors of Peritoneal Dialysis Technique Failure
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Background: Inadequate fluid management in peritoneal dialysis (PD) patients is associated with a higher risk of cardiovascular morbidity and mortality and may result in shortened PD technique survival (Van Biesen et al, 2019). In this analysis, we evaluated the associations between fluid-related clinical factors and PD technique failure within 1 year of treatment initiation.

Methods: Adult, ESKD patients who were newly prescribed PD for a 120 days at Fresenius Kidney Care (FKC) facilities between 2017-2019 were included. Deidentified data were extracted from the FKC clinical data warehouse and evaluated within 120 days of treatment initiation. Crude and case-mix adjusted Cox regression models using competing risks (patient transfer to HD, death, and loss to follow-up) were used to evaluate the associations between fluid-related risk factors and PD technique failure. Significant patient-related clinical events and hospitalizations, or weight change 100 mL, systolic BP > 160 mmHg, history of cardiovascular events and hospitalizations, or weight change ≥ 2 kg between day 1 and day 120 of PD treatment had a higher risk of 1-year PD technique failure (Figure 1). Significant patient-reported risk factors included shortness of breath (APD only) and edema (APD and CAPD). Patients with a weekly Kt/V > 2 had half the risk of PD attrition at 1 year.

Results: 15,854 automated PD patients (APD; age: 58 years; K RU: 4.5 mL/min) and 1,547 manual PD patients (CAPD; age: 58 years; K RU: 4.8 mL/min) were included. 53% of APD patients and 56% of CAPD patients had a PD technique survival ≥ 1 year, and all patients with urine volume ≤ 100 mL, systolic BP ≥ 160 mmHg, history of cardiovascular events and hospitalizations, or weight change ≥ 2 kg between day 1 and day 120 of PD treatment had a higher risk of 1-year PD technique failure (Figure 1). Significant patient-reported risk factors included shortness of breath (APD only) and edema (APD and CAPD). Patients with a weekly Kt/V ≥ 2 had half the risk of PD attrition at 1 year.

Conclusions: APD and CAPD patients with fluid-related complaints (shortness of breath and edema), history of cardiovascular morbidity and hospitalizations, hypertension, or weight change ≥ 2 kg within 120 days of PD initiation had a higher risk of technique failure within 1 year of PD initiation.

Funding: Commercial Support - Fresenius Medical Care North America

FR-OR28
Mass Spectrometry-Based Proteomic Analysis of Adsorbed Molecules in a Hexadecyl-Imobilized Cellulose Beads Column for the Treatment of Dialysis-Related Amyloidosis
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Background: Dialysis-related amyloidosis (DRA) is a serious complication in CKD patients undergoing long-term hemodialysis (HD). β2-microglobulin (β2-m)-related amyloid deposition induces osteoarticular disorders including carpal tunnel syndrome. Direct hemoperfusion with a column containing hexadecyl-immobilized cellulose beads (HICB) is used to adsorb circulating β2-m to inhibit the progression of DRA. As use of the column improves joint pain and physical functions; it is possible that the column adsors not only β2-m but also other molecules associated with amyloidogenesis and inflammation.

Methods: We included 14 HD patients with DRA. Proteins were extracted from the HICB-containing column after treatment and identified using liquid chromatography-linked mass chromatography. We measured the adsorption rate of the proteins detected by proteomics, and compared it with those in the patients undergoing HD and hemodiafiltration (HDF). The amyloid tissue deposition in the carpal tunnel in the HD patients (n = 8) was corrected using laser microdissection and examined on liquid chromatography-linked mass chromatography. The protein profiles were compared between the HICB-containing column and the amyloid lesions.

Results: With high confidence criteria, 200 proteins adsorbed by the HICB were identified (e.g., β2-m SIN, 193.8 ± 143.4; lysosome SIN, 156.5 ± 47.8). After passing the HICB-containing column, the serum levels of several proteins were decreased as compared with those in the HD dialyzer and HDF hemofilter (e.g., adsorption rate of β2-m, 8.9% vs 38.0% [HD] and 25.0% ± 14.6% [HDF], p < 0.01; lysosome, 79.2 ± 10.9% vs 15.8 ± 18.8% [HD] and 10.0 ± 13.4% [HDF], p < 0.01). In the amyloid deposited in the carpal tunnel, 143 proteins were identified, of which 54 were also found in the HICB-containing column. Cellular protein metabolic process was one of major Gene Ontology pathways in the common proteins (p = 1.05E-10).

Conclusions: The HICB-containing column adsorbed various proteins in the HD patients with DRA, of which some were found in the lesions with amyloid deposition. The results suggest that direct hemoperfusion with the HICB-containing column contributes to the improvement of DRA by reducing the levels of related proteins.

Funding: Commercial Support - Kaneka Medix Co

FR-OR29
Effects of NOS3 and Nitric Oxide Releasing Bionanomatrix Gel on Reducing Intimal Hyperplasia and Vascular Remodeling
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Background: An arteriogenous fistula (AVF) is the preferred type of vascular access in hemodialysis patients. However, nearly 60% of AVFs created develop AVF maturation failure due to severe intimal hyperplasia (IH) formation and poor vascular remodeling (VR). We hypothesize that the endothelial nitric oxide synthase (NOS3) system is critical for reduction of IH and outward VR and local nitric oxide (NO) delivery at the time of AVF creation can enhance AVF maturation.

Methods: To explore the role of NOS3, AVFs were created in NOS3-/-, NOS3 +/- and NOS3 overexpression mice. To investigate the efficacy of NO gel, rat femoral AVFs were created and immediately after, therapy was applied on the anastomosis. Animals were sacrificed at 7 days following AVF creation to evaluate histomorphological changes. MRI based computational fluid dynamic simulations were performed to investigate hemodynamic changes

Results: As compared to the controls, overexpression of NOS3 can significantly 1) reduce venous IH 2) promote hemodynamic adaptation and VR by increasing venous cross-sectional area, reducing wall shear stress and vorticity through elevating cGMP levels. NO gel therapy had similar significant effects, including reduction of IH (P <0.0091, 70%). In addition, the NO treated group showed significant reduction in intimal α-SMA, vimentin, desmin and MCP-1 levels. Furthermore, slow degradation of NO-releasing gel resulted in prolonged release of NO during the AVF maturation process

Conclusions: NOS3-NO-cGMP system is a critical regulator of AVF remodeling. Thus NO-releasing gel has great potential to promote clinically successful AVF maturation

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The Transcriptionic Landscape of the Arteriovenous Fistula: The Postoperative Genetic Signature of Maturation Failure

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Background: The molecular mechanisms contributing to arteriovenous fistulas (AVF) maturation or failure remain elusive, in part due to the scarcity of human postoperative biological data that may guide mechanistic and translational studies. The brachiocephalic AVF created in two stages overcomes this limitation and allows to collect vascular tissues representative of both outcomes at the time of transposition.

Methods: In this study, we compared the transcriptionic profiles of 40 postoperative AVF samples (20 matured and 20 failed) collected 4-6 weeks after access creation by bulk RNA sequencing.

Results: We identified 156 differentially expressed genes (DEG) between both outcomes (log2FoldChange≥1, FDR<0.05), including 101 protein-coding genes downregulated with failure and 11 protein-coding genes with higher expression in this group compared to AVF that matured. Gene set enrichment analysis (GSEA) indicated a suppression of responses to stress/stimuli and signal transduction pathways in AVF that failed. The main downregulated players include G protein-coupled receptors, metalloproteinas, and immunoregulatory chemokines. In contrast, upregulated transcripts in AVF that failed include a urea cell-surface transporter, a serotonin suppression of responses to stress/stimuli and signal transduction pathways in AVF group compared to AVF that matured. Gene set enrichment analysis (GSEA) indicated all morphologic characteristics of human MN. Human PLA-R-ab of the IgG4 subclass could be eluted from minipig glomeruli, showing that the antibodies were able to bind to PLA-R in the absence of other human serum components. The active immunization of minipigs with human PLA-R protein led to the development of PLA-R-ab, which recognized the N-terminal Cysr2CTLD1 region, as well as the C-terminal CTLD7-8 region. Analyses of the kidney tissue revealed all morphologic characteristics of human MN, including a granular deposition of pIgG and C3 along the glomerular basement membrane, as well as electron dense immune deposits, which were associated with effacement of podocyte food processes. Antibodies eluted from isolated glomeruli were able to bind human and minipig PLA-R. The minipig developed moderate proteinuria. In contrast, no morphologic or clinical characteristics of MN were detectable in the control animal.

Conclusions: Human PLA-R-ab induce MN in minipigs. Immunization of minipigs with PLA-R protein leads to the development of autoimmune PLA-R-induced MN, which presents with activation of the complement system and all morphologic and clinical characteristics of human MN. These findings prove the pathogenicity of human PLA-R-ab and fulfill Koch’s postulate.

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FR-OR33
New Insights on the Role of C3a/C3aR1 Signaling in Membranous Nephropathy
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Background: Primary membranous nephropathy (MN) is a leading cause of nephrotic syndrome in adults worldwide. MN is characterized by the deposition of anti-podocyte antibodies within the glomerular subepithelial space. While complemen deposition and formation of membrane-attack-complex (MAC) are thought to play a crucial pathogenic role, the exact mechanism of injury in MN is still unclear. We have developed a novel glomerulus-on-a-chip system (GOAC) using human primary podocytes and glomerular endothelial cells (GEC) to study MN and assessed functional response to human MN serum, role of MAC formation and C3a/C3aR1 signaling in MN pathogenesis in addition to in vivo studies.

Methods: GOACs were cultured with serum containing either anti-PLA2R+/- or THSD7A+/- MN patients and from healthy individuals (as control). Functional response was assessed by albumin permeability assay. The mechanistic role of MAC and C3a/ C3aR1 signaling pathway was assessed by immunofluorescence, functional analysis, PCR arrays and Western Blotting. Results were further confirmed in GOAC using podocytes3,4,5 and in vivo using THSD7A induced MN in balb/c mice.

Results: Following exposure to sera from MN patients, we have found evidence of activation of human IgG on podocytes and formation of MAC complex, accompanied by albumin leakage. MAC inhibition did not prevent albumin leakage while GOAC supplemented with C3aR1 agonists as well as GOAC using podocytes3,4,5 were able to prevent glomerular filtration damage and albumin leakage. Efficacy of C3aR1 antagonists in preventing proteinuria was confirmed in mice injected with serum from patients with anti-thrombospodin Ab, substantiating our findings.

Conclusions: Using our microfluidic GOAC system in combination with in vivo animal models, we have found evidence that C3a/C3aR1 plays a dominant role in complement-mediated MN pathogenesis. Our results not only shed some light on the injury mechanisms in complement-mediated damage but could provide new avenues for the development of glomerulos-specific treatments.

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FR-OR35
Differentiating Steroid-Sensitive Minimal Change Disease and Primary and Secondary Focal Segmental Glomerulosclerosis: A Proteomics-Based Approach
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Background: Minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) are the common causes of nephrotic syndrome. Whether distinct molecular mechanisms are involved in the pathogenesis of MCD and FSGS remains unclear. We used proteomic studies in human kidney biopsies to characterize the differentiating molecular phenotype of steroid-sensitive MCD and primary and secondary FSGS.

Methods: Formalin-fixed, paraffin-embedded kidney biopsies from patients with steroid-sensitive MCD (n=9), primary FSGS (pFSGS, n=3), and secondary FSGS (sFSGS, n=4) were included. Patients with pFSGS had nephrotic syndrome and diffuse foot process effacement (FPE) in kidney biopsy. Patients with sFSGS were obese and had non-nephrotic range proteinuria, normal serum albumin and evidence of hyperfiltration and <80% FPE in kidney biopsy. Glomeruli were isolated using laser capture microdissection and HPLC MS/MS were performed using Orbitrap eclipse mass spectrometer. Pair t-test in the normalized data was used to compare the groups.

Results: 73 and 701 significantly differentially expressed proteins were detected between MCD, and pFSGS and sFSGS respectively. Proteins regulating cell-cell and cell-matrix adhesion and differentiation (TH1, TRIP6, ACTN3, ACTN1, ITGA7, ITGB2, COL6A1, MMP9, FN1) were significantly upregulated in glomeruli of pFSGS compared to MCD. In the glomeruli of sFSGS, immune regulatory pathways predominantly from the promoter (C1QB, C1RB, C1RC, C1QA, C1QB, THSD7A, C1RB, C1RC, C1QA, C1QB, C1RC) were upregulated compared to MCD (Figure 1). FN1, EIF2AK4, MAP2K3, PKH2, INTS12, BET1 were the most significantly overexpressed proteins in pFSGS compared to MCD.

Conclusions: Proteomic signature of glomeruli of primary and secondary FSGS are distinct from MCD. The differential upregulation of cell-cell, cell-matrix interacting proteins in pFSGS and immune regulatory proteins in sFSGS suggest distinct underlying pathogenic mechanisms. The causal role of novel molecules dysregulated in pFSGS compared to MCD needs to be investigated. A larger cohort of patient samples needs to be interrogated to validate the observation.

Funding: Clinical Revenue Support

FR-OR36
Association of HLA-DPB1*04:01 and Maintenance of Remission in ANCA-Associated Vasculitis
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Background: Genome wide association studies identified HLA-DPB1*04:01 in ANCA vasculitis and observational studies suggest a biological role. We explored the interaction between HLA/PR3 peptide and association with clinical disease remission.

Methods: Peripheral blood mononuclear cells from patients with ANCA vasculitis and healthy controls with HLA-DPB1*04:01 were utilized for mRNA and protein expression assays. PR3 peptides associating with HLA-DPB1*04:01 were identified via in silico and in vitro assays. Antigen-presenting cells were analyzed for co-fluorescence of HLA-DPB1 and fluorescently tagged PR3 peptide. HLA/peptide multimers were used to identify autoreactive T cells.

Results: Carriers of HLA-DPB1*04:01 were less likely to maintain remission in PR3-ANCA vasculitis (adjusted hazard ratio for leaving remission 2.06 (1.01,4.20)), though similar effect was not observed in MPO-ANCA or the combined cohort. In silico prediction of HLA and PR3 peptide interactions showed strong affinity between PR3,225-239 and HLA-DPB1*04:01 and confirmed by in vitro assays. Expression of HLA-DPB1 did not differ among patients and controls. Circulating APCs analyzed by flow cytometry demonstrated higher fluorescence overlap between peptide and HLA among patients on therapy compared to healthy controls or patients in long-term remission off therapy (Figure). We also found that there is a dynamic autoreactive CD4+ T cell response. Affinity between PR3,225-239 and HLA-DPB1*04:01 is reduced among patients in long-term clinical disease remission. These data suggest that the interaction is dynamic and that it could determine the subsequent immune response of T cell activation and maintenance of immunological remission. When HLA-DPB1*04:01 does present PR3,225-239, as an antigen, it is recognized by autoreactive T cells. The peptide-HLA interaction may be the link explaining why patients with PR3-ANCA and HLA-DPB1*04:01 are unable to maintain disease remission.

Funding: NIDDK Support
FR-OR37

Leukotriene B4-BLT1 Axis Controls Neutrophil Accumulation via Fcy Receptor-Dependent Leukotriene B4 Production in Experimental Glomerulonephritis

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Background: Eicosanoids are biologically active lipid mediators generated rapidly at sites of inflammation. Leukotrienes and prostaglandins are synthesized by a cytochrome P450-dependent arachidonic acid cascade. Although it is generally known that leukotriene B4 (LTB4) functions as a potent chemotactic factor for neutrophils via its receptor BLT1, the role of LTB4-BLT1 axis on glomerulonephritis has not been clarified.

Methods: We used the nephrotoxic serum nephritis model, which mimics human glomerulonephritis. To investigate the effect of LTB4-BLT1 axis on glomerulonephritis, we used BLT1-knock out (KO) mice. Specifically, serological and histological analyses were performed in acute and chronic phases. We used LCM/MS to measure LTB4 in the kidney. To confirm LTB4 production by neutrophils, we activated the Fcγ receptor of neutrophils by cross-linking with IgG.

Results: On day 7 after onset of nephritis, wild-type (WT) mice showed severe proteinuria, crescent formation accompanied by macrophage infiltration, which was markedly attenuated in BLT1-KO mice. Next, we examined neutrophil infiltration in glomeruli in acute phase; the number of neutrophils in glomeruli peaked at 6 hours after onset both in WT and BLT1-KO mice, but was markedly lower in BLT1-KO mice. Complement activity and chemokines were comparable in both groups. Then, we measured LTB4 in the kidney and found that LTB4 production occurred within an hour of onset, indicating a dominant effect of the LTB4-BLT1 axis on early neutrophil infiltration. In vitro studies demonstrated that LTB4 production was dependent on activation of Fcγ receptors. On day 1 after onset, BLT1-KO mice exhibited reduced proteinuria and attenuated endothelial damage. Furthermore, administration of BLT1 receptor antagonists after onset relieved nephritis, strongly indicating its therapeutic effect. Finally, BLT1-positive cells infiltrated glomeruli of patients with ANCA-associated vasculitis, suggesting that the LTB4-BLT1 axis might play important roles in human glomerulonephritis.

Conclusions: Our results revealed that blockage of initial neutrophil infiltration by inhibition of the LTB4-BLT1 axis mitigated nephritis and could counteract subsequent macrophage infiltration. The LTB4-BLT1 axis might be a promising therapeutic target for glomerulonephritis.

FR-OR38

mTOR Activity of Macula Densa (MD) Cells Is a Major Determinant of Glomerular Structure and Function

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Background: Macula densa (MD) cells are paracrine regulators of renal hemodynamics and renin and were recently reported to feature a high rate of protein synthesis. Since the central regulator of protein synthesis is the mTOR pathway, the purpose of the present study was to examine the role of MD mTOR signaling in the maintenance of glomerular structure and function.

Methods: Inducible MD-specific mTOR gain-of-function (MD-mTOR+/-) mice were generated by crossing nNOS-CREERT2-mdTg and TSC2/0 mice. Protein synthesis activity in vivo at the single-cell level was quantified using O-proargyl-puroycin (OPP) fluorescence imaging and histological analysis in Sox2-tdTomato and MD-GFP mice. Glomerular filtration rate (GFR) was measured via transradial detection of FITC-sinistrin plasma decay (MediBeacon) and renal blood flow (RBF) was quantified by intravital microscopy.

Results: Sox2-tdTomato mice and the OPP assay showed the highest protein expression in the MD among all renal cell types. Immunolabeling validated MD-specific TSC2 KO and upregulated pS6K in MD-mTOR+/- mice. MD-mTOR+/- significantly increased the overall rate of protein synthesis in MD cells (1.300±0.057) vs control (1.944±0.039). Physiological activation of MD cells by low salt diet further enhanced MD protein synthesis in both WT (1.365±0.035) and MD-mTOR+/- (1.482±0.039) mice, which was blocked by Rapamycin treatment. MD-enriched proteins such as CCN1, CCN3, Papp2 and CxCl14 had significantly higher expression in response to MD-mTOR+/- than controls.

Conclusions: We report for the first time that MD-mTOR signaling is an important regulator of MD cell protein synthesis, proliferation, differentiation and presen signaling to the glomerulus via classical hemodynamic and novel, non-traditional glomerular tissue remodelling elements that may be therapeutically targeted to increase RBF, GFR and endogenous tissue remodeling in kidney diseases.

Funding: NIDDK Support

FR-OR40

Intravital Imaging Reveals Glomerular Capillary Enlargement and Endothelial/Immunocyte Cell Activation Early in Alport Syndrome

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Background: Alport syndrome (AS) is a rare genetic disorder caused by mutations in type IV collagen that lead to defective glomerular basement membrane, damage of the glomerular filtration barrier (GFB), and progressive kidney disease. While the genetics of AS is well known, the molecular and cellular mechanistic details of disease pathogenesis have been elusive, hindering the development of effective, specific, and mechanism-based therapies. Here we aimed to obtain direct visual clues on the major drivers of AS pathology by performing high-power intravital multiphoton microscopy (MPM) of the local kidney tissue microenvironment in a mouse model of AS, with translation to the human condition.

Methods: In vivo kidney MPM imaging of transgenic Alport mice (Col4a5 mutant) at 2 and 5 months of age was compared with urinalysis and histology. Endothelial glycoalyx was labeled with FITC-WGA, T cells with anti-CD3-Alexa594/CD44-Alexa488 antibodies, and plasma with Albumin-Alexa680. Animals received hyalurondase (50U iv). AS patient renal biopsy specimens with minimal change disease controls were labeled with seminiferous fluorescence histological analysis and single glomerular spatial proteomics (NanoString).

Results: Severely distended glomerular capillaries and aneurysms were found in AS mice accompanied by numerous microthrombi, increased glomerular endothelial glycoalyx, recruitment of immune cells and albumin leakage through the GFB, glomerulosclerosis and interstitial fibrosis by 5 months of age with an intermediate phenotype at 2 months. Histological and single glomerular spatial proteomics analysis of AS patient biopsies confirmed the presence of distal glomerular capillaries, activated T cells, endothelial...
FR-OR41
Comparative Human and Mouse Kidney Transcriptomics Identify ELF4 as Potential Therapeutic Target
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Background: Mouse models provide an excellent tool to study kidney disease pathogenesis, but little is known how well mouse models recapitulate molecular changes of human CKD.

Methods: Here we created four different mouse kidney disease models a) unilateral ureteral obstruction, b) folic acid injection c) tubular specific overexpression of Notch1 and d) podocyte specific overexpression of risk variant APO1. We performed detailed phenotyping and molecular profiling by RNA Sequencing of mouse models. We also generated RNA Sequencing for 95 human kidney samples. We used the CRISPR technology to generate mice with ELF4 deletion. We used antisense oligonucleotides for test the therapeutic potential of ELF4 inhibition.

Results: Using comparative bioinformatics we identified 1256 genes and 47 transcription factors that were commonly regulated in all mouse CKD and in patients with CKD. In particular we identified ELF4 and ELF4 transcription factors as they were elevated in both all mouse models and patient samples. Mice with genetic deletion of ELF4 was healthy at baseline and showed protection from FA and cisplatin induced kidney fibrosis and disease. We found that ELF4 is mostly expressed in immune cells and influenced inflammation. Therapeutic inhibition of ELF4 was tested by injection of siRNA, which showed similar protection of kidney disease.

Conclusions: Comparative transcriptomics identified ELF4 as one of the key conserved transcription factor in human and mouse CKD. Genetic deletion or pharmacological inhibition of ELF4 protected mice from fibrosis.

FR-OR42
Proteome-Wide and Transcriptome-Wide Association Studies of Kidney Function
Paige Schlosser,1 Jingning Zhang,3 Hongbo Liu,1 Aditya P. Surapaneni,4 Bing Yu,1 Eric Boerwinkle,5 Nielsan Chatterjee,5 Katalin Susztak,4 Anna Kotggen,1 Joseph Coseres,1,2 Morgan Grams.1,2 Johns Hopkins University. Department of Epidemiology, Baltimore, MD; 1Institute of Genetic Epidemiology, Medical Center - University of Freiburg, Freiburg, Germany; 2Johns Hopkins University Department of Biostatistics, Baltimore, MD; 3Johns Hopkins University Welch Center for Prevention Epidemiology and Clinical Research, Baltimore, MD; 4The University of Texas Health Science Center at Houston, Houston, TX; 5Baylor College of Medicine, Houston, TX; 6Johns Hopkins University School of Medicine, Baltimore, MD; 7Department of Medicine and Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA.

Background: Large-scale genome-wide association studies (GWAS) have implicated 424 loci associated with eGFR and 320 loci associated with eGFR based on creatinine (eGFRcr). However, the mechanisms by which genetic variation in these loci lead to differences in kidney function remain largely unknown. Combining genetic association statistics from GWAS of eGFR with those from the plasma proteome and gene expression in multiple tissues can reveal potentially causal genes and proteins affecting kidney function.

Methods: We applied proteome-wide and transcriptome-wide association studies (PWS) for eGFRcr and eGFRcys using summary-statistics from the CKDGen Consortium (EA, N_eGFRcys=1,004,041; N_eGFRcr=460,826) and 1,318 genetic plasma protein level prediction models developed in the Atherosclerosis Risk in Communities (ARIC) study (N=7,213 European American (EA), 2,479 African American (AA), 2,432 Hispanic (HIS), and 2,031 Asian (AS) individuals). We conducted genome-wide association studies (GWAS) on eGFRcys and eGFRcr based on prediction models developed in 49 human tissues (GTEx) and from 121 kidney tubule samples.

Results: We identified 62 proteins which were associated with eGFRcr and 42 genes with eGFRcys using summary-statistics from the CKDGen Consortium (EA, N_eGFRcys=1,004,041; N_eGFRcr=460,826) and 1,318 genetic plasma protein level prediction models developed in the Atherosclerosis Risk in Communities (ARIC) study (N=7,213 European American (EA), 2,479 African American (AA), 2,432 Hispanic (HIS), and 2,031 Asian (AS) individuals). We conducted genome-wide association studies (GWAS) on eGFRcys and eGFRcr based on prediction models developed in 49 human tissues (GTEx) and from 121 kidney tubule samples.

Conclusions: We were able to consistently identify 13 genes/proteins for eGFRcys and eGFRcr across both PWS and GWAS. Based on our human in vivo data these proteins are excellent candidates for downstream functional studies and for potential drug repurposing in the context of chronic kidney disease.

Funding: Government Support - Non-U.S.

FR-OR43
CTGF Aggravates the Oxidative Stress-DNA Damage-Cellular Senescence Sequence Following Renal Ischemia-Reperfusion Injury
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Background: Recent data suggest that AKI to CKD progression may be driven by cellular senescence evolving from prolonged DNA damage response following oxidative stress. Connective tissue growth factor (CTGF; CCN2) is a major contributor to CKD development and was found to aggravate DNA damage and the subsequent DNA damage response (DDR)-Cellular Senescence-Fibrosis sequence following renal ischemia reperfusion injury (IRI). Here, we investigated the impact of CTGF inhibition on the immediate (4 hours) and early (3 days) renal response to IRI.

Methods: We induced AKI by bilateral IRI in wild type and conditional CTGF-KO mice and euthanized the mice 4 hours and 3 days after reperfusion. We performed full transcriptome RNA sequencing to identify major dysregulated pathways and validated the findings by qPCR and immunohistochemistry.

Results: IRI resulted in upregulation of CTGF 4 hours and 3 days after reperfusion (Figure 1AC). Four hours after reperfusion, CTGF-dependent differentially regulated genes were enriched in multiple signaling pathways related to oxidative stress and DNA damage. Consistently, decreased staining for H2AX and p-p53 (Figure 1B) indicated reduced DNA damage response in tubular epithelial cells of CTGF-KO mice, although decline in kidney function, acute tubular damage score, and KIM1- and NGAL expression were similar between both groups. Three days after IRI, oxidative stress response markers (HINE, nitrosytroseine, and Nε2 target genes HMOX1 and NQO1), DDR markers (γH2AX, p-p53, p21), and anti-apoptotic factors (Bcl-xL, HMGB1) were less elevated in CTGF-KO than in wild type mice.

Conclusions: Together, our observations suggest that CTGF inhibition might mitigate AKI to CKD progression by reducing oxidative stress induced DNA damage and the subsequent DDR-cellular senescence-fibrosis sequence response.

FR-OR44
Urinary mRNA Expression of Glomerular Podocyte Markers in Glomerular Disease and Renal Transplant
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Background: The search for urinary markers to monitor the progression of kidney disease is still ongoing and previous works have demonstrated the useful of quantifying mRNA expression of urinary cells. It is well known that in podocytes the slit diaphragm integrity and the function of the molecules shared with neuronal signaling pathways are essential for the maintenance of cell physiology. Our study focuses on the identification of the urinary mRNA expression of a panel of podocytes genes useful to identify possible biomarkers of glomerular pathological processes.

Methods: We studied the urine obtained from patients, native and renal transplant, affected by renal disease and undergone, with clinical indication, to renal biopsy (Rbx). We investigated the presence and the morphology of podocytes by immunocytochemistry and measured the expression of genes responsible for their structure and function by RTqPCR.

Results: Our results demonstrate in urine the presence of podocytes with cytoskeletal alterations. Furthermore, we detected the increment of WIF1 mRNA in the urine of both groups. After all kinds of normalization for the number of podocytes, it was found that in podocytes the slit diaphragm integrity and the function of the molecules shared with neuronal signaling pathways are essential for the maintenance of cell physiology. Our study focuses on the identification of the urinary mRNA expression of a panel of podocytes genes useful to identify possible biomarkers of glomerular pathological processes.

Conclusions: We considered and applied possibly alternative methods to correct gene expression in respect to the total number of podocytes to compare different groups of patients.

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Conclusions: We considered and applied possibly alternative methods to correct gene expression in respect to the total number of podocytes to compare different groups of patients.
Conclusions: We suggest the expression of WT1 mRNA as a surrogate for quiescent podocytes. We propose the increase of TRPC5 and GRM1 mRNA in urinary podocytes as a marker helpful to provide complementary information to RXr. These genes are useful for monitoring actin cytoskeleton remodeling in podocytes that contributes to glomerular damage in course of renal disease.

Urinary cells culture. Podocytes are recognizable by their processes (A-E), a large cytoskeleton and processes in podocyte. The enhanced interactions of FKBP12 with Synp treatment to normal cells increased the expression of FKBP12 at F-actin in processes and impaired (40.4% to normal, P<0.005) in the podocytes treated with FKBP12 siRNA. Tac enhanced the interaction of FKBP12 with Synp. The IP assay with the HEK expression system also showed FKBP12 interacted with endogenous 14-3-3β. FKBP12 interacted with Synp in the HEK cells co-transfected with 14-3-3β and Synp. The interaction of 14-3-3β and Synp was not altered by the treatment of 14-3-3β siRNA. Tac enhanced the interaction of FKBP12 with Synp. The expression of 14-3-3β was decreased (63.0% to normal, P<0.001), the structure of F-actin is deranged (staining score, 2.0 vs. 2.9 of normal, P<0.05), and the process formation was impaired (40.4% to normal, P<0.005) in the podocytes treated with FKBP12 siRNA. Tac treatment to normal cells increased the expression of FKBP12 at F-actin in processes and enhanced process formation.

Conclusions: FKBP12 interacts with 14-3-3 and Synp to maintain actin cytoskeleton and processes in podocyte. The enhanced interactions of FKBP12 with Synp and 14-3-3 by Tac treatment restores FKBP12 at actin cytoskeleton in podocyte.

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FR-OR46
Soluble SFlt1 Binds to Anti-Inflammatory Macrophages in the Kidney
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Background: Soluble Flt1 (sFlt1), a decoy receptor of VEGF ligands, is a key regulator of angiogenesis. High systemic levels of sFlt1 have been linked to the pathogenesis of preclampsia. However, we have previously reported that treatment with low concentrations of sFlt1 ameliorates kidney damage and inflammation. Specifically, sFlt1 targets macrophages, suggesting that sFlt1 has nephroprotective immunomodulating effects. Here, we studied the presence of sFlt1 in human kidney diseases and investigated the expression and direct binding of sFlt1 to macrophages.

Methods: Renal biopsies of patients with various kidney diseases (IgA, DN, FSGS, MCD) and pre-transplant control biopsies were stained for sFlt1, CD163 and CD68. Cultured macrophages were incubated with increasing concentrations of sFlt1-His, after which membrane binding was measured using flow cytometry. For this, THP-1 monocytes were differentiated with PMA and activated with IFN-γ and LPS or IL-4, primary macrophages were differentiated using GM-CSF or M-CSF.

Results: A patchy pattern of sFlt1 staining colocalizes with CD163/CD68-positive cells in tubulointerstitial areas and with CD68-positive cells in glomeruli. No quantitative differences in renal sFlt1 levels were observed in patients with kidney disease and controls. Flow cytometric analysis revealed that sFlt1 binds to PMA-differentiated THP-1 macrophages but does not bind to THP-1 monocytes. Activation with IFN-γ and LPS increased sFlt1 binding to THP-1 macrophages. However, IL-4 activation of THP-1 macrophages strongly increases membrane sFlt1 binding. Furthermore, IL-4 activation upregulates sFlt1 mRNA expression in THP-1 macrophages. In primary macrophages, sFlt1 binding was higher in macrophages differentiated with GM-CSF compared to M-CSF.

Conclusions: Our results suggest that sFlt1, while typically associated with angiogenesis, binds to anti-inflammatory macrophages in the human kidney. Alternative activation of macrophages by IL-4 strongly induces sFlt1 production and increases direct binding of sFlt1 to the cell surface membrane. We infer that sFlt1 functions as an autocrine stimulus of anti-inflammatory macrophages, independent of its antiangiogenic properties. Since anti-inflammatory macrophages mediate repair after kidney injury, our work suggests the potential of sFlt1 as a therapeutic tool.

FR-OR47
Cytokines of Kidney Origin Are Retained in the Heart and Induce Cardiac Injury in CKD: A Renal-Caroid Axis
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Background: Chronic kidney disease (CKD) is a major contributor to heart failure (HF), but the mechanisms underpinning CKD-induced HF remain to be fully elucidated. We hypothesize that inflammatory signaling from the kidney drives the development of cardiac injury in CKD.

Methods: CKD was induced in 4 pigs (bilateral renovascular disease and dyslipidemia) and observed for 14 weeks. Normal pigs served as controls. Renal hemodynamics (RRF, GFR) were quantified by multi-detector CT, and cardiac morphology and function by echocardiography. Renal vein, coronary sinus, and systemic blood was collected to quantify renal and cardiac markers of TNF-α and IL-6. In a biomimetic heart culture system, pig heart slices were exposed to plasma from CKD or normal pigs and contractile.relaxation kinetics were measured. The effect of TNF-α stimulation on cardiac mitochondrial respiration and Ca2+ dynamics were investigated.

Results: Loss of renal function in CKD was accompanied by positive renal (renal release) and negative cardiac (cardiac retention) cytokine gradients, left ventricular (LV) hypertrophy, diastolic dysfunction (E/A, E/e’ ratio) and abnormal LV strain. Cardiomyocytes exposed to CKD plasma showed impaired contractility and speed of relaxation, and altered Ca2+ cycling, which improved after TNF-α and IL-6 neutralization (Figure).

Conclusions: This study supports a link between TNF-α/IL-6 inflammatory signaling from the kidney in causing cardiac dysfunction in CKD. Cardiac impairment in vivo was mirrored by altered cardiomyocyte kinetics and Ca2+ cycling after exposure to CKD plasma in vitro, supporting an inflammatory renal-cardio axis in CKD-to-HF pathophysiology.

Funding: Other NIH Support - NHLBI

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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FR-OR48

Complementary Quantification of Interstitial Fibrosis and Tubular Atrophy (IFTA) for CKD Cases of the Kidney Precision Medicine Project

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Background: Quantification of interstitial fibrosis and tubular atrophy (IFTA) is critical in the evaluation of kidney diseases. In this study, we previously developed a computational IFTA segmentation model tested on an independent dataset of renal biopsy whole slide images (WSIs) from kidney Precision Medicine Project (KMP) and compared to visual assessment.

Methods: A computational model for the IFTA segmentation was trained using 48 PAS stained WSIs from kidney biopsy specimens obtained at three non-KMP institutions. Twenty-six KMP WSIs from the KMP chronic kidney disease (CKD) cohort were used as independent testing dataset. Quality control (QC) of the KMP WSIs was performed using HistoQC, a previously developed QC tool for digital pathology images. Computationally derived percent IFTA scores were calculated using morphological processing to segment IFTA tissue regions in WSIs. Three KMP pathologists independently estimated the percent IFTA on the same KMP dataset. The pathologists’ estimates and the computationally predicted percent IFTA values were compared pairwise using Pearson correlation.

Results: Computationally derived IFTA segmentations from select cases are shown in Fig. 1a. The Pearson correlation showed a high degree of agreement between both pathologists and the computational model. The pairwise correlations are shown in the confusion matrix in Fig. 1b.

Conclusions: Computational segmentation of IFTA has the potential to add enhanced reproducibility, precision, and efficiency to clinical tasks such as the estimation of percent IFTA.

Funding: NIDDK Support

FR-OR49

Complement Convertases in Glomerulonephritis: An Explainable Artificial Intelligence-Assisted Renal Biopsy Study

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Background: Complement activation is crucial in the pathogenesis of C3 glomerulopathy (C3G). It is likely also involved in other forms of glomerulonephritis (GN), however, here, intensity, significance, and predominant activation pathways are less clear.

Methods: Proximity ligation assays (PLA) were used to visualize C3/C5 convertase complement convertases in renal biopsies. Close proximity of C3b and C4b2 and C4b4 was interpreted as assembled alternative or classical/C3/C5 convertases, respectively. For quantification we used deep learning based on explainable artificial intelligence (xAI) in a two-stage workflow: 1. detection of the glomeruli and 2. detection of the PLA signals. Signal densities were calculated as numbers of signals per glomerular area [signals/sqmm]. Cases of C3G (n=10), immune complex-mediated membranoproliferative GN (IC-MPGN; n=10), IgA nephropathy (IgAN; n=10), postinfectious GN (PIGN; n=10), (IC-MPGN; n=10), IgA nephropathy (IgAN; n=10), postinfectious GN (PIGN; n=10), however, here, intensity, significance, and predominant activation pathways are less clear.

Results: A 75-year-old European female patient with past history of hypertension, type 2 diabetes and stage G3/A1 CKD was referred for rapid decline in kidney function. At presentation, the patient’s serum against normal kidney brush border, consistent with the diagnosis of ABBA, immunofluorescence failed to detect LR2P within biopsy tissues. Protein and IgG immunoprecipitation followed by mass spectrometry revealed cubulin (CUBN), another representative of the multiligand, endocytic-membrane glycoprotein of the proximal tubule, to be uniquely present within immune complexes eluted from frozen biopsy tissue. Confocal microscopy confirmed CUBN significantly colocalized with IgG in the TB. Such colocalization was specific to the disease and not observed in other immune complex-mediated tubulointerstitial diseases, including LR2P nephropathy, IgG4-related kidney disease, idiopathic hypocomplementemic interstitial nephritis, lupus nephritis, or polyclamivus nephritis.

Conclusions: CUBN is a novel target antigen in ABBA.

Funding: NIDDK Support

FR-OR50

Cubulin Is a Novel Target Antigen in Anti-Brush Border Disease

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Background: Anti-brush border antibody disease (ABBA) is an autoimmune kidney disease that frequently progresses to kidney failure. It is characterized by proximal tubular damage, IgG-positive immune deposits along the tubular basement membrane (TBM), and circulating autoantibodies directed against the brush border. To date, the multifid receptor megalin (also known as LDL receptor-related protein 2, LR2P) is the only target antigen associated with ABBA.

Methods: Here, we investigated a patient with LR2P-negative ABBA and applied mass spectrometry and confocal microscopy to identify a novel target antigen.

Results: The patient was a 71-year-old woman with type 2 diabetes and stage G3/A1 CKD. She was referred for rapid decline in kidney function. At presentation, the patient’s serum against normal kidney brush border, consistent with the diagnosis of ABBA, immunofluorescence failed to detect LR2P within biopsy tissues. Protein G immunoprecipitation followed by mass spectrometry revealed cubulin (CUBN), another representative of the multiligand, endocytic-membrane glycoprotein of the proximal tubule, to be uniquely present within immune complexes eluted from frozen biopsy tissue. Confocal microscopy confirmed CUBN significantly colocalized with IgG in the TB. Such colocalization was specific to the disease and not observed in other immune complex-mediated tubulointerstitial diseases, including LR2P nephropathy, IgG4-related kidney disease, idiopathic hypocomplementemic interstitial nephritis, lupus nephritis, or polyclamivus nephritis.

Conclusions: CUBN is a novel target antigen in ABBA.

Funding: NIDDK Support

FR-OR51

The Effect of Dapagliflozin on Rate of Kidney Function Decline in Patients with CKD: A Prespecified Analysis from the DAPA-CKD Trial

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Background: Dapagliflozin reduced the risk of kidney failure in patients with chronic kidney disease (CKD) with and without type 2 diabetes in the DAPA-CKD trial (NCT03036150). This prespecified analysis assessed the effect of dapagliflozin on the rate of change in estimated glomerular filtration rate (eGFR) slope.

Methods: DAPA-CKD included patients aged ≥ 18 years with urine albumin-to-creatinine ratio (UACR) ≥ 200–5000 mg/g and eGFR 25–75 mL/min/1.73m2 to dapagliflozin 10 mg or placebo once daily, added to standard care. We analysed eGFR slope using
mixed effect models with different slopes from baseline to Week 2 (acute change); Week 2 to end-of-treatment (chronic eGFR slope); and baseline to end-of-treatment at median 2.3 years (total eGFR slope).

Results: In the overall cohort, dapagliflozin compared to placebo slowed mean eGFR decline from baseline to end-of-treatment by 0.9 mL/min/1.73m²/year (95% CI 0.6–1.3). Dapagliflozin compared to placebo caused an acute eGFR decline of 2.6 mL/min/1.73m² (95% CI 2.3–3.1) and 2.0 mL/min/1.73m² (95% CI 1.4–2.7), in patients with and without type 2 diabetes, respectively. Thereafter, dapagliflozin compared to placebo reduced the mean rate of eGFR decline by a greater amount in patients with type 2 diabetes (chronic eGFR slope mean difference 2.3 mL/min/1.73m²/year (95% CI 1.9–2.6)) than in those without type 2 diabetes (1.3 mL/min/1.73m²/year (95% CI 0.7–1.8)); interaction p=0.005). The effect of dapagliflozin compared to placebo on total slope in patients with and without type 2 diabetes was 1.2 mL/min/1.73m²/year (95% CI 0.8–1.6) and 0.5 mL/min/1.73m²/year (95% CI -0.1–1.0); interaction p=0.04, respectively. The total eGFR slope was steeper in patients with higher baseline HbA1c and UACR; the beneficial effect of dapagliflozin on eGFR slope was also more pronounced in patients with higher baseline HbA1c and UACR.

Conclusions: Dapagliflozin significantly slowed long-term eGFR decline in patients with CKD. The mean difference in eGFR slope between dapagliflozin- and placebo-treated patients was greater in patients with type 2 diabetes, with higher baseline HbA1c and UACR; the beneficial effect of dapagliflozin on eGFR slope was also more pronounced in patients with higher baseline HbA1c and UACR.

Funding: Commercial Support  - AstraZeneca

FR-OR52
Phenome-Wide Association Study of Common Genetic Variants in SGLT2 and Health Disparities in Kidney Outcomes
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Background: SGLT2 inhibition represents one of the greatest therapeutic achievements of the last two decades, improving cardiovascular outcomes and slowing the progression of CKD to ESRD by 30% in patients with diabetes. Whether common genetic variants in SGLT2 gene contribute to kidney disease progression and to health disparities in kidney disease is unknown.

Methods: We tested the association of two SNPs in the SLC5A2 gene encoding SGLT2 with clinically diagnosed phenotypes in a phenome-wide association study in 428,438 whites and 114,536 non-Hispanic blacks (NHB) from the Million Veteran Program. Using logistic regression adjusted for age, sex, and 10 principal components of ancestry, we regressed 250 phenotypes against the two SNPs (rs9934336; rs3116150), stratified by race and diabetes status. Minor allele frequencies for rs9934336 were 0.26 and 0.20 and for rs3116150 were 0.24 and 0.04 in White and non-Hispanic Black participants, respectively.

Results: The rs9934336 variant was associated with multiple kidney phenotypes in NHBs as shown in the table, while no associations of rs9934336 and kidney phenotypes were observed in whites. When stratified by diabetes, renal failure NOS remained significantly associated in diabetics, and anemia of CKD in non-diabetics. The rs3116150 variant was also associated with several kidney phenotypes in NHBs, while no associations were observed in whites. When stratified by diabetes, most of the associations of rs3116150 and kidney phenotypes remained.

Conclusions: Our study shows that SGLT2 variants are associated with CKD and ESRD in non-Hispanic blacks. This novel association with health disparities needs to be further evaluated. Mendelian randomization studies for SLC5A2 variants are underway. Funding: Veterans Affairs Support

Table 1. SGLT2 Variants and Renal Disease ICD Codes in Non-Hispanic Blacks (odds ratio with unadjusted p-value)

FR-OR53
Effects of Daprodustat on Hemoglobin and Quality of Life in Patients with CKD: Results of the ASCEND-NHQ Randomized, Double-Blind, Placebo-Controlled Trial
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Background: Daprodustat (dapro) is a hypoxia-inducible factor prolyl hydroxylase inhibitor being developed for treating anemia of chronic kidney disease (CKD). In a Phase 3 trial in non-dialysis dependent (ND) CKD patients, we evaluated the effect of dapro vs placebo (PBO) on hemoglobin (Hb) and the SF-36 quality of life Vitality score (fatigue) over 28 weeks.

Methods: Adults with CKD stage 3–5, Hb 8.5–10.0 g/dL, transferrin saturation ≥15%, ferritin 450 ng/ml without recent rhEPO use were randomized 1:1 to dapro or PBO to maintain Hb 11–12 g/dL (NCT03409107). Primary endpoint was mean change in Hb between baseline (BL) and the evaluation period (mean over Wk 24–28). Principal secondary endpoints were 1) proportion with ≥1 g/dL increase in Hb, 2) mean change in SF-36 Vitality score (fatigue) between BL and Wk 28. SF-36 Vitality responder (≥6 point increase) and blood pressure (BP) elevations were secondary endpoints. Superiority for all endpoints was tested (1-sided α=0.025).

Results: 614 ND-CKD patients were randomized. BL demographic characteristics were balanced; Hb was similar (9.73 g/dL, dapro, 9.71 g/dL PBO). The adjusted mean difference (AMD) in change in Hb was 1.40 g/dL (95% CI 1.23, 1.56; P<0.001). A greater proportion on dapro had a ≥1 g/dL increase in Hb from BL (77% vs 18%; P<0.001). Adjusted mean (SE) SF-36 Vitality score increased by 7.3 (1.1) points (dapro vs dapro 5.4 (95% CI 2.2, 8.6; P<0.001, Figure). 58% on dapro vs 40% on PBO were SF-36 Vitality responders (difference 13%; 95% CI 4%, 22%). While more BP elevations occurred in dapro vs PBO (32% vs 26%, p=0.07), dapro’s overall effect on BP was similar to PBO. Rates of adverse events were similar (dapro 69% vs PBO 71%).

Conclusions: In patients with ND-CKD, dapro effectively increased Hb, significantly improved the vitality score (fatigue) and was well tolerated. Funding: Commercial Support  - GlaxoSmithKline

FR-OR54
Integrated Efficacy and Safety of Bardoxolone Methyl in CKD
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Background: Bardoxolone methyl (Bard), an Nrf2 activator, has been studied in multiple CKD trials. To further characterize the safety and efficacy of Bard, we performed integrated analyses across all studies conducted with Bard in CKD.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: Data from the following placebo-controlled trials, CARDINAL Phase 3 (NCT01969185) in 157 patients with Alport syndrome, TSUBAKI (NCT02316082) in 120 patients with T2DM and CKD, and BEACON (NCT01351675) in 2185 patients with T2DM and CKD, were pooled in a CKD Placebo-Controlled Set. An Overall Integrated Analysis Set included additional data from open-label Phase 2 studies. Patients with CKD were sustained four weeks after treatment were included in the CKD Placebo-Controlled Set (2462 patients (1232 placebo, 1230 Bard)). The median and maximum duration of exposure for the Bard group was 0.5 years and 1.9 years, respectively. The Overall Integrated Analysis Set included 3448 patients (1340 placebo, 2108 Bard) with a maximum Bard exposure of 4.8 years. In the overall integrated analysis set, Bard significantly increased eGFR from baseline by 6.4±2 mL/min/1.73m² (p<0.0001) vs baseline and vs placebo). Fewer events in a composite of ESKD, ≥30% decline in eGFR, and eGFR <15 mL/min/1.73m² were seen in the Bard group (111 [9%]) compared to placebo (274 [22%]). The Overall Integrated Analysis Set showed similar results. Common adverse events (AEs) in both integrated sets included muscle spasms, decreased appetite, hypogammaglobulinemia and decreased weight. No serious AEs of cardiac failure were reported with Bard in CKD trials conducted after BEACON.

Conclusions: Across all studies in CKD, Bard preserved kidney function with on-treatment benefit and was generally well tolerated. Studies in persons with CKD conducted after BEACON mitigated the risk for heart failure previously observed in patients with type 2 diabetes and Stage 4 CKD.

Funding: Commercial Support - Reata Pharmaceuticals

FR-OR5

Renal Outcomes Associated with Direct Acting Antiviral Therapy in Patients with Hepatitis C Virus Infection

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Background: Direct Acting Antiviral (DAA) agents are effective treatments for chronic Hepatitis C virus (HCV) infection, leading to sustained viral response in the majority of treated individuals. While HCV infection is associated with poorer renal outcomes in chronic observations, the effect of DAA therapy on long term renal outcomes remains unclear.

Methods: We identified a national cohort of US Veterans with HCV infection based on positive quantitative RNA viral load testing and extracted data on any DAA therapy using pharmacy dispensation data. We examined the association of DAA therapy (compared to no DAA therapy) with the incidence of end stage kidney disease (ESKD) and the composite of ESKD or death, using time dependent Cox models adjusted for demographic characteristics, socio-economic characteristics including alcohol and illicit substance use, comorbid conditions and baseline kidney function and proteinuria.

Results: We identified 114,358 patients with HCV infection, of whom 58,045 (51%) received a course of DAA therapy between 2013-2018. The overall mean (SD) age at HCV diagnosis was 55.0 (7.5) years, 97% were male, 38% were African American, the mean (SD) eGFR was 92 (17) mL/min/1.73 m² and 8% had proteinuria. There were 497 ESKD events and 26,684 composite events over a median follow-up of 11.5 years. DAA therapy was associated with lower risk of ESKD and the composite event (multivariable adjusted HRs and 95%CI: 0.43, 0.31-0.61 and 0.62, 0.60-0.63) [table].

Conclusions: In a large national cohort of US veterans DAA therapy was associated with significantly lower risk of ESKD and the composite of ESKD or death, supporting the long term benefit on kidney function of HCV cure.

Funding: Veterans Affairs Support

FR-OR56

The Comparative Effectiveness and Safety of Direct Oral Anticoagulant (DOAC) and Warfarin Initiation in Adults with Atrial Fibrillation (AF) by eGFR Category

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Background: There is ongoing uncertainty regarding the risk-benefit ratio of DOACs in patients with AF and CKD.

Methods: We conducted an international multicenter cohort study (2011-2018) using healthcare data from 5 jurisdictions across Australia (666 participants of the 45 and Up Study [among 267153 recruited in 2006-09] with data linked to hospital/laboratory data [by GenRed]) and the Medicare Benefits Schedule and Pharmaceutical Benefits Scheme data provided by Services Australia; all linked data accessed via SURE) and Canada (73876 patients in AB,BC,MONB; record linkage of provincial administrative/ laboratory data). We propensity score matched adults with a new dispensation of a DOAC (rivaroxaban, apixaban, dabigatran) who were warfarin, who had AF and a recorded eGFR grouped as ≥60,45-59,30-44, <30mL/min/1.73m². Chronic dialysis or kidney transplant recipients were excluded. We assessed 2 composite outcomes within 1 year of initiating either therapy: ischemic (all-cause death, ischemic stroke or TIA) and bleeding (intracranial, gastrointestinal or other). We used Cox regression to estimate the hazard ratios (HRs [95%CI]) of outcomes across eGFR categories and summarized centre data in random effects meta-analysis.

Results: A total of 74542 eligible patients were included, among whom there were 6923(9.2%) ischemic and 1572(2.1%) bleeding events recorded. Across eGFR groups, DOAC initiation was associated with lower or similar risk for the ischemic outcome compared with warfarin initiation (pooled HRs [95%CI] for eGFR groups: 0.74(0.69-0.79), 0.75(0.64-1.07), 0.68(0.61-0.75) and 0.80(0.76-0.98), respectively). Similar results were observed for bleeding (0.75[0.65-0.86], 0.81[0.65-1.01], 0.82 [0.66-1.02], 0.71[0.52-0.99], respectively). There was no evidence of heterogeneity across jurisdictions except for eGFR 45-59/mL/min/1.73m² for the ischemic outcome (I²=77%).

Conclusions: In this cohort of AF patients initiating DOAC or warfarin, compared to warfarin, DOAC use was associated with lower or similar risk of both ischemic and bleeding outcomes independent of eGFR. Our results suggest DOAC therapy may have a favourable risk-benefit ratio in AF patients with non-dialysis dependent CKD that is similar to that seen in AF patients with preserved kidney function. Adequately powered randomized trials are needed to confirm these findings.

Funding: Government Support - Non-U.S.
FR-OR58

Association Between the Gut Microbiota and Kidney Function
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Background: The human gut microbiota is composed of the bacteria, fungi and other microorganisms that live in the lower intestines in a symbiotic relationship with the host. Disruption of the gut microbiota has been associated with cardiovascular and metabolic diseases, but the association with kidney disease is still largely unknown.

Methods: We studied the composition and predicted function of the gut microbiota based on shotgun whole-genome sequencing of microbial DNA in fecal samples collected from 9,788 adults enrolled in the longitudinal, population-based Swedish SCAPIS cohort study. Linear regression adjusted for technical variables, age, sex, Shannon diversity index and (in sensitivity analysis) established kidney disease risk factors was used to identify associations between the log(1+x)-transformed relative frequencies of 1,900 antagonistic species and estimated glomerular filtration rate (eGFR). Additional sensitivity analyses included stratified analyses for gender, hypertension and diabetes mellitus. The Benjamini-Hochberg false discovery rate (FDR) multiplicity correction was used.

Results: We included 5,130 women (57.5±4.3 years) and 4,658 men (57.6±4.4 years). The mean eGFR was 86.5±12.1 for women and 85.±4.4 for men. Amongst all participants, 42% had an eGFR above 90, 39% had an eGFR between 75-90, 17% had an eGFR between 60-75, 2% had an eGFR between 45-60, and less than 0.1% had an eGFR below 45. In the age- and sex-adjusted model, we identified four bacteria that were associated with an eGFR at FDR < 0.05. Additional adjustment for kidney disease risk factors rendered one of the associations no longer significant. The kidney function-associated bacteria could be identified down to the species level and belonged to the order Eubacteriales (two bacteria), Coriobacteriales, and Verrucomicrobiales. Gene set enrichment analysis indicated significant (FDR < 0.05) enrichment in 48 metabolic pathways.

Conclusions: In the largest gut microbiome association study of kidney function on healthy adults to date, we identified four bacteria associated with glomerular filtration rate. The functional enrichment of kidney function-associated microbiota provides further insights into its possible role in kidney health.

FR-OR59

Genetic Determinants of Serum Calcification Propensity and Mortality Risk in CKD
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Background: Serum calciprotein particle maturation time (T50), a measure of calcification propensity, is associated with cardiovascular morbidity and mortality in patients with chronic kidney disease (CKD). Here, we aimed to identify genetic loci for serum T50 and examine whether these loci are linked with adverse outcomes.

Methods: We performed a genome-wide association study (GWAS) of serum T50 in 2,739 community-dwelling individuals of mostly European descent. Subsequently, we used the community-based Rotterdam study (RS) to examine the association between the identified variants and all-cause mortality in the general population and in a subgroup of CKD patients, applying multivariate logistic regression analysis.

Results: We identified three independent genome-wide significant single nucleotide polymorphisms (SNPs), rs4917 (p=7.2 x 10^-12), rs2077119 (p=3.3 x 10^-12), and rs9870756 (p=3.3 x 10^-10) in the AHSG gene encoding fetuin-A. The three SNPs together explained 18.3% of the variation in serum T50. Quantitative trait locus analysis revealed that all three SNPs have effects detectable at blood protein level of fetuin-A. Associations with these SNPs were studied in 8,556 RS participants (age 65±9.9 y, 57% female, 63% hypertension, BMI 27.3±4.2 kg/m²), of whom 833 had CKD (age 75.5±8.7 y, 59% female, 85% hypertension, BMI 27.4±4.1 kg/m²). The minor allele of rs9870756, linked with a reduced T50 and thus a higher calcification propensity, was significantly associated with a higher risk of all-cause mortality, both in the general population [OR (95% CI)=1.14 (1.00-1.30)] and in the CKD subgroup [OR (95% CI)=1.60 (1.05-2.42)]. In the fully adjusted model, the minor allele of rs9870756 was only associated with all-cause mortality in the CKD subgroup [OR (95% CI)=1.93 (1.21-3.08)]. The other two variants were not associated with all-cause mortality.

Conclusions: We identified three independent SNPs in the fetuin-A gene as strong genetic determinants of calcification propensity. The minor allele of rs9870756 was significantly associated with a higher risk of all-cause mortality in CKD patients. Our findings connect genetic susceptibility to calcification with adverse outcome in CKD patients.

Funding: Commercial Support - Sanofi Genzyme

FR-OR60

Decision Aid for Renal Therapy (DART) Reduces Decision Conflict and Improves Knowledge Among Older Adults with Advanced CKD: A Randomized Clinical Trial
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Background: For older adults, making decisions about kidney failure treatments is challenging, and dialysis may be inconsistent with life goals. Greater decisional conflict is associated with regret, poor outcomes, and worse satisfaction. The DART trial assessed the effectiveness of an interactive, web-based decision aid on decisional conflict and knowledge among older CKD patients facing dialysis decisions.

Methods: Randomized trial evaluating the web-based DART versus usual education, enrolling adults age 70+, English-fluent, with CKD stage 4-5 from 4 US sites. The primary outcome was change in decisional conflict scale (DCS) score from baseline to first follow-up (~3 months) compared using ANCOVA. The validated 16-question DCS (100 point scale; lower score indicates less decisional conflict) measures personal perception of uncertainty in choosing among treatment options and modifiable factors contributing to uncertainty. Twelve knowledge questions about CKD and treatment options were assessed at both visits.

Results: Among 363 participants, 180 were randomized to education and 183 to DART; 162 (89%) completed DART. Mean age was 78 years, mean eGFR was 23 ml/min/1.73 m², 78% were white and 48% had diabetes. Groups were balanced at baseline. At first follow-up, DCS score improved significantly more among the DART group [mean difference 5.2 (2.2, 12.3)]. Between the groups, the decisional conflict score decreased 3.7 (1.7, 5.7) in the DART group. DART was also associated with a 7.2% (3.7, 10.7) greater improvement in knowledge.

Conclusions: DART reduced decisional conflict and improved knowledge among older adults facing kidney failure treatment decisions, emphasizing that the decision-making process for older adults with advanced CKD can be improved with use of this effective educational intervention. Funded by PCORI, CDR-2017C1-6297

Funding: Private Foundation Support

Decisional Conflict by Randomization Group

FR-OR61

Identification of a Special Cell Type as a Determinant of the Kidney Tropism of SARS-CoV-2
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Background: Coronavirus disease-2019 (COVID-19) is an infectious disease caused by a novel discovered coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The kidney tropism of SARS-CoV-2 has been well-validated clinically and often leads to various forms of renal damage in COVID-19 patients. However, the underlying mechanisms and diagnostic approaches remain to be determined.

Methods: To determine the kidney tropism of SARS-CoV-2, we investigated the expression of SARS-CoV-2 receptors and other immune-related proteins in renal tissues from patients with COVID-19 and healthy controls. Immunohistochemistry, RNA sequencing, and virion tracking were performed in renal tissues from patients with COVID-19.

Results: SARS-CoV-2 tropism in kidney tissue was determined by the expression of angiotensin-converting enzyme 2 (ACE2) and the membrane-bound form of angiotensin 1-7 receptor (MasR). We found that the expression of ACE2 and MasR was significantly increased in renal tissues from patients with COVID-19 compared to healthy controls. Additionally, we observed increased expression of interleukin-6 (IL-6), interleukin-1beta (IL-1β), and tumor necrosis factor-alpha (TNF-α) in renal tissues from patients with COVID-19.

Conclusions: Our findings suggest that renal tropism of SARS-CoV-2 is associated with upregulation of the ACE2/MasR axis, which can be a potential target for the development of antiviral therapies. Further studies are needed to explore the role of these proteins in the COVID-19 pathogenesis and identify potential therapeutic targets.

Funding: Private Foundation Support

SA-OR01

Identification of a Special Cell Type as a Determinant of the Kidney Tropism of SARS-CoV-2

Friday, Saturday
SA-OR03
The Spike Protein of the Causative COVID-19 Virus Induces Heme Oxygenase-1: Pathophysiologic Implications
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Background: Acute kidney injury (AKI) is both a consequence and determinant of outcomes in COVID-19. The kidney is one of the major organs infected by the causative virus SARS-CoV-2. The spike protein of SARS-CoV-2 is required for viral entry into cells and is present in the urine of patients with COVID-19 and AKI. The present study examined cellular effects that result from transfecting the spike protein of SARS-CoV-2 in HEK293 kidney cells.

Methods: HEK293-ACE2 cells stably overexpressing ACE2 were used. Codont optimized pcDNA encoding SARS-CoV-2 spike (7788bp) or empty vector (4033bp) plasmid was transfected using Lipofectamine LTX. For studies examining the effect of quercetin (an inducer of heme oxygenase-1, HO-1), full media containing quercetin or vehicle was added at 4-6 hours post transfection. mRNA and protein expression was assessed by quantitative real-time RT-PCR and western blot respectively. Synergy formation was assessed by acquiring phase contrast images using Olympus CX40 microscope and the area covered by syncytia was measured using ImageJ software.

Results: HEK293-ACE2 cells expressed SARS-CoV-2 spike protein upon spike transfection. Such expression led to syncytia formation, the sloughing of sheets of cells, and focal denudation of the cell monolayer. Spike protein expression upregulated potentially nephrotoxic genes such as TNF-α, MCP-1, and ICAM1. Spike protein expression also upregulated potentially cytoprotective genes such as HO-1, as demonstrated by HO-1 mRNA and protein expression and relevant signaling pathways (p-Akt, p-STAT3, and p-p38) involved in inducing the HO-1 gene. Quercetin, a naturally occurring compound that induces HO-1, markedly reduced syncytia formation and spike protein expression.

Conclusions: These findings introduce a clinically relevant, spike protein-induced, in vitro model for the study of AKI in COVID-19. The major conclusions of the study are: 1) Spike protein expression in kidney cells provides a useful and timely model for the study of maladaptive and adaptive responses in these cells relevant to AKI observed in COVID-19; 2) spike protein expression in kidney cells upregulates HO-1; and 3) quercetin, an inducer of HO-1, may provide a clinically relevant/feasible protective strategy in AKI occurring in the setting of COVID-19.

Funding: NIDDK Support

SA-OR04
A Novel Soluble ACE2 Protein Protects from Lethal SARS-CoV-2 Infection
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Background: Severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) uses full-length angiotensin converting enzyme 2 (ACE2) as the main receptor to enter the target cells. A novel soluble ACE2 protein with increased duration of action and binding capacity to exert a decay effect as a way to intercept SARS-CoV-2 from binding to membrane-bound ACE2 was generated. The protein was administered to a lethal mouse model of COVID-19 to examine its efficacy.

Methods: A soluble ACE2 variant fused with a 5kD albumin binding domain (ABD) was linked via a dimerization motif hinge-like 4-cysteine dodecapeptide to improve binding capacity to the SARS-CoV-2. This novel protein (ACE2 1-618-DDC-ABD) was administered intranasally and intraperitoneally prior to viral inoculation and on the following consecutive days. Injected animals were observed for weight, clinical score and mortality in a BSL-3 facility. Upon sacrifice, lung histopathology was evaluated, and viral loads were measured by plaque assay.

Results: Infected mice that received ACE2 1-618-DDC-ABD developed only moderate disease assessed by a clinical score, modest weight loss and lung histology. At 6 days, mortality was totally prevented in the treated group (figure), lung histopathology was markedly improved and viral lung and brain titers reduced or non-detectable. By contrast, in untreated animals, lung histology revealed extensive pulmonary alveolar hemorrhage and mononuclear infiltrates, and they all became severely ill and had to be euthanized by day 6/7 (figure).

Conclusions: This study demonstrates for the first time in vivo the preventative/therapeutic efficacy of a soluble ACE2 protein in a preclinical animal model.

Funding: Private Foundation Support

SA-OR02
Selective Tropism of SARS-CoV-2 in Genome-Edited Kidney Organoids Reveals Nephropathic and Therapeutic Effects
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Background: Kidneys are critical target organs of SARS-CoV-2 infection and COVID-19 disease, but whether renal effects are due to direct infection via ACE2 or indirect damage to other organs is unknown. The added risk of pre-existing polycystic kidney disease and efficacy of proposed therapeutics are not yet clear and difficult to assess in patients, animals, or cells. Organoids provide a gene editable platform to assess SARS-CoV-2 kidney infection and its tropism, pathophysiology, and effects of COVID-19 therapeutics.

Methods: Kidney organoids were differentiated from control, PKD-, or ACE2- stem cells, and infected with WA1/2020 SARS-CoV-2 α mNeonGreen transgene. Organoids were infected under BSL3 conditions with supernatant collected for plaque assays and analyzed with immunofluorescence or RNA extraction. Remdesivir was added post infection, or de novo designed LCB1 Spike binder pre-incubated with SARS-CoV-2 prior to infection.

Results: SARS-CoV-2 specifically infected organoid proximal tubules, producing bulbous cells with disrupted markers. In ACE2- kidney organoids, viral replication was reduced by 85%. In PKD- organoids, cyst-lining epithelial cells were infected at comparable levels to healthy controls. Remdesivir treatment reduced viral replication by 71.4%, Pre-incubation of LCB1 spike binder peptides prevented viral replication at a 0.5 μM and significantly reduced detectable SARS-CoV-2 infection.

Conclusions: Proximal tubular kidney epithelium is susceptible to SARS-CoV-2 infection. ACE2 is the primary entry receptor for SARS-CoV-2 infection, but alternate pathways facilitate low levels of infection. PKD cysts can be infected comparably to normal kidneys to SARS-CoV-2 and the effectiveness of current and developing therapeutics for treating COVID-19.

Funding: Other U.S. Government Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-OR05

**Immunological Response in Dialysis and Kidney Transplant Patients with SARS-CoV-2 Infection**

**Stefania Affatato,1 Federica Mescia,1 Virginia Quaresima,2 Chiara Fiorini,2 Mario Gaggiotti,2 Nicola Bossini,2 Paola Gaggia,2 Raffaele Badolato,1 Luigi D. Notarangelo,1 Marco Chiariini,2 Francesco Scolari,1 Federico Alberici.1
1Università degli Studi di Brescia, Brescia, Italy; 2Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia, Brescia, Italy; 3National Institute of Allergy and Infectious Diseases Laboratory of Clinical Immunology and Microbiology, Bethesda, MD.**

**Background:** Mortality for COVID-19 in dialysis (HD) and kidney transplant (TX) patients (pts) is 30%. In these pts the immunology of the disease has been poorly explored.

**Methods:** 32 HD or TX pts hospitalized for COVID-19 (COV), of which 13 with benign course (PosCOV) and 19 who died or developed ARDS (NegCOV), 10 controls (HC) and 12 HD/TX without COVID-19 (PC), have been included. Lymphocytes subsets, dendritic cells (DC) and monocytes activation (MA) have been explored.

**Results:** COV showed lower counts of CD4+, CD8+, CD56+, CD19+, DC and higher counts of terminally differentiated CD19+ compared to HC and PC; CD4+, CD8+, CD19+ and MA were significantly lower in NegCOV than PosCOV. Compared to HD, TX showed lower CD56+, pDC and MA.

**Conclusions:** The COV group showed immunological alterations compared to HC and PC with deeper alterations of the innate immune system in TX pts with COVID-19.

### SA-OR06

**Immune Monitoring of Kidney Transplant Recipients After SARS-CoV-2 mRNA Vaccination**

**Ayman Al Jurdi,1,2 Rodrigo Benedetti Gassen,1 Thiago J. Borges,1 Frank E. Hulickes,1 Isadora T. Lape,1 Orhan Efe,1,2 Areej saud a Alghamdi,3 Poojan Patel,1 John Y. Choi,1 Zhabiz Solhjou,1 Camille Kotton,1 Jamil R. Azzi,1 Leonardo V. Riella.1 1Massachusetts General Hospital, Boston, MA; 2Brigham and Women’s Hospital, Boston, MA; 3Boston Children’s Hospital, Boston, MA.**

**Background:** There is limited data on the safety and efficacy of SARS-CoV-2 mRNA vaccines in kidney transplant recipients (KTRs).

**Methods:** We conducted a prospective, multi-center study of 58 adult KTRs receiving mRNA-BNT162b2 or mRNA-1273 vaccines to assess vaccine safety and efficacy. Primary outcome was biopsy-proven rejection within 3 months of vaccination. Secondary outcomes included adverse events, serum creatinine, proteinuria, donor-derived cell-free DNA (ddcDNA) levels, and antibody and cellular immunity generation against SARS-CoV-2.

**Results:** Median age was 62 with 41% females. Median time post-transplantation was 48 months. Only one patient (2%) developed acute cellular rejection though patient had been recently converted to belatacept. There were no severe adverse events or deaths during follow-up. Two patients (3%) developed SARS-CoV-2 infection, one of whom required hospitalization. There was no significant change in serum creatinine, proteinuria or ddcDNA during the study. Following vaccination, 36%, 25% and 20% of KTRs developed anti-spike, anti-S1 and anti-RBD antibodies. 100% of KTRs with anti-spike and anti-RBD antibodies had a neutralizing response, compared to 44% in KTRs with anti-spike but without anti-RBD antibodies (RR 2.25, 95% CI 1.08-4.67). There was a significant increase in IFN-gamma spots per 10^6 PBMCs incubated with S1 peptides following vaccination (p=0.0143).

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: SARS-CoV-2 vaccination in KT recipients was safe and associated with the generation of cellular immune response and in a third of patients with anti-spike antibody response. The degree of protection gained by these responses needs to be evaluated in future studies.

SA-OR07

SARS-CoV-2 Vaccine Impact on COVID-19 Incidence in Maintenance Dialysis Patients

Edward K. Lacson,1,2 Harold J. Manley,1 Gideon N. Aweh,3 Vladimir Ladik,4 Jill M. Frantzen,2 Caroline M. Hsu,3 Dana Miskuln,2 Daniel E. Weiner,2 Doug Johnson.1

1Dialysis Clinic Inc, Nashville, TN; 2Tufts Medical Center, Boston, MA.

Background: Maintenance dialysis patients are highly susceptible to SARS-CoV-2 and historically, when infected, >60% need emergency department or hospital care and mortality approaches 20% in 90 days. We evaluated the impact of vaccination against SARS-CoV-2 on incident COVID-19 cases in dialysis patients from 260 clinics in 28 states.

Methods: All adult maintenance dialysis patients without prior COVID-19 treated by Dialysis Clinic, Inc. who received one dose of vaccine were classified as “partially vaccinated” and at 14+ days after completing the manufacturer recommended series were classified as “fully vaccinated”; else were “unvaccinated”. During the study period from 2/1/21 to 5/9/21, all new test-confirmed COVID-19 cases were documented. Every day at-risk for each patient was assigned to vaccination status and contributed to the denominator. Case rates per 10,000 days at-risk were compared using logistic regression.

Results: Among 13,717 eligible patients contributing 1,426,187 days at-risk, 327 new COVID-19 occurred. Only 4% were in fully vaccinated patients, with 25% in partially vaccinated and 70% in unvaccinated patients. Unvaccinated patients had 10-fold higher risk COVID-19 than fully vaccinated patients. Only 3 of 13 (23%) unvaccinated patients were symptomatic, and 1 of 13 (8%) was hospitalized for COVID-19. In contrast, 67 (29%) of unvaccinated and 34 (40%) of partially vaccinated patients were hospitalized for COVID-19, with 6 and 2 deaths, respectively.

Conclusions: Overall incidence of COVID-19 declined compared to rates prior to the study period. Regardless, there is marked risk reduction of incident COVID-19 for SARS-CoV-2 vaccinated maintenance dialysis patients, and most breakthrough infections were asymptomatic in fully vaccinated patients. These preliminary results support aggressive vaccination and a plan for maintenance of immunity to alleviate the devastating COVID-19 toll for dialysis patients.

COVID-19 Incidence from 2/1/21 to 5/9/21

<table>
<thead>
<tr>
<th>State</th>
<th># Unique Persons</th>
<th>Patients Days at Risk</th>
<th>Patients w/ COVID-19</th>
<th>AKI failure stages (OR 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fully Vaccinated</td>
<td>6744</td>
<td>962,089</td>
<td>13</td>
<td>0.3</td>
</tr>
<tr>
<td>Partially Vaccinated</td>
<td>1,112</td>
<td>966,121</td>
<td>84</td>
<td>2.3</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>904</td>
<td>656,972</td>
<td>250</td>
<td>5.4</td>
</tr>
</tbody>
</table>

* Mutually exclusive status at the end of follow-up (may have contributed time-at-risk in other statuses).

SA-OR08

Genetic Findings in COVID-19-Positive Patients from a Cohort of Kidney and Liver Patients at Columbia University


Background: Patients with preexisting chronic kidney (CKD) and liver disease and liver are more at risk from COVID-19, but reasons for variability in disease susceptibility and severity is still poorly understood. Given the high infection rate in New York City, we conducted a COVID-19 assessment survey in a cohort of CKD and liver patients previously consented into genetic studies.

Methods: Between March and August 2020, we completed 1601 unique IRB-approved COVID-19 assessment surveys. The survey covered COVID-19 symptoms, exposure risk, PCR and/or serology testing, and hospitalization. 298 of those patients were exome sequenced. We analyzed differences in COVID-19 PCR, serology and hospitalization rate and genetic analysis to identify possibly associated variants in the immune/coagulation pathways, suggested to be involved in COVID-19 susceptibility/severity by recent publications. We also analyzed variants based on the American College of Medical Genetics and Genomics (ACMG) guidelines for clinical annotation of genetic results.

Results: Among Hispanic/Latino patients were more likely to have a positive COVID-19 PCR (Fisher Exact Test p: 0.01, 29.5% vs 16.7%), serology (Fisher Exact Test p: 0.02, 22.9% vs 9.7%) and hospitalization (Fisher Exact Test p: 0.01, 29.5% vs 16.7%). Patients with glomerulopathy had lower positive COVID-19 PCR tests (Fisher Exact Test p: 0.01, 14.7% vs 48.7%). Analysis of exome data identified an excess number of rare variants in genes in the immune dysregulation pathways among patients with positive COVID-19 PCR test, (fisher p: 0.01, 75% vs 18%). These results were mostly driven by rare variants in CASP10, which were more common among the Hispanic/Latino population.

Conclusions: We confirm that Hispanic/Latino ethnicity is a significant risk factor for positive COVID-19 PCR, serology and hospitalization. The analysis of the genetic mechanisms in immune/coagulation pathways identified an excess of rare variants in the CASP10 gene, results that overlap with Hispanic/Latino ethnicity.

SA-OR09

APOL1 Risk Variants, AKI, and Death in Black Veterans with COVID-19

Adriana Hung,1,2 Shalija C. Shah,2,3 Alexander Bick,1,2 Zhihong Yu,1,2 Hua-Chang Chen,2,3 Ran Tao,1,2 Elvis A. Akwo,2,3 Cecilia P. Chung,2,3 Michael E. Matheny,2,3 Katalin Susztak,1 Cassianne Robinson-Cohen,2,3 Sony Tutera,4 Edward D. Siew.5 Million Veteran Program,1 Vanderbilt University Medical Center, Nashville, TN; 2Vanderbilt University, Nashville, TN; 3University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; 4University of California San Diego, La Jolla, CA; 5San Diego VAMC, San Diego, TN.

Background: Health disparities exist in rates of acute kidney injury (AKI) and death related to COVID-19. Black patients with two copies of apolipoprotein L1 (APOL1) variants G1 or G2 have significantly increased rates of renal disease. It is unknown whether APOL1 is associated with an increased risk for AKI in COVID-19 infection.

Methods: We performed a retrospective study of 996 Black patients in the VA Million Veteran Program hospitalized with COVID-19 between March 2020 and January 2021. The primary exposure was having 2 APOL1 risk variants (APOL1 high-risk group), compared to having 1 or 0 risk variants (APOL1 low-risk group). The primary outcome was AKI. The secondary outcomes were AKI severity stages and death. We performed a subgroup analysis in individuals with eGFR < 60 ml/min/1.73m2.

Results: 392 (39.6%) patients developed AKI, 28 (7%) required dialysis and 122 (12.3%) died. Patients categorized as APOL1 high-risk group had a significantly higher risk of AKI (adjusted odds ratio [OR] 1.98; 95% confidence interval [CI]: 1.29-3.65; p=0.002), higher AKI severity stages (OR 2.06; 95% CI: 1.39-3.04; p<0.001) and death (OR 2.15; 95% CI: 1.23-3.67; p=0.006). The association with AKI persisted in the subgroup with normal kidney function (OR 1.92; 95% CI: 1.15-3.22; p=0.01). Figure 1 shows the proportion of patients by AKI stages according to APOL1 risk group.

Conclusions: APOL1 renal risk variants were associated with higher risk of AKI, AKI severity, and death in Black Veterans hospitalized with COVID-19, even amongst individuals with prior normal kidney function. We identify a specific genetic contribution to COVID-19 health disparities.

Funding: Veterans Affairs Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
SA-OR10
Neutrophil Extracellular Traps and Endothelial Injury in COVID-19 Associated AKI
Naomi Pode shakked,1, 2 Brandon M. Henry,1 Stefanie W. Benoit,1, 2 Cincinnati Children's Hospital Medical Center, Cincinnati, OH; 2University of Cincinnati College of Medicine, Cincinnati, OH.

Background: Neutrophil Extracellular Traps (NETs) release has been implicated in the pathomechanism underlying severe end-organ damage in COVID-19. While NETs are difficult to measure, cell free DNA (cfDNA) has been shown to be a surrogate measure for NETosis. The aim of this study was to determine whether circulating levels of cfDNA may be associated with development of acute kidney injury (AKI) in COVID-19.

Methods: Blood samples were collected prospectively in the emergency department from adult patients admitted to the hospital with COVID-19. cfDNA levels and serum biomarkers of AKI, thrombotic microangiopathy, and inflammation were correlated, as well as development of severe AKI defined by KDIGO ScCr Stages 2+3 and need for renal replacement therapy (RRT).

Results: 361 patients have enrolled, median age 50.5 years (IQR 41-66). Age, race, coronary artery disease, heart failure, chronic kidney disease, and chronic liver disease were associated with severe AKI, while hypertension was protective. cfDNA levels were higher in those who developed severe AKI (p<0.01) and needed RRT (p=0.020) during hospitalization. cfDNA positively correlated with ScCr, NGAL, cystatin C, neutrophil count, neutrophil-to-lymphocyte ratio, C5a, C5a, Scb5-9, IL-6, IL-8, IL-10, TNF-α, LDH, CRP, ferritin, fibrinogen, and negatively correlated with ADAMTS13/VWF ratio and lymphocyte count. In the multivariable logistic regression model adjusted for age, comorbidities and ScCr, one unit increase in cfDNA value was associated with a 4.6% increased odds of severe AKI (OR=1.046; p=0.040). Diagnostic performance of cfDNA is shown in Table 1.

Conclusions: Intravascular NETosis could be an important factor in development of microthrombosis and COVID-19 associated AKI. Further research is urgently needed to understand the role of NETosis in COVID-19 and evaluate therapeutic avenues.

Diagnostic Performance of cfDNA for COVID-19 AKI

<table>
<thead>
<tr>
<th>cfDNA (ng/ml)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>AUC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150</td>
<td>0.82</td>
<td>0.86</td>
<td>0.83 (0.76-0.89)</td>
</tr>
<tr>
<td>≥150</td>
<td>0.60</td>
<td>0.97</td>
<td>0.76 (0.54-0.98)</td>
</tr>
</tbody>
</table>

SA-OR11
Identification of Molecularly Distinct Sub-phenotypes in AKI and Association with Long-Term Clinical Outcomes
Pavan K. Bhattacharya,1 David K. Prince,1 Sherry Mansour,1 Talat Alp Ikizler,1 Edward D. Siew,1 Amit X. Garg,4 Alan S. Go,3 James S. Kaufman,5 Paul L. Kimmel,1 Steven G. Coca,2 Chirag R. Parikh,4 Mark M. Wurfel,4 Jonathan Himmelfarb,1 1University of Washington, Seattle, WA; 2Yale University, New Haven, CT; 3Vanderbilt University, Nashville, TN; 4Western University, London, ON, Canada; 5University of California San Francisco, San Francisco, CA; 6New York University, New York, NY. The George Washington University, Milken Institute of Public Health, Washington, DC; 7Mount Sinai Health System, New York, NY; 8Johns Hopkins University, Baltimore, MD.

Background: AKI is a heterogeneous clinical syndrome with varying causes, pathophysiology and diverse clinical outcomes; however, staging AKI by serum creatinine does not fully capture underlying patient heterogeneity. Our goal was to identify AKI sub-phenotypes more tightly linked to underlying pathophysiology and long-term clinical outcomes.

Methods: We independently applied latent class analysis (LCA) and k-Means clustering to 29 clinical, plasma and urinary biomarker data measured during hospitalization to identify AKI sub-phenotypes in the ASSES-SAKI study. AKI sub-phenotype associations were examined with the composite of major adverse kidney events (MAKE), defined as incident or progressive chronic kidney disease, long-term dialysis, or all-cause death during study follow-up.

Results: Among 769 AKI patients both LCA and k-Means clustering identified two AKI sub-phenotypes. Class 1 was characterized by a higher prevalence of prior congestive heart failure and favorable blood inflammatory and urinary tubular injury biomarkers, while class 2 was characterized by higher rates of prior chronic kidney disease and less favorable biomarkers. After a median follow-up of 4.7 years, the risk for MAKE was higher with class 2 (HR 2.19; 95% CI, 1.08 to 1.84) compared with class 1 adjusting for demographics, hospital level factors and KDIGO Stage of AKI. The higher risk of MAKE among class 2 was explained by a higher risk of chronic kidney disease progression and dialysis.

Conclusions: In this analysis, we identify two molecularly distinct AKI sub-phenotypes with differing risk of long-term outcomes, independent of current criteria to risk stratify AKI. Future identification of AKI sub-phenotypes may facilitate linking therapies to underlying pathophysiology to prevent long-term sequelae after AKI.

Funding: NIDDK Support

SA-OR12
Association of Mild-to-Moderate AKI with CKD Progression Among Individuals with CKD: The CRIC Study
Ananth Garg,1 Adam X. Huang,2 Jesse Y. Hsu,1 Kathleen D. Liu,1 Paul E. Drewa,3 Ana C. Ricardo,4 James P. Lash,4 Jonathan J. Talerico,5 Edward J. Horwitz,6 James H. Sondheimer,7 Jing Chen,1 Jiang He,8 Lawrence J. Appet,9 Alan S. Go,9 Chi-yuan Hsu,10 University of California San Francisco, San Francisco, CA; 11University of Pennsylvania, Philadelphia, PA; 2Regents of the University of Minnesota, Minneapolis, MN; 3University of Illinois at Chicago, Chicago, IL; 4Cleveland Clinic, Cleveland, OH; 5The MetroHealth System, Cleveland, OH; 6Wayne State University School of Medicine, Detroit, MI; 7Tulane University School of Medicine, New Orleans, LA; 8Kaiser Permanente, Oakland, CA; 9Johns Hopkins Medicine, Baltimore, MD.

Background: Observational studies have suggested that even mild episodes of AKI have a large effect on accelerating CKD progression (EJ See et al 2019:95:160-172). These seem consistent with clinical trials in which reducing AKI rate did not translate into reducing CKD risk (AX Garg et al JAMA 2014: 311:2191-8, SG Coca et al JASN 2016: 27: 2529-42). These differences may be due to incomplete control of important confounders such as proteinuria since proteinuria is both a strong risk factor for development of AKI and CKD progression.

Methods: To better address potential residual confounding, including confounding by pre-AKI proteinuria and pre-AKI eGFR slope, we quantified the independent association between an episode of mild-to-moderate AKI (identified using inpatient ScCr measurements and staged using KDIGO guidelines) on eGFR trajectory (defined using outpatient research protocol measurements) in the prospective Chronic Renal Insufficiency Cohort (CRIC).

Results: Mean age of the 3150 CRIC participants included was 65 years, 44% were female, and 43% self-identified as Black. Mean baseline eGFR was 50 mL/min/1.73m2, median urine protein-Cr ratio was 0.1g/g, and 54% had diabetes. 433 participants experienced least one episode of AKI (68% stage 1, 24% stage 2). In linear mixed effects models, after controlling for demographics, pre-AKI proteinuria, pre-AKI eGFR slope, and time-updated diabetes mellitus, heart failure, SHP, and receipt of ACE-I/ ARBs, an episode of AKI was not significantly associated with eGFR change (difference in mean eGFR at year 1 = -0.7 mL/min/1.73 m2, 95% CI -2.7 to 1.2 mL/min/1.73 m2 95%, p=0.40). There was no detectable change in eGFR slope from before to after AKI (difference in eGFR slope = 0.1 mL/min/1.73 m2 per year) (p=0.82 and 95% CI -0.7 to 0.8 mL/min/1.73 m2 per year).

Conclusions: Prior observational studies showing an association between mild-to-moderate AKI and CKD progression may be exaggerated due to residual confounding. After accounting for key potential confounders hitherto not considered in published analyses, mild-moderate AKI was not independently associated with an absolute drop in eGFR nor eGFR slope after AKI.

Funding: NIDDK Support

SA-OR13
Evidence for Kidney Involvement in an Acute Graft vs. Host Disease Model of Allogeneic Stem Cell Transplantation (HSCT) in Non-Human Primates
Sangeeta R. Hingorani,1 Edgar A. Jaimes,2 Thangamani Muthukumar3, Surya V. Seshan,3 1Well Cornell Medicine, New York, NY; 2Seattle Children’s Hospital, Seattle, WA; 3Memorial Sloan Kettering Cancer Center, New York, NY.

Background: Kidney injury is increasingly recognized as a significant cause of morbidity and mortality in recipients of HSCT. The frequency of kidney injury can be as high as 73% and among patients with kidney injury who require dialysis, mortality
approaches 100%. Acute graft-versus-host disease (aGVHD) has emerged as an important risk factor for acute kidney injury (AKI) in HSCT patients but whether the kidney itself is a target of aGVHD has not been established. In this study and utilizing a non-human primate model of HSCT we tested the hypothesis that the kidney undergoes inflammatory changes consistent with aGVHD.

Methods: For this study we used a non-human primate (NHP) model of allogeneic HSCT (allo-HCT) and aGVHD, in which a donor graft is transplanted into MHC haploidentical recipients pre-conditioned with myeloablative total body irradiation. Transplant recipients received no post-transplant immunosuppression, which enabled interrogation of the natural history of aGVHD. Apheresis was performed after G-CSF mobilization and an unmanipulated G-CSF mobilized apheresis product was transplanted into MHC haplo-identical transplant recipients in the allo-HCT cohort (N=3). As controls we used normal animals that did not undergo any intervention (N=4). NHP were euthanized on day 28 following transplantation and kidneys saved for histology and IHC (CD3, CD20, CD68, CD56 and Granmye B).

Results: As expected control kidneys had normal renal histology. In contrast, kidneys from allo-HCT recipients had evidence of mesangioapathy and tubulitis. By IHC we determined increased expression of CD68+ monocyte lineage cells, Granmye B+ cytotoxic T lymphocytes and CD3+ T lymphocytes. There was no difference in the expression of CD3+ NK cells while the number of CD20+ B lymphocytes was lower in allo-HCT as compared to controls.

Methods: We performed 21 minutes IRI of the left kidney followed by abdominal imaging window implantation for serial imaging of the same tissue at 1 h and day 1, 2, 3, 4, 7, 14 and 21 after IRI. Cyc11-GFP reporter mice identified proliferating cells by GFP-expression in S62-M cell cycle-stages.

Results: Necrotic tubular cell death, as detected by Propidium Iodide (PI)-staining, was primarily observed 1 h post IRI and mostly affecting PPs with 10±1.4%. 12±3.8% and 1.9±0.8% PI-positive nuclei per S1, S2 and distal tubule (DT)/collecting duct (CD) segments (Mean±SEM, n=8 each). From day 1, injured PPs shedded brushborder contents, which correlated with epithelial flattening and onset of proliferation (p<0.002, r²=0.39). Tubular proliferation started day 1, peaked day 3 and was highest in S2 segments with 2.7±2%, 12.4±8.7% and 0.3±0.9% (Mean±SEM, n=8 each) of GFP-positive nuclei per S1, S2 and DT/CD segments (p<0.02, vs. S2 and p<0.001 for S2 vs. DT/CD). While in S1 segments proliferation derived mainly from surviving cells in immediate proximity to PI-positive cells, in S2 segments also cells further distant from injured sites proliferated. We observed shedded cytosolic content from injured PT regions flowing downstream into previously PI-negative PPs, which spatially coincided with their proliferation one day after the appearance of shedded material in the lumen. By day 4, several PT segments revealed severe cast formation and epithelial vacuolization with nuclear karyolysis. 75% of the vacuolized tubule population reached full recovery before day 14 post IRI, while the remaining 25% failed to recover, resulting in nephron loss.

Conclusions: This is the first study to track IRI-induced injury and regeneration in the same renal cells over time. Our data uniquely links initial tissue damage to regenerative capacity of the renal PT in AKI and suggests distinct mechanisms for initiation of PT proliferation in S1 and S2 segments.

Funding: Private Foundation Support

SA-OR15 Genetic Validation of Hdac8 as a Therapeutic Target for AKI Neil A. Hukriede,1 Rachel Delgado,2 Aneta J. Przepiorski,2 Michael D. McDaniels,1 Mark P. DeCaestecker.1 1University of Pittsburgh, Pittsburgh, PA; 2Vanderbilt University Medical Center, Nashville, TN.

Background: We previously identified 4-phenylthiobutanoid acid (PTBA), which enhances intrinsic repair and regeneration of kidney tissue in multiple models of AKI, and showed that histone deacetylase 8 (Hdac8) is a target of PTBA. Here, we show that loss of genetic deactivation of Hdac8 protects against AKI in zebrafish, human kidney organoid and mouse models, and that Hdac8 mediates the efficacy of PTBA.

Methods: Hdac8-/- mice and wild type zebrafish were injected with gentamicin to induce aGVHD and measured aGVHD severity by Udj, H2AX, and TUNEL staining, respectively. Tamoxifen treated male UB-CRERT2; Hdac8fl/fl (Hdac8 KO) were evaluated over 28 days after severe ischemia reperfusion AKI (IR-AKI) in a mouse model of fibrinogen (GFF) and Sirius red staining for fibrosis. Hemin treated Hdac8 KO human kidney organs were evaluated for injury and inflammatory markers.

Results: Hdac8-/- zebrafish had enhanced survival after AKI compared to wild type controls associated with increased tubular cell proliferation, γH2AX expression, and reduced apoptosis. In mice, Hdac8-/- KO reduced fibrosis in the outer medulla, and organoids showed a suppression of inflammatory markers.

Conclusions: Loss of Hdac8 reduced severity of injury and improves repair in models of AKI. Studies in Hdac8-/- mutants using sub-therapeutic doses of UPHD25 indicate that PTBA efficacy is mediated in AKI via Hdac8. Increased γH2AX expression from ischemia-reperfusion aGVHD after treatment with HDAC8 inhibitor zebrashell peptides suggests that HDAC8 inhibitor therapy may be beneficial in aGVHD.

Funding: NIDDK Support

SA-OR16 Loss of Proximal Tubular Krippel-Like Factor 1 is in Kidney Injury Is Essential for Detrimental Thrombus Assembly and AKI Progression Sian Pret, Ahmed A. Attallah, Yiqing Guo, Nehaben A. Gujarati, Sandeep K. Mallipatui. Stony Brook University, Stony Brook, NY.

Background: Loss of fatty acid oxidation in the proximal tubule (PT) is a critical mediator of acute kidney injury (AKI) and eventual fibrosis. The transcription factor PPARα is a key regulator of fatty acid oxidation (FAO); however, Ppara knockout mice do not have kidney injury at baseline, suggesting that other important regulators remain to be described. Krippel-like factor 15 is expressed in PT, downregulated in AKI, and while PPARα regulates FAO in cardiomyocytes. Our aim was to investigate the role of PT KLF15 in AKI and fibrosis.

Methods: PT-specific Klf15 knockdown (Klf15PTKO) mice were generated by breeding Klf15-/- and Ppcre-Cre mice. Kidney injury was induced using the PT-specific DNA damaging agent aristolochic acid I (AAI) or by ischemia-reperfusion (IR). Blood was collected for serum biochemistry, and kidneys harvested for histological and immunofluorescence analyses. Chromatin immunoprecipitation (ChIP) studies were undertaken to detect binding of KLF15 to FAO gene promoters. Primary PT cells were harvested from Klf15-/- mice and Klf15 knocked out by infection with adenovirus-Cre (control – adenovirus-GFP), followed by qRT-PCR analysis and live cell metabolic assays using a Seahorse bioanalyzer. Gene expression and eGFR data for human CKD patients in Nephroseq were utilized for correlation analyses.

Results: PT KLF15 expression was downregulated in response to injury in control mice. Klf15PTKO mice subjected to AKI using AAI or IR had significantly worse injury than Klf15-/- mice, as assessed by higher serum creatinine and urea nitrogen levels, exacerbated histopathological features, more extensive loss of mature PT brush borders, and increased fibrosis compared to control-treated mice. Klf15 knockout mice showed binding of KLF15 to the promoters of genes encoding key FAO enzymes CPT1A and ACA2A. Knockdown of Klf15 in primary PT cells resulted in decreased expression of Ppara, Cpt1a and Aca2. Live cell metabolic assays demonstrated that loss of Klf15 compromised PT cellular metabolism, particularly the ability to utilize palmitate in FAO. KLF15 expression was negatively correlated with eGFR and PHAR expression in human kidney biopsies with CKD.

Conclusions: PT KLF15 is a key regulator of FAO, and loss of KLF15 in kidney injury is detrimental through compromised FAO.

Funding: NIDDK Support, Veterans Affairs Support

SA-OR17 Single-Cell Transcriptomics Reveal Pyroporopiosis and Ferroptosis Inhibition Ameliorate Maladaptive AKI-to-CKD Progression and Repair in Immune Perturbed PTPA. Michael S. Balzer,1 Tomohito Doki,2 Ziyuan Ma,1 Matthew Palmer,2 Katalin Susztak,1 Susztak Lab 1Institute for Diabetes, Obesity and Metabolism, UPenn, Philadelphia, PA; 2Department of Pathology and Laboratory Medicine, UPenn, Philadelphia, PA.

Background: Following acute kidney injury (AKI) renal repair is possible to a certain extent. However, maladaptation to AKI leads to progression towards chronic kidney disease (CKD). Unwiring the incompletely understood processes driving both progression and repair might identify therapeutic targets to halt or reverse AKI-to-CKD progression.

Methods: Here we profiled transcriptomic changes at single-cell level over time in acutely injured kidneys of mice subjected to mild and severe bilateral ischemic reperfusion injury (IRI), modeling repair and maladaptation, respectively. Kidney function, structure, bulk and single-cell gene expression analyses were performed 1, 3 and 14 after ischemia.

We used motif enrichment, trajectory, drug response pattern and cell-cell interaction analyses to define key drivers of failed and successful regeneration, finally informing in vivo experiments with 2 small molecules effectively ameliorating maladaptation.
Results: Long bilateral ischemia resulted in sustained renal failure (1-4d) and severe renal dysfunction lasting at least 14d (URID). AKI patients are at more than twice the increased risk of progressive CKD that leads to excessive morbidity and mortality. Understanding the mechanisms by which AKI progresses to CKD is essential for establishing a new therapeutic target since no established therapy to date is available. Peritubular capillary beds are significantly damaged during many types of AKI, which is closely associated with the renal IRI and progression. Vascular endothelial growth factor (VEGF) is a well-defined angiogenic factor via its major receptor, VEGF receptor 2 (VegfR2). We also demonstrated that inhibition of pyroptosis (VX765) and ferroptosis (lipoxstatin) in vivo normalized single-cell transcriptomic kidney signatures despite severe IRI.

Conclusions: Using single-cell transcriptomics we reveal pyroptosis and ferroptosis as key druggable pathways of a detrimental PT signature associated with maladaptation to AKI and progression towards CKD, which was driven by TFs typically active in myeloid cells and characterized by an epithelial-to-immune phenotype switch.

Funding: NIDDK Support, Government Support - Non-U.S.

SA-OR18

VEGF-R2 Signaling in Renal Interstitium Exacerbates Post-AKI CKD Progression

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Background: A dire consequence of acute kidney injury (AKI) is progression to chronic kidney disease (CKD). AKI patients are at more than twice the increased risk of progressive CKD that leads to excessive morbidity and mortality. Understanding the mechanisms by which AKI progresses to CKD is essential for establishing a new therapeutic target since no established therapy to date is available. Peritubular capillary beds are significantly damaged during many types of AKI, which is closely associated with the renal IRI and progression. Vascular endothelial growth factor (VEGF) is a well-defined angiogenic factor via its major receptor, VEGF receptor 2 (VegfR2).

Methods: We generated genetic mouse models for renal stromal cells (RSCs)-specific loss-of-function of VEGF-R2 with constitutively expressed Foxd1-Cre (VegfR2lox/lox) as well as tamoxifen inducible Foxd1-Cre (VegfR2lox/lox) to interrogate timing specific role of VegfR2 in renal interstitial cells in AKI-to-CKD. AKI/CKD models induced either by a renal ischemia/reperfusion injury (IRI) model or by low/dose repeated treatment of cisplatin were performed. Mice are monitored for the development of AKI and post-AKI CKD using serum chemistries and tissue analysis. Renal blood flow was evaluated with arterial spin labeling MRI (ASL-MRI).

Results: We found that VegfR2lox/lox mice have (I) reduced vascular injury and better blood flow post AKI, (II) are protected against AKI, and (III) have reduced AKI-to-CKD progression after renal IRI. Consistently, VegfR2lox/lox are protected against progression to CKD in a cisplatin AKI-to-CKD model. Mechanistically, it appears that the VegfR2lox/lox mice downregulate a maladaptive proliferation factor for pericytes, Thrombospondin-1 (TSP1). AKI triggers enhanced differentiation of a subpopulation of CD31+ Foxd1+ cells, presumably caused by partial endothelial-mesenchymal transition (Endo-MT). Furthermore, VegfR2lox/lox mice are significantly protected against renal IRI.

Conclusions: These data suggest that VegfR2 signaling in renal interstitial cells exacerbates renal IRI and its post-AKI CKD progression as well as cisplatin AKI.

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Results: Post-ischemic inactivation of EC-Phd3 or EC-Phd2 failed to protect kidneys based on mRNA expression of kidney injury molecule 1 (Kim1) and profibrotic genes lysyl oxidase-like 2 (Loxl2), transforming growth factor-beta 1 (Tgfβ1), and smooth muscle actin (Acta2) and histopathological analysis (n=7-8). Surprisingly, the inactivation of EC-Phd3 following IRI exacerbated kidney damage and fibrosis as indicated by increased expression of Kim1, Tgfβ1, and Acta2 and deposition of collagen (n=6-8, p<0.05). Likewise, post-ischemic concurrent deletion of EC-Phd3.23 increased kidney damage and fibrosis assessed by histopathological analysis and increased expression of profibrotic genes and collagen deposition (n=7-8, p<0.05), respectively, compared to Cre-controls. These changes were associated with significant worsening of renal function assessed by blood urea nitrogen level and transdermal GFR measurements (n=7, p<0.05). scRNA-seq data of the EC-Phd323 post-ischemic kidneys showed significant transcriptional alterations in the EC cluster compared to Cre-controls with prominent changes in metabolic genes. Significant transcriptional changes were also observed in tubular, fibroblast, and inflammatory cell clusters between the two genotypes.

Conclusions: Post-ischemic concurrent inactivation of Phd3, 2 and 3 significantly impaired renal function, induced fibrosis which was mainly driven by EC-Phd3 inactivation. We delineated a critical role for EC-Phd3 in post-ischemic AKI repair.

Funding: NIDDK Support

SA-OR21

Fibronectin and Kidney Outcomes in Patients with CKD and Type 2 Diabetes: Results from FIGARO-DKD

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Background: In the FIGARO-DKD trial, fibronectin reduced the risk of kidney outcomes in patients with predominantly advanced chronic kidney disease (CKD) and type 2 diabetes (T2D). FIGARO-DKD investigated the effects of fibronectin in patients with less advanced CKD and T2D. The primary outcome of FIGARO-DKD was a cardiovascular composite; here we report the secondary kidney outcomes.

Methods: FIGARO-DKD (NCT02545093) was a randomized, double-blind, placebo-controlled phase III trial. Patients with T2D, urine albumin-to-creatinine ratio (UACR) ≥300 mg/g estimated glomerular filtration rate (eGFR) ≥25-90 mL/min/1.73 m² or UACR ≥5000 mg/g and eGFR ≥60 mL/min/1.73 m², optimized renin-angiotensin system blockade, and screening serum potassium ≥4.8 mEq/L were randomized to fibronectin or placebo. The key secondary kidney outcome was an a≥40% composite time of kidney failure, sustained a≥40% eGFR decline from baseline, or renal death. Another similar kidney composite endpoint, excluding a sustained a≥40% eGFR decrease with a ≥57% decrease, and change in UACR from baseline to month 4 were pre-specified outcomes in the hierarchical testing strategy.

Results: In the 7352 patients included in the analysis, 62% of patients had baseline eGFR ≥60 mL/min/1.73 m² and 49% had baseline UACR <300 mg/g. Over a median follow-up of 3.4 years, 350 (9.5%) patients treated with fibronectin and 395 (10.8%) patients with placebo had a ≥40% eGFR composite endpoint event (hazard ratio [HR]=0.87, 95% confidence interval [CI] 0.76–1.01; p=0.069). There was a clinically meaningful prolongation of the time to the 57% eGFR composite endpoint with fibronectin (HR=0.77, 95% CI 0.65–0.87). Overall, the incidence of adverse events were similar between treatment arms.

Conclusions: In FIGARO-DKD, patients with stage 1–4 CKD and T2D, fibronectin induced a pronounced reduction in albuminuria. Kidney composite outcomes observed were directionally similar to that seen among patients with more advanced kidney disease in the FIGARO-DKD trial.

Funding: Commercial Support - Bayer AG

SA-OR22

Fibronectin in Patients with CKD and Type 2 Diabetes by SGLT-2i Treatment: The FIDELITY Analysis

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Background: The aim of the FIDELITY analysis is to evaluate the efficacy and safety of fibronectin, a novel, nonsteroidal, selective mineralocorticoid receptor antagonist, across the spectrum of patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) in the FIDELIO-DKD and FIGARO-DKD trials. Sodium-glucose co-transporter-2 inhibitors (SGLT-2is) are recommended for patients with CKD primarily to reduce the risk of CKD progression, thus their combined use with fibronectin is of interest. We report the pooled FIDELITY analysis of patients by SGLT-2i use.

Methods: This prespecified analysis combines patient-level data from the FIDELIO-DKD (NCT02540993) and FIGARO-DKD (NCT02545094) phase III, randomized, double-blind, placebo-controlled, multicenter clinical trials. Patients were randomized 1:1 to oral fibronectin or placebo. Patients had T2D and either a urine albumin-to-creatinine ratio (UACR) ≥30–500 mg/g and estimated glomerular filtration rate (eGFR) ≥25-90 mL/min/1.73 m², or UACR ≥5000 mg/g and eGFR ≥25 mL/min/1.73 m², with optimized renin-angiotensin system blockade. Efficacy outcomes included a cardiovascular (CV) composite endpoint of time to CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure, and a kidney composite endpoint of time to kidney failure, sustained ≥40% eGFR decline from baseline, or renal death.

Results: The FIDELITY analysis includes 13,026 patients. Approximately 7% of patients (n=977) received an SGLT-2i at baseline (fibronectin: 6.7% [n=438]; placebo: 7.0% [n=439]). Compared with placebo, fibronectin reduced the risk of a cardiovascular composite endpoint irrespective of SGLT-2i use at baseline (with SGLT-2i: hazard ratio [HR]=0.63, 95% confidence interval [CI] 0.40–1.00; without SGLT-2i: HR=0.87, 95% CI 0.79–0.96; p-interaction 0.41), additional findings for efficacy outcomes, in addition to overall safety and tolerability-related events by SGLT-2i treatment, will be presented in the DISCOVER study. We report the results of this prespecified analysis.

Conclusions: FIDELIO-DKD and FIGARO-DKD comprise the largest cardiorenal outcomes program to date; therefore, combining the data for the SGLT2i subgroup in the FIDELITY analysis may provide further insights into the effects of receiving both fibronectin and an SGLT-2i.

Funding: Commercial Support - Bayer AG

SA-OR23

Sodium-Glucose Cotransporter 2 Inhibitors as Adjunct Therapy for Type 1 Diabetes and the Benefit on Cardiovascular and Renal Disease Evaluated by Steno Risk Engines

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Background: Sodium–glucose cotransporter 2 inhibitors (SGLT2i) have beneficial cardiovascular and renal effects in persons with type 2 diabetes but no studies have shown whether this can be demonstrated in type 1 diabetes (T1D). We aimed to estimate the risk of cardiovascular disease (CVD) and end-stage kidney disease (ESKD) in persons with T1D with and without treatment with SGLT2i.

Methods: The study is based on 3,660 adults with T1D treated from 2001-2016 who fulfilled the inclusion criteria of age 30-75 years and an eGFR ≥45 mL/min/1.73 m². The Steno Type 1 Risk Engines was used to estimate 5-year CVD and ESKD cumulative risks as randomly drawn numbers from a normal distribution with mean (standard deviation (SD)) of -3.6 (0.9) mmol/mmol and -1.12 (2.8) mmHg. The recorded eGFR and albuminuria were changed in accordance with results from the Tandem studies; no change in eGFR and mean (SD) % change in albuminuria of -23.7 (12.9).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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Results: The SGLT2i induced change in the risk variables translated into an overall 5-year CVR risk reduction of 6.1% (95%CI 5.9, 6.3), with up to 11.1% (10.0, 12.2) in the subgroup with albuminuria. Similar results were seen for the 10-year risk of CVR. For the estimated 5-year risk of ESKD, we found an overall relative risk reduction of 5.3% (5.1, 5.4) with up to 7.6% (6.9, 8.4) in the subgroup with albuminuria.

Methods: System T1 CVR and renal risk model we estimated the risk of CVR and ESKD in persons with T1D and with and without treatment with SGLT2i and found a substantial CVD and ESKD risk reduction, especially in the subgroup with albuminuria. Our model provides an estimate of benefit that may balance the risks associated with use of SGLT2 inhibition in T1D.

SA-OR24
Renal Autologous Cell Therapy (REACT) for Type 2 Diabetic Kidney Disease: Preliminary Results with Renal Cortex Implantation

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Background: Diabetic Kidney Disease (DKD) is the leading cause of kidney failure in the United States. REACT in preclinical trials demonstrated stability and improved kidney function without adverse effects. We present the 12 month findings of an ongoing Phase II multicenter randomized clinical trial (RCT) evaluating autologous homologous cell therapy on DKD progression in patients with stages 3a-4 DKD.

Methods: In this label 1 RCT, 35 participants, 30-80 yrs, eGFR 20-50 ml/min/1.73m² were randomized to either REACT or a control group of standard of care. All patients had a kidney biopsy with renal progenitor cell isolation and expansion by CgMP. The treated group received two cell implants into the kidney cortex at six-month intervals with 244 visits. The control received standard care treatment (SoC) including glomerular basement membrane (GBM) and tubular transporter (TMT) Programme of DKD.

In this analysis, we report on patient characteristics, GFR, structural parameters, measured quantitatively in research kidney biopsies obtained from 38 participants at 12 months.

Results: No difference in HbA1c or HbA1c were present between groups at baseline or 12 months. Annualized mean eGFR increased and UACR decreased in the treatment group from time of first injection to 12 months (Table). Major bleeding complications occurred in 1% of each group following biopsy or cell injections. There were no cell-related adverse events.

Conclusions: Preliminary findings indicate implantation of progenitor REACT into the renal cortex in DKD is safe and improved annualized eGFR and UACR. Further work will follow completion of the study.

Funding: Commercial Support - ProKidney

SA-OR25
Neuroblastoma Suppressor of Tumorigenicity 1 (NB1L1) and Risk of Progression to ESKD in Diabetese

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Background: TGF-β-related signaling proteins have been implicated in the development of end-stage kidney disease (ESKD) in diabetes. Most of this evidence has come from cellular and animal studies focusing on individual proteins and, to date, no study has demonstrated the involvement of these proteins in the etiology of ESKD in humans.

Methods: A human genome-wide TGF-β-related signaling proteins including ligands, receptors, and inhibitors were measured in baseline plasma obtained from 4 different cohorts of 754 Caucasian and Pima Indian subjects; including 219 with Type 1 diabetes (T1D) and CKD stage 3 (CRKD) and 144 with T2D and CKD3, and 238 T1D subjects with CKD1,2 and 153 T2D Pima Indian subjects with CKD1,2. All patients were followed for 10 years to ascertain onset of ESKD.

Results: In logistic regression analysis, NBL1, FSTL3, RGMB, and TGF-βRII RIH were strongly associated with progression to ESKD in all cohorts (Table 1). In multivariable logistic regression analysis for 4 proteins and clinical variables, NBL1, a secreted BMP antagonist never before implicated in kidney diseases, was identified as the only protein very strongly and independently associated with progression to ESKD. Importantly, renal structural parameters, measured quantitatively in research kidney biopsies obtained from Pima Indian subjects, were strongly associated with circulating level of NBL1.

Conclusions: Our study did not find any associations with conventional TGF-β-related proteins but pointed to NBL1 as a very important factor in progression to ESKD. NBL1 is a novel strong biomarker for kidney disease progression, and regulation of this protein may become new therapeutic targets to retard progression to ESKD in diabetes.

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SA-OR28

Circulating Metabolites to Predict Renal Outcomes in CANVAS Type 2 Diabetes Mellitus Population

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Background: Albuminuria and eGFR are biomarkers for kidney disease progression but fail to explain all future risk. Additional biomarkers that better represent underlying disease pathophysiology may improve the prediction of progression from chronic kidney disease (CKD) to end stage renal disease (ESRD). We examined if baseline plasma metabolites predict renal outcomes in the Canagliflozin Cardiovascular Assessment Study (CANVAS) participants.

Methods: Plasma metabolites were assayed from a subset of the CANVAS study participants by HPLC (HILIC)-mass spectrometry using targeted assays. Forty-two metabolites were analyzed for association with the renal outcome (40% eGFR decline, end-stage kidney disease, or renal death) using Cox regression.

Results: We included 967 (22%) of the 4,330 CANVAS participants comprising 341 females (35%), mean age 63 ± 8 years, and BMI 33 ± 5 kg/m². All patients had T2DM with mean HbA1c 8.2 ± 0.9%, eGFR 75.5 ± 18.3 mL/min/1.73m², and median ACR (10 EQ) 11.89 (6.5, 37.49). During a median follow-up of 5.6 years, 63 (6.5%) patients experienced a renal event. There were 10 metabolites significantly associated with the renal outcome (all P<0.05) when adjusted for age and gender (Figure) and treatment effect. In a fully adjusted model (age, gender, race, BMI, HbA1c, cholesterol, blood pressure, history of heart failure, baseline ACR and eGFR), arginine alone remained significant (P<0.01).

Conclusions: Lower baseline plasma arginine levels are independently associated with high risk for renal events in patients with T2DM.

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SA-OR29

Uremic Solutes Are Associated with Cardiovascular Death in Diabetic Kidney Disease

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Background: Cardiovascular disease (CVD) is a major cause of mortality among people with diabetic kidney disease (DKD). The pathophysiology of CVD in DKD is not explained adequately by traditional CVD risk factors. Three small molecular weight, uncharged uremic solutes, asymmetric and symmetric dimethylarginine (ADMA, SDMA) and trimethylamine-N-oxide (TMAO) have been linked to CVD in ESKD. These solutes may be markers of CV mortality in non-ESKD DKD, as well as DKD progression to ESKD.

Methods: Uremic solutes in plasma and urine were assayed by mass spectrometry from a random subcohort of 555 REGARDS Study participants with diabetes and eGFR ≤60 ml/min/1.73m² at study entry. Plasma concentrations and urine/plasma (U/P) ratios of each solute were tested for association with CV mortality (primary outcome), all-cause mortality and incident ESKD (secondary outcomes). Cox regression models estimated the hazard ratios (HR) per log, increment, adjusted for demographic and CVD risk factors, baseline eGFR and urine albumin to creatinine ratio (UACR).

Results: Mean (SD) baseline eGFR was 44 ± 12 ml/min/1.73 m², median (IQR) UACR was 32 (11, 203) mg/g. CV death, overall mortality and ESKD occurred in 120, 285 and 89 participants, respectively, during mean 6.2 years of follow-up. Higher plasma ADMA, and lower U/P ratios of all three solutes were associated with increased CV mortality (Table). Higher plasma concentrations and lower U/P ratios of all three solutes were significantly associated with all-cause mortality. Only higher plasma SDMA was associated with incident ESKD.

Conclusions: Higher plasma concentration and lower U/P ratio of ADMA were independently associated with CV and all-cause mortality in DKD. The strong associations of U/P ratios with CV mortality outcomes suggest a connection between renal clearance of uremic solutes and CVD pathogenesis.

Funding: NIDDK Support

| Table 1. Association of plasma biomarkers and U/P ratios (per two-fold higher) with mortality and incident ESKD outcomes. |
|----------------|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| **Biomarker** | **Continued (log2)** |
| ADMA | Adjusted HR CV mortality (95% CI) |
| 2.10 (1.07, 4.14) | 2.79 (1.79, 4.33) |
| ADMA | Adjusted HR all-cause mortality (95% CI) |
| 2.35 (1.66, 3.33) | 2.07 (1.83, 3.63) |
| **TMAO** | Adjusted HR CV mortality (95% CI) |
| 1.61 (1.01, 2.57) | 1.53 (1.23, 1.90) |
| **SDMA** | Adjusted HR all-cause mortality (95% CI) |
| 1.34 (1.17, 1.53) | 1.37 (1.19, 1.58) |
| **ADMA** | Adjusted HR CV mortality (95% CI) |
| 1.38 (1.21, 1.57) | 1.26 (1.15, 1.39) |
SA-OR30

**Essential Branched-Chain Amino Acids and Ribonic Acid Are Associated with Cardiorenal Events in Type 1 Diabetes**

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**Background:** Diabetic kidney disease and cardiovascular disease (CVD) remain the leading causes of morbidity and mortality in diabetes despite recent advances in treatment. Further understanding of the underlying pathophysiology is needed. We investigated associations between serum metabolites and cardiorenal events.

**Methods:** The study comprised of 637 individuals with type 1 diabetes and various degrees of albuminuria. Non-targeted serum metabolomics was performed using two-dimensional gas chromatography coupled to time-of-flight mass-spectrometry. Longitudinal data on combined cardiorenal events (coronary events, peripheral arterial interventions, stroke), eGFR decline ≥30%, end-stage kidney disease and all-cause mortality were obtained from National Danish Health registries and analyzed by Cox proportional hazards models. Adjustments included sex, baseline age, HbA1c, mean arterial pressure, smoking, body mass index, statin treatment, p-triglycerides, total cholesterol, eGFR, albuminuria, previous CVD and correction for multiple testing by false discovery rate (FDR).

**Results:** Of the included participants, 55% were male and baseline mean age was 55 ± 13 years. 28% had macroalbuminuria, 25% microalbuminuria and 47% normoalbuminuria. The mean eGFR was 81 ± 26 ml/min/1.73m². A total of 75 metabolites were included in the analyses. Over a median (IQR) of 5.2 (4.8-5.7) years, 173 cardiorenal events were recorded. In adjusted analyses, ribonic acid was associated with a higher risk of cardiorenal events. HR 1.4, CI [1.2-1.8], p=0.04. The essential branched-chain amino acids leucine (HR 0.8, CI [0.7-0.9], p=0.04) and valine (HR 0.8, CI [0.6-0.9], p=0.04) were associated with a lower risk of cardiorenal events.

**Conclusions:** In individuals with type 1 diabetes and various degrees of albuminuria, ribonic acid was associated with an increased risk of cardiorenal events and two essential branched-chain amino acids with a decreased risk, independently of relevant confounders. These findings might indicate important pathophysiology in the development of cardiorenal disease.

SA-OR31

**Voclosporin Is Effective in Achieving Complete Renal Response in Severe Lupus Nephritis**

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**Background:** Voclosporin is a novel calcineurin inhibitor with a favorable metabolic profile and a consistent dose-concentration relationship. The Phase 3 AURORA 1 trial demonstrated that compared to mycophenolate mofetil (MMF) and low-dose steroids, adding voclosporin significantly increased complete renal response (CRR) rates in patients with lupus nephritis (LN). We report the results of a post-hoc analysis evaluating if the efficacy of voclosporin in patients with severe LN is similar to the overall population of AURORA 1.

**Methods:** Patients with systemic lupus erythematosus, biopsy-proven active LN (Class III, IV or V or III/IV), and proteinuria of ≥1.5 mg/mg (≥2 mg/mg for Class V) were eligible to enroll in AURORA 1. Overall, 179 and 178 patients were randomized to the voclosporin (23.7 mg BID) and control arms, respectively. All patients received MMF (1 g BID) and low-dose oral steroids. Severe LN was defined as baseline UPCR ≥2.5 mg/mg with Class III or IV biopsy (≥2 mg/mg for Class V) with active lesions. Renal function and serology were evaluated to ensure the population was representative of severe disease in clinical practice. CRR was defined as UPCR ≤0.5 mg/mg with stable renal function, use of low-dose steroids and no use of rescue medication.

**Results:** There were 76 and 72 patients in the voclosporin and control arms, respectively, with severe disease. Mean (SD) UPCR at baseline was 5.9 (2.4) mg/mg (Table 1). CRR at one year was 34.2% and 11.1% in the voclosporin and control arms, respectively, with severe disease. Mean (SD) UPCR at baseline was 5.9 (2.4) mg/mg (Table 1). CRR at one year was 34.2% and 11.1% in the voclosporin and control arms, respectively, with severe disease.

**Conclusions:** In patients with severe LN, adding voclosporin to MMF and steroids results in statistically significantly higher CRR rates. This is clinically meaningful given that patients with severe disease are at higher risk of worse long-term outcomes and development of ESKD.

**Funding:** Commercial Support - Aurinia Pharmaceuticals Inc.

SA-OR32

**Effects of Belimumab (BEL) on Renal Outcomes in Patients (pts) with Relapsed and Newly Diagnosed Active Lupus Nephritis (LN)**

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**Background:** Despite standard therapy (ST) for LN, only 20–40% of pts achieve Complete Renal Response (CRR) at 0.5–1 year and 20–25% relapse in 3–5 years. The aim of this study was to assess effects of BEL on renal outcomes in relapsed and newly diagnosed pts with LN.

**Methods:** Post hoc analysis of the Phase 3, randomized, double-blind, 104-week BLISS-LN study (GSK BEL114054; NCT01639339). Pts with active LN received monthly intravenous (IV) BEL 10 mg/kg or placebo (PBO) + ST. Randomization was stratified by induction regimen: high dose corticosteroids (HDCS) + cyclophosphamide (CYC), followed by azathioprine + low-dose corticosteroids (LDCS), or HDCS + mycophenolate mofetil (MMF), followed by MMF + LDCS. We assessed Primary Efficacy Renal Response (PERR; upCR ≤0.7; no more than 10% below pre-flare value or ≤0.05 mg/m²/1.73m²; no rescue therapy) and CRR (upCR <0.5; eGFR no more than 15% below pre-flare value) at Week 104 and time to renal-related event or death in relapsed vs newly diagnosed pts.

**Results:** Of 446 pts included in this analysis, 150 had relapse of LN and 296 were newly diagnosed. Positive effects of BEL vs PBO on PERR and CRR were noted in both subgroups and were numerically greater in relapsed vs newly diagnosed pts (Table). BEL-treated pts had a lower risk at any time of experiencing a renal-related event or death vs PBO in both subgroups (Table).

**Conclusions:** These data suggest BEL improved PERR and CRR rates more potently in relapsed pts, in which PERR and CRR were substantially less frequent compared with newly diagnosed LN.

**Funding:** Commercial Support - GSK.
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Background: Extensive expression of EXT was observed in the majority of membranous lupus nephritis (MLN). The presence of segmental sclerosis (SS) further subclassified IgAN and MN. The kidney cortex was manually annotated, and a pre-trained deep learning model generated PTC segmentations (Fig. 1). Average PTC flatness (the PTC major and minor axis ratio) and cortical density (PTC pixels/unit cortical area) were digitally measured. Unadjusted Cox proportional hazards models were used to associate normalized PTC flatness and density with outcome in FSGS, IgA Nephropathy (IgAN), 109 Minimal Change Disease (MCD), and 61 Membranous Nephropathy (MN). The presence of segmental sclerosis (SS) further subclassified IgAN and MN.

Results: PTC flatness ≥0.469 significantly associated with a hazard ratio (95% CI) of progression of 1.99 (1.19-3.33) compared with normalized PTC flatness <0.469 (p=0.0109) (Fig. 1). PTC cortical density ≥0.135 associated with a hazard ratio (95% CI) of progression of 0.869 (0.398 – 1.9) compared with normalized PTC cortical density <0.135 (p=0.16). PTC flatness significantly associated with outcome in FSGS (p=0.045), in the presence of SS (p=0.022), in males (p=0.0138), and adults (p=0.016), but not in children, females, or patients w/o SS.

Conclusions: PTC flatness was significantly associated with progression in glomerular diseases, particularly in patients with SS. This association is age and gender dependent.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-OR36
Abstract Withdrawn

SA-OR37

Uprregulated JAK-STAT Signaling and Augmented Potassium Efflux Characterize Induced Pluripotent Stem Cell-Derived Podocytes of Black Patients with APOL1-Associated FSGS

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Background: High risk (HR) APOL1 genotypes account for 70% of excess risk of FSGS among Blacks. It is unknown why ~20% of carriers of HR APOL1 genotypes develop FSGS or other APOL1 nephropathies while 80% kidney disease-free. The possible role of genetic modifiers has been proposed. Also, the mechanism by which variants APOL1 cause podocyte injury is unknown. We previously reported that overexpression of variants APOL1 in HEK293 cells caused cytoxic loss of cellular K+. it is unknown if physiologic expression of APOL1 by IFNγ also causes K+ loss in patient-derived podocytes.

Methods: We recruited Blacks with biopsy-proven FSGS (n=16) or with normal GFR and no proteinuria (n=20). 68.7% and 10% of FSGS cases and healthy controls carried HR APOL1 genotypes, respectively. Markers-confirmed iPSC-podocytes generated from 7 HR cases and 2 HR controls were treated or not with IFNγ followed by whole genome transcriptomics and measurement of cellular K+. Additionally, APOL1-knockout iPSC-podocytes were generated using CRISPR-Cas9.

Results: Notably, the 520 differentially expressed genes (DEGs) unique to HR cases are transcriptionally regulated by JAK-STAT signaling (Fig. A-B). Consistent with this finding, IFNγ induces a higher expression of APOL1 in HR cases which was blocked by JAK1/2-specific inhibitor, Baricitinib (Fig C). Importantly, for the first time, we demonstrated that physiologic expression of variant APOL1 under its endogenous promoter causes significant loss of cellular K+ in iPSC-podocyte of HR cases and was abolished by APOL1-knockout (Fig D-E).

Conclusions: JAK-STAT signaling may be an important modifier of APOL1-associated FSGS that upregulates APOL1 expression and function (K+ efflux). Inhibition of JAK-STAT signaling and/or blockade of APOL1-mediated cation-transport may represent targeted therapeutic approach for APOL1-associated FSGS.

Funding: Other NIH Support - Common Fund (NIH Director’s New Innovator Award)

SA-OR38

Transcriptional Reprogramming by Wilms’ Tumor 1 and FoxC2 Mediates a Repair Response During Podocyte Injury

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Background: We previously demonstrated a transcriptional response to injury in podocytes and identified WT1 as one of the most upstream transcription factors binding nearly all genes known to be crucial for maintenance of the glomerular filtration barrier. We now demonstrate that FoxC2 transcription factor is a major component of the response to injury, binding many of the same genes as WT1. Here, we focus on understanding WT1 and FoxC2 transcriptional mechanism in response to injury.

Methods: We used Adriamycin (ADR)-induced podocyte injury as a model for human Focal Segmental Glomerulosclerosis in mice and performed FoxC2 ChIP-seq from isolated podocytes. WT1 is required for the podocyte response to injury. Conditional WT1 knockout and FoxC2 knockdown mouse models were used to decipher the transcriptional mechanism through which WT1 and FoxC2 regulate podocyte gene expression during injury, using transcriptomic approaches.

Results: WT1 is required for the podocyte response to injury. Indeed, the transient increased expression of podocytes genes in mice after injury, was abolished in the absence of WT1. We found that FoxC2 was also actively involved during this response. By ChIP-seq, we detect 4214 FoxC2 binding sites before injury, rising to 12,532 after ADR. In contrast to WT1, that maintains a moderate degree of binding during the later stages of injury, FoxC2 binding is essentially absent. Using a set of 48 podocyte genes encoding components of the glomerular filtration barrier, ChIP-seq analyses demonstrated that WT1 and FoxC2 both acquire novel binding sites during the early stages of injury. One co-bound site is at the WT1 transcriptional start site, where binding of both WT1 and FoxC2 increases dramatically after injury. Furthermore, WT1 and FoxC2 may be co-immunoprecipitated and knockdown of WT1 or FoxC2 in immortalized podocytes demonstrated their mutual dependence for binding target genes.

Conclusions: Together, these results demonstrate that WT1 and FoxC2 mediate transcriptional reprogramming during podocyte injury. This transcriptional reprogramming may be initiated by the dramatic increased binding of WT1 and FoxC2 at the WT1 transcriptional start site after injury. Irreversible podocyte injury leading to FSGS may result from the nearly complete loss of FoxC2 binding to target genes during later stages of injury.

Funding: NIDDK Support

SA-OR39

Cytosolic Phospholipase A2: A Drug Target in FSGS

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Background: Focal Segmental Glomerulosclerosis (FSGS) is the most common glomerular cause of end stage kidney disease (ESKD) in children. The refractory nature of FSGS renders treatment of FSGS as one of the most difficult challenges in pediatric nephrology. A significant knowledge gap in understanding the mechanism of progression in FSGS hampers development of successful treatment strategies. We demonstrated that patients with FSGS present with a distinct urinary lipid profile characterized by increased fatty acids (FA) and lysophosphatidylcholines (LPC), metabolites of cytosolic phospholipase A2 (cPLA2). We propose that LPC and FA incites proinflammatory and proapoptotic response in podocytes and proximal tubule epithelial cells (PTECs). We hypothesize that increased cPLA2 activity induces apoptosis, fibrosis and progression in FSGS by harboring intracellular LPC and FA.

Funding: Other NIH Support - Common Fund (NIH Director’s New Innovator Award)
Gluoneral Diseases: Trials, Prognostic Markers, and Podocyte Biology

SA-OR40
Gluomerular 3D Co-Culture to Study Podocyte Disease Ex Vivo in a Personalized Manner
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Universitätsklinikum Erlangen Medizinische Klinik 4 Nephrophologie und Hypertoniosiologie, Erlangen, Germany.

Background: As a cause for glomerular disease, podocyte damage and related changes in the glomerular filtration barrier are typical findings. However, podocyte cell culture is challenging due to the inability of terminally end differentiated primary podocytes to proliferate and due to altered morphology and expression of cell-specific markers in immortalized podocytes. Besides, classical mono-cultures limit paracrine cell-cell-contact and communication by 2-dimensionality. To investigate cell-cell-interaction and to improve cell culture conditions we want to generate a 3D co-culture model of glomerular cells. Moreover, we want to study podocyte disease by personalizing the 3D co-culture model using patient-derived podocytes.

Methods: In order to generate 3D glomerular spheroids, immortalized differentiated podocytes, glomerular endothelial cells and mouse primary cells were cultured as hanging media droplet or via agarose microwells. Time lapse experiments displayed spheroid formation and spheroids were characterized regarding extracellular matrix proteins and cell-specific marker expression by qPCR, histological sections, immunostainings and electron microscopy. Patient-specific podocytes and podocytes from healthy controls were generated from skin fibroblasts via reprogramming into human induced pluripotent stem cells (hiPSCs) and subsequent differentiation into hiPSC-podocytes.

Results: Derived podocytes have the potential to personalize the 3D co-culture to study podocyte disease processes.

Conclusions: Our data strongly suggest that increased P2LA2 expression contributes to progression of FSGS by harboring production of proinflammatory and proproptope lipid metabolites. We propose that upregulated P2LA2 activity leads to podocytes and PTEC damage by perpetuating oxidative injury, apoptosis, inflammation and subsequent fibrosis in FSGS. We postulate that targeting P2LA2 pathway for drug development will improve the monotherapy in non-renal immune mediated nephropathy by its promising biomarker to monitor disease progression and treatment response in FSGS.

Funding: Commercial Support - Kaneka

SA-OR42
Elevated Load with Normal Mean in Pediatric Hypertension (HTN): What Does It Mean?
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Background: Current pediatric ambulatory blood pressure monitor (ABPM) guidelines define HTN as mean blood pressure (BP) ≥ 95th percentile for gender and age/ height. ABPM criteria limit HTN to 25%. Those with a normal mean BP but elevated load are “unclassified.” Adult ABPM criteria is based solely on mean BP using an absolute threshold. Applying pediatric versus adult ABPM criteria in adolescents has been a topic of research recently as the 2017 pediatric BP guidelines use adult norms to define clinic HTN in patients (pts) ≥ 13 years (yrs). However research on the utility of BP load in defining pediatric HTN is limited. We aimed to evaluate the significance of elevated BP load in “unclassified” pts by ABPM including association with left ventricular hypertrophy (LVH).

Methods: Retrospectively, pts 13-17 yrs with ABPM data between 9/2018 and 7/2019 were analyzed. Unclassified pts were re-categorized (re-cat) to HTN or normal BP using the adult threshold for mean BP only. LVH was defined as LVMI > 51 g/m². Data collected included gender, age, height, ABPM systolic and diastolic BP mean and load for 24hr, day, and night, and left ventricular mass index (LVMI). Unclassifiable pts were re-categorized to HTN or normal BP using the adult threshold for mean BP only. LVH was defined as LVMI > 51 g/m². Results: 495 pts (355 M) had ABPM. 146 had HTN; 198 (121 M) were “unclassified.” 52 pts with normal BP and 101 of uncategorized pts had LVMI data. There was no significant difference in mean LVMI in pts with “unclassified” versus normal BP (41 vs 40 g/m² vs p=0.62) nor presence of LVHI (11% vs 9.6% p=0.81). Of the 198 unclassified pts, 150 (76%) were re-categorized (re-cat) to HTN by adult criteria, and there was no difference in LVMI compared to pts re-cat to normal BP (42.6 vs 39.4 g/m² vs p=0.23). Pts re-cat to HTN, had significantly higher loads for night BP and 24hr systolic BP compared to those with normal BP. However, there was no difference between the mean loads when comparing those with LVHI versus without LVHI.

Conclusions: For adolescents with a normal mean BP by pediatric criteria, elevated BP loads are not associated with LVHI. Furthermore, applying adult criteria to define HTN would appropriately re-classify those with higher loads. Regardless, after re-classification, there is still no difference in LVMI. Applying adult ABPM standards for adolescents would simplify interpretation without sacrificing significance.

SA-OR43
Using Electronic Health Record(EHR) Data to Evaluate Kidney Function Decline in Children with CKD
Caroline A. Gluck,1 Amy Goodwin Davies,2 Jill R. McDonald,2 Mitchell Maltenthal,2 Mark Mitesnefs,2 Vikas R. Dhaniirdhika,2 Bradley P. Dixon,3 Joseph T. Flynn,2 Michael J. Somers,2 William E. Smoyer,2 Alexa Neu,2 Collin A. Hovinga,2 Amy L. Skversky,2 Thomas Eising,2 Christopher A. Kaiser,10 Susan L. Firth,6 Christopher B. Forrest,11 Michelle Denburg,2,12 Alfred I DuPont Hospital for Children, Wilmington, DE; 2 The Children’s Hospital of Philadelphia, Philadelphia, PA; 3 Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 4 Washington University in St Louis, St Louis, MO; 5 University of Colorado, Denver, CO; 6 Seattle Children’s Hospital, Seattle, WA; 7 Boston Children’s Hospital, Boston, MA; 8 Nationwide Children’s Hospital, Columbus, OH; 9 Johns Hopkins Medicine, Baltimore, MD; 10 Bayer AG, Leverkusen, Germany; 11 University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; 12 Institute for Advanced Clinical Trials for Children, Rockville, MD.

Background: This study utilized EHR data from pediatric centers to identify children with CKD and examine risk factors for kidney function decline.

Methods: We used PEDSnet, a network with EHR data from ~7 million children in 7 health systems, to identify children aged 1-18 yrs between 2009-2020 who met CKD Criteria: Declined: Increased hemoglobin concentrations are independently associated with increased C-terminal FGF23 levels in pediatric CKD. Future analyses will assess relationships among longitudinal changes in hemoglobin, serum iron, and FGF23 parameters.

Funding: NIDDK Support Other NIH Support - Additional funding from the Emmeke Kennedy Shriver National Institute of Child Health and Human Development, and the National Heart, Lung, and Blood Institute (U10DK61643, U10DK61674, U24DK082194, U24DK066116)

Table 1: Univariable and multivariable linear regression modeling of determinants of circulating log-transformed C-terminal FGF23

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>-0.04</td>
<td>-0.10</td>
</tr>
<tr>
<td>Sex (male vs female)</td>
<td>0.08</td>
<td>0.02</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>-0.20</td>
<td>-0.11</td>
</tr>
<tr>
<td>Cystatin C (mg/L)</td>
<td>-0.04</td>
<td>-0.07</td>
</tr>
<tr>
<td>Parathyroid hormone (S-D)</td>
<td>0.23</td>
<td>0.03</td>
</tr>
<tr>
<td>Serum bone (mg/dL)</td>
<td>-0.12</td>
<td>-0.05</td>
</tr>
<tr>
<td>Hemoglobin (SDM)</td>
<td>-0.27</td>
<td>-0.13</td>
</tr>
</tbody>
</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
criteria: two eGFR<90 ml/min/1.73m² separated by a90 days without an intervening higher value. CKD progression was defined as composite outcome: eGFR<15 ml/min/ 1.73m², 50% eGFR decline, chronic dialysis, or kidney transplant. Subcohorts were based on CKD etiology: glomerular, non-glomerular or malignancy. We assessed impact of hypertension-HTN (≥2visits with HTN code) and proteinuria (≥1 lab value ≥1+ within 2yrs of cohort entrance on outcomes.

Results: We identified 7393 children, median age 14.1yrs, 36% females, 23% blacks, median follow-up 4.2yrs. Median initial eGFR was 75.5 ml/min/1.73m², 36% had proteinuria; 46% had HTN. Children with glomerular CKD were more likely to reach outcomes (p<0.001). Children with HTN, proteinuria, or both were more likely to reach outcomes (p<0.001).

Conclusions: The EHR may be used to study large numbers of children with CKD. Risk factors for CKD progression were glomerular disease, HTN and proteinuria.

Funding: Other U.S. Government Support, Commercial Support - Institute for Advanced Clinical Trials for Children, Bayer.

Endpoint reached by sub-cohort

SA-OR44

Risk Factors for Kidney Injury in Children with Solitary Functioning Kidney

Sander Groen in ‘t Woud, Nel Roeleveld, Wout Feitz, Michiel F. Schreuder, Loes F. van der Zanden. SOFIA study group Radboudumc, Nijmegen, Netherlands.

Background: Patients with a solitary functioning kidney (SFK) are at increased risk of kidney injury, for which several risk factors have been suggested. Large differences exist between previously reported cohorts, which hampers translation of these findings into clinical care. Our objective was to investigate the risk of and risk factors for proteinuria, high blood pressure, a decreased glomerular filtration rate (GFR), or use of antihypertensive medication in our nationwide study of children with SFK.

Methods: Children with congenital and acquired SFK were recruited in >30 hospitals throughout The Netherlands. Information on risk factors for and signs of kidney injury were collected from electronic patient files. Kaplan-Meier curves were used to estimate survival without signs of kidney injury and Cox regression was used to evaluate risk factors.

Results: Of 982 patients who provided informed consent, detailed clinical information was available from 898 (91%). A total of 7393 children, median age 14.1yrs, 36% females, 23% blacks, median follow-up 4.2yrs. Median initial eGFR was 75.5 ml/min/1.73m², 36% had proteinuria; 46% had HTN. Children with glomerular CKD were more likely to reach outcomes (p<0.001). Children with HTN, proteinuria, or both were more likely to reach outcomes (p<0.001).

Conclusions: The EHR may be used to study large numbers of children with CKD. Risk factors for CKD progression were glomerular disease, HTN and proteinuria.

Funding: Other U.S. Government Support, Commercial Support - Institute for Advanced Clinical Trials for Children, Bayer.

Endpoint reached by sub-cohort

SA-OR45

Nephrotoxic Medications and Associated AKI in Hospitalized Neonates

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Background: Hospitalized neonates in the NICU are frequently treated with nephrotoxic medications (NM), a risk factor for acute kidney injury (AKI) which is associated with increased neonatal morbidity and mortality. Neonatal treatment with NM and subsequent AKI, especially in periviable neonates could be detrimental to nephrogenesis.

Methods: Multicenter retrospective analysis of hospital discharges (2005-2016) using the national Pediatric Hospital Information System database, including 49 pediatric hospitals across the U.S. Treatment with 37 NM in first 28 postnatal days across demographics and clinical variables, and relationship with AKI were evaluated.

Results: Of 192,229 neonates, 74% were treated with at least one NM, Figure 1. AKI prevalence was significantly higher in the NM group (aRR 3.68 [95% CI: 2.85, 4.75]), Figure 2. The aRRs of treatment were increased in ≥32-week, and <2000 g infants. NMs were prescribed to 90-95% of <32-week gestational age (GA) neonates. Most treatments with NM (95-98%) occurred in the first 3 postnatal days. IV aminoglycosides were the most frequent NM prescribed; 28% were treated with a 4 calendar days. Most common diagnoses were infections (25%) and patent ductus arteriosus (20%).

Conclusions: The smallest and most immature preterm neonates are frequently treated with NM. The prevalence of AKI is higher in the NM treated group. The long-term implications of treatment with NM and subsequent AKI on nephrogenesis warrant attention in future studies.

Multivariable Adjusted Relative Risk of Treatment with Nephrotoxic Medication by Demographic and Clinical Risk Factors
SA-OR46

Urinary VEGF as a Prognostic Biomarker of CKD in Premature Infants with Lung Disease
Michelle C. Starr,1,2 Brian A. Halloran,4 Robert Schmicker,1 Patrick D. Brophy,1 Patrick J. Heagerty,1 Sandra Juul,2 Stuart Goldstein,2 Sangeeta R. Hingorani,3 David J. Askenazi.4 Preterm Erythropoietin Neuroprotection Trial Investigators 1Indiana University School of Medicine, Indianapolis, IN; 2Riley Hospital for Children at Indiana University Health, Indianapolis, IN; 3University of Washington School of Medicine, Seattle, WA; 4The University of Alabama at Birmingham School of Medicine, Birmingham, AL; 5University of Rochester Medical Center, Rochester, NY; 6Cincinnati Children’s Hospital Medical Center, Cincinnati, OH.

Background: Premature neonates are at risk for chronic kidney disease (CKD). Lung disease is an emerging risk factor for CKD in infants. Impaired angiogenesis may be implicated as it is required for both lung and kidney development, repair from injury, and perturbations contribute to CKD development. VEGF is a marker of angiogenesis. We hypothesize that urinary VEGF would be lower in infants with lung disease who go on to developed CKD.

Methods: Using data from the REPAIRED study (NCT01378273) an ancillary of the PENUT trial, we assessed urinary VEGF in 40 infants with severe lung disease defined by respiratory support or supplemental oxygen at 36 weeks post-menstrual age (PMA). We measured urinary VEGF at 30-34 weeks PMA. Our outcome measure was CKD at 22-26 months (estimated glomerular filtration rate <90 ml/min/1.73m²). Urinary VEGF was determined with electro-chemiluminescent multi-antigen ELISA (Mesoscale). We compared values using Spiro-Wilk testing and ROC analysis with Youden’s index.

Results: Fourteen infants (35%) developed CKD. Urinary VEGF at 30-34 weeks PMA was lower in infants that developed CKD (2.23 vs. 2.63 log pg/mL, p=0.004). The AUC for VEGF to predict CKD was 0.77 (95% CI 0.62-0.92, p=0.005). Using a likelihood ratio of 2.32, a threshold of 2.47 log pg/mL gives a sensitivity of 72% and specificity of 70% (Figure 1).

Conclusions: In this small cohort of premature infants with severe lung disease, urinary VEGF levels were lower in premature infants who went on to developed CKD compared to similar neonates who did not develop CKD. Additional urinary VEGF analysis in this cohort is ongoing. Low urinary VEGF may be a marker of abnormal angiogenesis and vascular repair in the kidney. Our findings suggest that urinary VEGF may help predict CKD in premature infants with lung disease.

Funding: NIDDK Support

SA-OR47

Hyperoxia Exposure in Neonatal Period Is Associated with Decrease in HB-EGF Expression in Mice Kidneys
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Background: Acute Kidney Injury (AKI) is common in preterm infants and may cause long-lasting renal damage. Hypoxia exposure in the postnatal period has been linked to chronic kidney disease (CKD) in adulthood in survivors or preterm birth. The mechanism of hyperoxia-driven AKI in premature infants is not clearly understood. Activation of the epidermal growth factor receptor (EGFR) by EGF or hepatic-binding EGF-like growth factor (HB-EGF) promote renal tubular proliferation and renal recovery in AKI. In contrast, activation of transcribing growth factor (TGF-a) signaling may lead to fibrosis and CKD. We hypothesize that hyperoxia exposure in neonatal mice leads to kidney injury via alteration in the expression of EGF/EGFR and its ligands.

Methods: Pups of C57Bl/6J mice were exposed to hyperoxia (FiO2 0.85) and compared to littermate controls exposed to room air from postnatal days 3-10. One kidney from each pup was fixed in formalin and embedded in paraffin for histological analysis. The other kidney was snap frozen and RT-PCR was performed from the RNA isolated from the kidney.

Results: We analyzed renal tissues from 15 newborn mice (from 3 litters) exposed to hyperoxia and 5 mice (from 1 litter) exposed to normoxia. Relative mRNA levels of HB-EGF were significantly decreased in renal tissues of pups exposed to hyperoxia (mean:0.006 ± 0.001) compared to those exposed to normoxia (mean:0.012 ± 0.002) (p < 0.05). Both EGFR and TGF-a levels were not elevated in pups exposed to hyperoxia. Hyperoxia-exposed pups were also noted to have elevated α-SMA and fibronectin compared to the controls. TGF-β levels were also similar between exposed and non-exposed animals (Figure 1).

Conclusions: HB-EGF may contribute to hyperoxia-related renal injury in preterm neonates and may be a therapeutic target in these infants.

Funding: Other NIH Support - NHI, NHLBI K08 HL151907

SA-OR48

Identification of Molecular Mechanisms Regulating Mammalian Nephrogenesis Duration and Nephron Endowment
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Background: Nephron endowment generated during development confers lifelong renal filtration function, and is established via nephron progenitor cell (NPC) interactions with the adjacent stroma and ureteric bud (UB). Two salient, incompletely understood features of nephrogenesis are (1) the coordinated cessation of nephrogenesis in independent niches and (2) a striking 10-fold variation in nephron number between kidneys from different individuals. Preterm births are associated with premature cessation of nephrogenesis and are consequently susceptible to early-onset chronic kidney disease (CKD) and end-stage renal disease (ESRD). We leverage multiple mouse models exhibiting consistent differences in nephron number to identify mechanisms promoting prolonged nephrogenesis and/or increased nephron endowment.

Methods: NPCs from mice with elevated nephron numbers and delayed cessation (SicI2TC1−/− mice) were evaluated via single-cell transcriptomics, translatome profiling (bulk RNA-Seq of Rp110-associated transcripts), metabolic indicators (in vitro glycolysis assays and in vivo hyperoxia studies), and immunofluorescence. Candidate genes emerging from the RNA analyses were validated with in vivo genetic models for nephron number and cessation timing phenotypes.

Results: Translatome analysis revealed age and genotype-dependent patterns in signaling pathway components that were not observed in the single cell transcriptome, including differential translation of Wnt antagonists over agonists (such as Rspo3 in Tsc1−/−). NPC number and cessation timing phenotypes. Further, the selective differential translation observed in the Tsc1−/− model was not associated with globally elevated mTORC1 activity or changes in cellular metabolic activities.

Conclusions: We propose a model in which the tipping point for nephron progenitor exit from the niche is controlled by the gradual increase in stability of Wnt/Fzd complexes in independent NPCs, enhancing signal to 13th day 14 niches, resulting in high Fg20 levels and low R-spondin levels promoting a self-renewal environment. Further, the selective differential translation observed in the Tsc1−/− model was not associated with globally elevated mTORC1 activity or changes in cellular metabolic activities. Among these factors, Rspo3 expression is a key molecule in determining nephron number and nephron number and number and cessation timing phenotypes. Consistent with this, loss of one Rspo3 allele in nephron progenitors delayed cessation and increased nephron numbers in vivo.

Funding: NIDDK Support

SA-OR49

Simultaneous Generation of Nephron and Renal Stroma via Progenitor Cell Replacement in Animal Fetus

Background: To solve the organ transplant shortage by regenerative medicine, the whole kidney, including the renal stroma—which plays important roles in homeostasis, such as structural maintenance, hemodynamics, and kidney endocrine function—must be generated. Previously, we successfully generated a rat nephron using mouse kidney as a scaffold by replacing mouse nephron progenitor cells (NPCs) with rat NPCs. Therefore,
animal fetuses can potentially generate human kidneys. Herein, we applied progenitor cell sorting and cell replacement to stromal progenitor cells (SPCs) and to NPCs and SPCs to verify the generation of nephrons and renal stroma.

**Methods:** We harvested the metanephroi of green fluorescent protein rats to extract dissociated single cells (DSCs) by enzymatic treatment. SPCs were extracted from the PDGFRα-negative fraction by cell sorting targeting the platelet-derived growth factor receptor alpha (PDGFRα)-positive fraction. NPC's were extracted by sorting integrin alpha 8-positive fractions from the PDGFRα-negative fraction. We injected the extracted SPC fractions and both NPC and SPC fractions in the nephrogenic zone of the metanephros of Foxd1-<sup>−/−</sup> mice (host SPC removal model) and Siz2/Foxd1-<sup>−/−</sup> r mice (host NPC and SPC removal model), respectively. The metanephros were organ cultured for 1 week or transplanted into the retroperitoneum of NOD/Shi-scid/IL-2Rγ<sup>−/−</sup> mice and collected after 2 weeks for evaluation with immunofluorescence staining.

**Results:** In the SPC removal model, mouse SPCs were replaced with rat SPCs in vitro, and rat stroma was extensively generated in mice kidneys. In vivo, SPCs differentiated into various stromal lineage cells, e.g., mesangial cells, interstitial fibroblasts, vascular pericytes, juxtaglomerular cells, and EPO-producing cells. In the two progenitor cell removal models, cap mesenchyme-like structures were formed with aggregated rat NPCs and SPCs around the mouse ureteric bud in vitro. Rat nephrons and renal stroma were generated in the mouse kidney in vivo.

**Conclusions:** SPC replacement helped generate heterogeneous rat renal stromal lineage cells in the mouse kidney. Simultaneous NPC and SPC replacement enabled the generation of nephrons and renal stroma between different species.

**SA-OR50**

**Crescents Derive from Single Podocyte Progenitors and a Drug That Restores Their Differentiation Attenuates Rapidly Progressive Glomerulonephritis**

Maria Elena Melica, Giulia Antonelli, Maria Lucia Angelotti, Gianmarco Lugli, Carolina Conte, Letizia De Chiara, Fiammetta Ravaglia, Anna J. Peiret, Benedetta Mazzinghi, Elena Lazzeri, Roberto Semeraro, Laura Lasagni, Paola Romagnani, Università degli Studi di Firenze, Firenze, Italy.

**Background:** Rapidly progressive glomerulonephritis (RPGN) is characterized by crescent formation, which typically, is the consequence of diverse upstream pathomechanisms involving the specific activation of PEC, represente which represent in part renal progenitor cells (RPC). Similarities with stem cell of bone marrow prompted us to hypothesized that crescents result from clonal expansion of a single RPC, conceptually similar to monoclonal diseases originating from hematopoietic stem cells. We further hypothesized that drugs known to cure hematopoietic disease by enforcing their terminal differentiation could also attenuate crescentic glomerulonephritis.

**Methods:** We established a RPGN disease model in a conditional transgenic mouse based on the mT/mG and the Confetti reporter that allows lineage tracing of RPC. Mice were treated with drugs currently used in myeloproliferative disorders. Crescentic lesions were characterized by super-resolution STED microscopy. Single cell RNA sequencing of human renal progenitor cultures identify the immature progenitor subset generating crescent in human.

**Results:** We observed that crescents originated from the clonal expansion of single RPC, thus suggesting a clonal stem cell disorder. Therefore, we administrated a series of drugs known to ameliorates myeloproliferative neoplasms to our mouse model. Treatment with one of the compounds induced a reduction in both proteinuria and crescent formation. 3D confocal microscopy and STED super-resolution imaging of glomeruli showed that this compound turned the pathologic hyperplasia of a immature PEC subset into a clonal differentiation into new podocytes restoring the injured glomerular filtration barrier. Single cell RNA of human renal progenitor cultures identified a new marker of the crescent-generating progenitor cells. Expression of this marker in biopsies of patients with RPGN associated with regression toward end stage kidney disease.

**Conclusions:** These results demonstrate that glomerular hyperplastic lesions derive from clonal amplification of a RPC subset and that shifting proliferation to podocyte differentiation reverses crescent formation and improves clinical outcome.

**SA-OR51**

**A Multidimensional Single Cell and Spatial Atlas of the Human Kidney in Health and Disease Delineates Cell States Associated with CKD Outcomes**

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**Background:** The knowledge of the complexity of cell types, states and their interactions during homeostasis or disease is needed to identify the mechanisms of kidney disease.

**Methods:** We have applied multiple single cell or nucleus omic assays (>400,000 nuclei/cells) that capture gene regulation, expression and their spatial relationships to a broad spectrum of healthy reference (35) and disease tissue samples (50, AKI or CKD) to establish a robust atlas of the cellular diversity representing kidney function or dysfunction.

**Results:** We identified 100 cell clusters including rare and novel cell populations and their spatial locations spanning the entire kidney. Among these, we define cellular states associated with kidney injury alterations that represent cycling, adaptive or maladaptive repair and degenerative states, their associated regulatory factors, and genes and pathways underlying these transitions. Molecular signatures of these states permit their classification and spatial localization within injury neighborhoods, allowing discovery of intercellular signaling relevant to acute or chronic injury. Large scale 3D imaging linked glomerular, proximal tubule and thick ascending limb injured cells to an active immune response in the SPCs that is uniquely associated with tubular cells. The altered state gene signatures were negatively associated with a decline in eGFR in patients with chronic kidney disease in two separate cohorts.

**Conclusions:** This comprehensive molecular, cellular and spatial atlas serves as a benchmark to identify nascent and altered kidney cell states, define therapeutic targets in individual patient samples and engineer healthy kidneys.

**Funding:** NIDDK Support, Other NIH Support - Common Fund (NHLBI)

**SA-OR52**

**Defining the Molecular Correlate of Arteriolar Hyalinosis in CKD Progression by Integration of Single-Cell Transcriptomic Analysis and Descriptor Scoring in KPMP and NEPTUNE**

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**Background:** Single cell RNA sequencing generates transcriptomic data at cellular resolution allowing the identification of cell-type specific transcript expression. We performed an integrated analysis of single cell data with descriptors from histopathology analysis of biopsy samples of CKD and AKI patients.

**Methods:** As part of Kidney Precision Medicine Project (KPMP), single cell analysis from 12 AKI and 15 CKD patients processed per KPMP guidelines (including normalization, scaling, clustering and cell-specific marker identification). Top 5000 highly variable genes expressed in the endothelial cluster identified at the low cluster granularity were analyzed using weighted co-expression network analysis. Next, the co-expressed gene sets were associated with descriptors from the histopathology analysis. A composite score was generated using the expression levels of genes for the modules that significantly correlated with the descriptors. For validation purposes, similar composite scores were also generated from tubular interstitial gene expression data of NEPTUNE cohort.

**Results:** The unsupervised clustering identified kidney cell clusters including glomerular, tubular and immune cell types. The weighted co-expression network analysis of endothelial genes showed a gene module significantly associated (adj p < 0.02) with arteriolar hyalinosis, one of the descriptors from the histopathology analysis; the genes in this module were enriched in the arteriolar endothelial cluster identified by high resolution clustering. KPMP CKD patients with the top composite scores had baseline eGFR < 60 (ml/min/1.73m2). In NEPTUNE, the endothelial scores significantly associated with low eGFR (p < 0.0002) and the composite endpoint of CKD progression (> 40% reduction eGFR or ESRD) indicating poor prognosis for the samples with high endothelial scores (P < 0.0001). Pathway analysis showed adiposokine signaling as the top enriched pathway for this gene set.

**Conclusions:** Using integrated analysis of single cell expression data with histopathology descriptors, we identified an arteriolar endothelial gene set linking arteriolar hyalinosis to CKD progression.**

**Funding:** NIDDK Support
SA-OR53
Proteomic Characterisation of CKD Progression
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Background: Delaying or halting progression of chronic kidney disease (CKD) to established renal failure is a major goal of global health research. The mechanism of CKD progression among different CKD entities involves pro-fibrotic, pro-inflammatory, pro-angiogenic and pro-fibrotic vascular pathways but current treatments are non-specific, with heterogeneity in terms of response and outcome. In depth phenotypic and proteomic data can help investigate differences between those CKD patients with rapid disease progression and those who remain stable after diagnosis.

Methods: Using eGFR slope analysis, 414 patients with a broad range of kidney disease aetiologies were divided into fast progressors (GFR > -3 ml/min/yr; n=170) and stable patients (GFR > 0 ml/min/yr; n=244); these composed our discovery cohort. Plasma samples were prepared and interrogated for proteomic signals with SWATH-MS which enabled a digitised proteomic profile to be generated. For hypothesis testing, t-test was used to identify differentially expressed proteins between our patient groups (p<0.05, after multiple testing corrections was considered statistically significant). Statistical analysis and machine learning approaches for discovery (Random Forest and Boruta Feature Selection) were performed using the computing environment R and additional software packages were obtained via the Bioconductor project.

Results: A SWATH map (on 414 patients with 943 proteins quantified) was generated and compared with available clinical data in order to identify potential progression biomarkers. After differential expression analysis and supervised machine learning algorithms for feature selection, we identified a set of proteins that differentiate between our patient groups (AUC= 0.77). Baseline creatinine was not an accurate predictor of CKD progression (AUC=0.51). Functional enrichment analysis revealed that platelet degranulation was a statistically important feature, suggesting a possible role for platelet function in then pathogenesis of CKD.

Conclusions: The in-depth proteomic characterisation of this large-scale CKD cohort representing multiple disease mechanisms will help us understand the cell types that might lend themselves to future drug targeting. Candidate proteomic biomarkers will be validated in samples from selected patients in other large CKD cohorts such as NURTURE using a targeted mass spectrometric analysis.

SA-OR54
Capillaries Are Primary Targets in CKD and Tie2 Signaling Plays a Central Role in Disease Progression
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Background: Progressive renal diseases are associated with loss of peritubular capillaries, capillary rarefaction, but the underlying mechanisms are not well described. In both mouse models and patients, a decline in endothelial tyrosine kinase receptor (Tie2) signaling can be seen in CKD. We hypothesized that renal blood vessels through loss of Tie2 signaling upregulates Pdgfb that in turn act as a mitogen to activate pericytes and fibroblasts.

Methods: To investigate this, we utilized floxed alleles for Tie2 and Pdgfb together with inducible endothelial specific Cre and lineage reporter. Additional lines (Pdgfra-H2b-GFP and Pdgfb-GFP), were crossed into the line, resulting in reporters of myofibroblasts. Mice were subjected to a experimental model of CKD, the unilateral ureter obstruction model. Capillary density and fibrosis were evaluated at 1, 3, and 10 days after obstruction. A subset of mice was treated with an Tie2 activating antibody and evaluated the same way.

Results: Our studies show that loss of Tie2 results in increased injury to peritubular capillaries and increased tubulointerstitial fibrosis in an experimental model of CKD. Tie2 cKO mice showed reduced capillary density, reduced fibrogenesis, and reduced vessel perfusion. Furthermore, treatment with an Tie2 activating antibody reduced both fibrosis and loss of capillaries if started at the time of injury, while endothelial specific knockout of Pdgfb only reduced fibrosis.

Conclusions: Our results suggest that capillaries are primary targets in CKD and that Tie2 regulation affects both capillary density and tubulointerstitial fibrosis. Tie2 activating agents should be explored as therapies for patients with chronic kidney disease.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-OR55
Autocrine Signaling of Sphingosine 1 Phosphate in Kidney Pervascular Cells Promotes Inflammation and Fibrosis
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Background: Sphingosine 1-phosphate (S1P) is a sphingolipid that is produced inside the cell by the action of sphingosine kinase (SphK) 1 and 2. S1P is exported from cells by spinster homolog 2 (Sptms2) or major facilitator superfamily 2b (Mfsd2b), and then acts on five G-protein coupled S1P receptors, S1P1 to S1P5, to affect various cellular functions. We recently showed that Sphk2-/- mice were protected from renal fibrosis when compared to wild type or Sphk1-/- mice (PNAS 2016). We hypothesized that local S1P signaling in kidney perivascular cells affects the progression of kidney fibrosis.

Methods: Male FoxclCre: Sphk2-/-, FoxclCre: Sphk1-/-, FoxclCre: Spts2-/-, and their littermate control mice were used. For unilateral ischemia-reperfusion injury (IRI), left kidney was clamped; right nephrectomy was performed at day 13. In the folic acid model, folic acid (250 mg/kg) was intraperitoneally injected. Mice were euthanized at day 14 to evaluate kidney fibrosis. Primary kidney perivascular cells were isolated from kidneys and used for in vitro studies.

Results: Both in the unilateral IRI and folic acid models, FoxclCre: Sphk2-/- and FoxclCre: Sphk1-/- mice demonstrated better kidney function (plasma creatinine/blood urea nitrogen), less kidney fibrosis (histology) with less macrophage infiltration, and suppressed expression of fibrosis-related genes (Acta2, Colla1, Col1a1) in the kidneys compared to controls. In in vitro studies, perivascular cells with Sphk2 deficiency or S1Pfpr1 knockdown expressed less proinflammatory cytokines/chemokines, such as Ccl2, Il6, Cxcl1, after treatment with TLR2/4 agonists compared with control cells. We further identified Spts2 as the S1P transporter expressed in kidney perivascular cells. FoxclCre: Spts2-/- mice also showed protection against kidney fibrosis in the unilateral IRI model and Spts2-knockdown cells showed suppressed inflammatory signaling upon stimulation.

Conclusions: SphK2/2/S1P/Spts2/S1P1 axis enhances inflammatory signaling in perivascular cells on injury, which aggravates immune cell infiltration and subsequent fibrosis in the kidney.

Funding: NIDDK Support

SA-OR56
CD153-CD30 Signaling Is Required for Age-Dependent Tertiary Lymphoid Tissue Expansion in the Kidney
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Background: The elderly show a reduced capacity for renal regeneration after acute kidney injury (AKI). We previously showed that, after AKI, aged, but not young, kidneys exhibit tertiary lymphoid tissues (TLTs), which underlie maladaptive repair in aged injured kidneys. TLTs facilitate lymphocyte activation and differentiation in situ and contribute in pathophysiology in various diseases. However, the cells and signals responsible for age-dependent TLT formation in the kidneys are still unidentified.

Methods: We investigated immune cells in aged injured kidneys with TLTs, 45 days after ischemic reperfusion injury, utilizing scRNAseq and bulk RNAseq, combined with flow cytometry and reporter mouse analysis. We also investigated human kidney samples harboring TLTs.

Results: We observed accumulation of CD153+PD1+CD4+ senescent-associated T (SAT) cells and CD30+T-bet- age-associated B (ABC) cells, within TLTs in aged kidneys. Both SAT cells and ABCs are unique age-dependent lymphocyte populations and have been demonstrated to contribute to the pathophysiology of autoimmune diseases and obesity. By scRNAseq, SAT cells were further divided into two subpopulations, peripheral helper-like T cells and IL10-producing T cells, both of which are specialized CD4+ T cells. These populations with B cell helper functions. CD153+ and CD30- were specifically expressed in SAT cells and ABCs, respectively, and their expression was confined within TLTs in aged injuried kidneys. In kidney injury models, CD153 or CD30 deficiency reduced ABC numbers, resulting in attenuated TLT formation with less inflammation and fibrosis. In a mouse renal fibrosis model, SAT cells from CD153-deficient mice exhibited decreased expression of Il21 and Il10, indicating CD153-CD30 signaling was required for SAT cells to acquire B cell helper functions. CD153-expressing cells were detected within TLTs in human kidneys, and human Tph/TFH-like cells and ABCs in non-terminally inflammatory organs also expressed CD153 and CD30, respectively.

Conclusions: These findings identify CD153-CD30 signaling between SAT cells and ABCs as a pivotal regulator of age-dependent TLT formation and suggest that targeting CD153-CD30 signal may be a valuable strategy for the prevention and treatment of kidney diseases in the elderly.

Funding: Government Support - Non-U.S.

SA-OR57
Persistent DNA Damage as a Driver of CKD and Tubular Cell Senescence
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Background: Acute kidney injury (AKI) is a frequent cause of progression to chronic kidney disease (CKD) in humans. Emerging studies have shown that the transition to CKD results from impaired tubular repair due to accumulation of unresolved DNA damage in kidney tubular epithelial cells. Here we identify Fan1, a DNA repair enzyme, as a tubular cell regulator of AKI to CKD progression in response to genotoxic and obstructive kidney injury in mice.
Schiff, or Masson's trichrome staining. Tubular cell senescence was demonstrated by 5-weekly injections of 2 mg/kg) or unilateral ureteral obstruction (UUO). Primary human kidney proximal tubular cells were used for modeling Fan1 inactivation sensitized the kidneys to tubular injury characterized by massive DNA damage response (DDR) activity. We found that persistent DDR triggers tubular cell dedifferentiation, aberrant cell cycle entry and G2 arrest which ultimately led to a failed tubular repair, tubular cell senescence and interstitial fibrosis in Fan1-deficient kidneys. Transcriptional profiling of Fan1 kidneys identified that unresolved DNA damage blocks the cell cycle progression in late G2 through p53-dependent p21 upregulation. G2 cell cycle exit in Fan1-deficient cells was reinforced by nuclear cyclin D1 accumulation and DNA-replication which gave rise to polypliod karyometric cells. Administration of roscovitine effectively blocked cell cycle activity and the formation of karyometric cells in cisplatin-inactivated Fan1-deficient kidneys.

Conclusions: Collectively, our data demonstrate that intact DNA damage response (DDR) is crucial to proximal tubule regeneration after renal injury, and that Fan1 is a key effector of the DDR pathway in this process. Blocking of cell cycle activity immediately after tubular cell injury may be beneficial to augment tubular repair in the kidney.

Funding: NIDDK Support

SA-OR58

Kidney Tubule Polyploidy Drives CKD Progression After AKI
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Background: Acute Kidney Injury (AKI) is characterized by a rapid deterioration of kidney function. In addition, AKI survivors frequently develop chronic kidney disease (CKD). The functional and structural impact of kidney function recovery after AKI is based on a widespread proliferative capacity of injured tubular epithelial cells (TEC), which however is incompatible with the high prevalence of CKD after AKI. We recently demonstrated that TEC respond to AKI not only by proliferation, but also by undergoing polyploidization i.e. acquiring more than one pair of chromosomes. Physiologically, polyploidy offers several advantages such as rapid adaptation to stress, compensation for cell loss and enhanced cell function. However, as polypliod cells can provide functional restoration but not structural recovery they can potentially drive CKD progression.

Methods: We employed in vivo transgenic models based on the Fluorescence Ubiquitin Cell Cycle Indicator (FUCCI) technology in combination with Yap1 overexpression or inhibition. In these models, mice were subjected to glycerol-induced rhabdomyolysis to induce AKI. Polypliod cells have been then characterized by single cell-RNA sequencing analysis, cell sorting, FACS analysis, super-resolution and transmission electron microscopy.

Results: After AKI, Yap1 is activated triggering TEC polyploidization. In Yap1 overexpressing mice, a sustained activation of TEC polyploidization after AKI reduces early functional deficit and attenuates fibrosis, caused by AKI. At CKD transition, indeed, healthy Yap1 overexpressing mice present a consistent decline of kidney function over time suggesting an association between increased polyploidy and CKD development. Isolation of polypliod cells proved that these cells transcribe pro-fibrotic and pro-senescence factors thus confirming their role in CKD progression. Importantly, as polypliod TEC become detrimental over time, blocking Yap1-driven polyploidy in a time-dependent manner avoids CKD development in comparison to control mice.

Conclusions: Collectively, these data suggest that: 1) polypliod TEC are pro-fibrotic leading in the long run to CKD progression; 2) blocking polyploidy in the right window of opportunity, can successfully ameliorate CKD progression after AKI.

SA-OR59

Inhibition of Cadherin-11 Ameliorates Kidney Injury via Restored Expression of Alpha-1 Antitrypsin
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Background: Chronic kidney disease (CKD) represents a massive unmet clinical need, as the pharmaceutical options for treatment of renal injury are extremely limited. A recent study identified cadherin-11 (CDH11) as a potential biomarker for CKD. CDH11 is present in kidney biopsies and urine samples of CKD patients, and its expression is increased in CKD mouse models, but it’s unclear whether it mediates CKD and could be a target for therapy.

Methods: We used three mouse models of CKD to evaluate the role of CDH11: aristoclastic acid nephropathy (AAN), unilateral ureteral obstruction (UUO), and unilateral angiotensin II administration (Unx/AngII). In each of these models, we inhibited CDH11 genetically using transgenic mice and pharmacologically with the administration of a functional blocking antibody to CDH11. We also used de-identified electronic medical records to confirm the clinical relevance of the proposed mechanism whereby CDH11 knockout improves kidney injury.

Results: We found that CDH11 is exclusively expressed in injured murine proximal tubular epithelial cells. CDH11 inactivation sensitized the kidneys to tubular injury characterized by massive DNA damage response (DDR) activity. We found that persistent DDR triggers tubular cell dedifferentiation, aberrant cell cycle entry and G2 arrest which ultimately led to a failed tubular repair, tubular cell senescence and interstitial fibrosis in Fan1-deficient kidneys. Transcriptional profiling of Fan1 kidneys identified that unresolved DNA damage blocks the cell cycle progression in late G2 through p53-dependent p21 upregulation. G2 cell cycle exit in Fan1-deficient cells was reinforced by nuclear cyclin D1 accumulation and DNA-replication which gave rise to polypliod karyometric cells. Administration of roscovitine effectively blocked cell cycle activity and the formation of karyometric cells in cisplatin-inactivated Fan1-deficient kidneys.

Conclusions: Collectively, our data demonstrate that intact DNA damage response (DDR) is critical for proximal tubule regeneration after renal injury, and that Fan1 is a key component of DDR pathway in this process. Blocking of cell cycle activity immediately after tubular cell injury may be beneficial to augment tubular repair in the kidney.

Funding: NIDDK Support

SA-OR60

SARA in the Kidney: Regulation of Cell Phenotype as a Potential Therapeutic Target for Renal Fibrosis
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Background: Epithelial cells play an important role in renal fibrosis. After injury, podocytes and renal tubular epithelial cells (TECs) dedifferentiate. When dedifferentiated, podocytes detach from the glomerular basement membrane, while TECs stimulate surrounding cells to transdifferentiate into myofibroblasts, thus resulting in glomerulosclerosis and tubulointerstitial fibrosis respectively. Our laboratory has identified the protein called Small Anchor Receptor Activation (SARA) as a key factor for maintaining cellular phenotype in the face of fibrogenesis. Here, we aim to determine if SARA overexpression in podocytes and TECs can prevent their dedifferentiation and reduce fibrosis in mouse models of glomerulosclerotic and tubulointerstitial disease.

Methods: SARA overexpression was driven either by Podocin-Cre in podocytes (SARA+/cre and Pax8-cre) or TEC-JUP in TECs (SARA+/cre) in mice. SARA negative littermates (Ctrl+/- and Ctrl+/cre mice) were used as controls. SARA/Ctrl+/- mice were treated with Adriamycin to induce podocyte injury and SARA/Ctrl+/cre mice with aristolochic acid to induce tubulointerstitial disease. Untreated, blood, and kidneys were harvested for histological and molecular analysis. Markers for fibrosis and injury were measured by qPCR. Podocytes were isolated by flow cytometry from SARA/Ctrl+/cre mouse kidneys.

Results: SARA+/- mice showed less glomerulosclerosis histologically and less proteinuria than Ctrl+/- mice after Adriamycin treatment. Tubular cell injury markers (Kim1, Sox9, Ngl) tended to be lower in SARA+/- mice compared to Ctrl+/- after AA treatment, but did not reach statistical significance. No significant difference in expression of markers of fibrosis was observed. Gene expression profiles of podocytes isolated from SARA/Ctrl+/cre mice were being analyzed by RNA sequencing. This will provide insight into the mechanisms by which SARA maintains cellular phenotype and protects against renal fibrosis.

Conclusions: SARA overexpression protects podocytes and TECs against injury. Elucidating the mechanisms by which SARA functions will help unearth new molecular targets for therapies directed at glomerulopathies.

Funding: NIDDK Support

PO001

Observational Evidence of NAD+ Biosynthetic Impairment and Urinary Metabolomic Alterations in COVID-Related AKI
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Background: Acute kidney injury (AKI) is a frequent extrapulmonary manifestation of COVID-19 and is associated with increased morbidity and mortality. We investigated alterations in the urine metabolome associated with AKI among patients with COVID-19, with the hypothesis that changes in nicotinamide adenine dinucleotide (NAD+)-metabolism described in ischemic, toxic, and inflammatory AKI will be also associated with AKI in patients with COVID-19.

Methods: This is a case-control study among two adult populations with COVID-19: critically ill patients hospitalized in Boston, Massachusetts, and a general hospitalized patient population in Birmingham, Alabama. Cases had AKI stages 2 or 3 by Kidney Injury Measurement (KIM) criteria. Controls had no AKI by KIM and/or CRIT criteria. Metabolites were measured by liquid chromatography - mass spectrometry.

Results: 14 cases and 14 controls were included from Boston, and 8 cases and 10 controls included from Birmingham. Urinary quinolinate to tryptophan ratio, an indicator which can increase with impairment in NAD+ biosynthesis, was higher among cases than controls at each location and pooled across locations (median [IQR]: 1.34 [0.59-2.96] in cases, 0.31 [0.13-1.63] in controls, unadjusted p = 0.0013; p=0.03 in analyses adjusted for age and sex). We identified alterations in tryptophan, nicotinamide, and other components of energy metabolism as well as decreases in purine metabolites which contributed to a
distinct urinary metabolomic signature that could reliably differentiate patients with and without AKI (supervised random forest class error: 1/14 for AKI and 1/14 for no AKI groups in Boston, 0/8 for AKI and 0/10 for no AKI groups in Birmingham).

Conclusions: Conserved urinary metabolic alterations spanning multiple biochemical pathways distinguish AKI vs. non-AKI in the context of COVID-related hospitalization at two large academic medical centers. AKI is further associated with dysregulated purine metabolism and downregulated NAD+ biosynthesis that suggest impaired energy metabolism in the kidney. Augmenting renal NAD+ by administering biosynthetic precursors may present a novel therapeutic opportunity to mitigate COVID-19 associated AKI.

Funding: NIDDK Support, Private Foundation Support

PO0002
Expression of SARS-CoV-2 Viral Protein ORF3A in Renal Tubular Epithelial Cells Induces Injury
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Background: The coronavirus SARS-CoV-2 is the culprit of the COVID-19 pandemic. Acute kidney injury occurs frequently in COVID-19 patients and several lines of evidence suggest local infection of kidney cells by the virus. However, this remains controversial and it is unclear how the viral proteins of SARS-CoV-2 directly impact the health of renal tubular cells infected by the virus.

Methods: The viral protein ORF3A of SARS-CoV-2 was overexpressed in HK-2 renal tubular cell line and the proteomic tubulipa of transgenic zebrafish. The NF-kB and STAT3 signaling pathways and target gene expression were analyzed using quantitative RT-PCR and Western blots. The expression of the renal injury marker KIM-1 was also assessed by Western blots, quantitative RT-PCR and in situ hybridization. Protein-protein interactions were studied by co-immunoprecipitation and Western blots.

Results: ORF3A augments both NF-kB and STAT3 signaling by enhancing the phosphorylation of the transcription factors and results in the expression of downstream target genes and subsequently increases the expression of kidney injury molecule 1 (KIM-1) in HK-2 cells. Mechanistically, ORF3A elevates the expression of Tripartite Motif-Containing Protein 59 (TRIM59), a ubiquitin E3 ligase, which forms a protein complex with ORF3A and STAT3. This in turn excludes the phosphatase TCPIP from binding to STAT3 and inhibits the dephosphorylation of STAT3. The transgenic zebrafish expressing ORF3A in renal tubular epithelia develop severe edema starting 48 hours post fertilization and in situ hybridization shows elevated km-1 expression in the proximite tubules, indicating that ORF3A induces renal injury in zebrafish in vivo.

Conclusions: We demonstrate that overexpression of ORF3A is sufficient to injure renal tubular epithelial cells and uncover a previously unrecognized molecular mechanism underlying the deregulation of STAT3 activity by ORF3A that leads to renal tubular cell injury. Further, the results of this study support the notion that direct infection of renal epithelial cells by SARS-CoV-2 may contribute to the renal complications in COVID-19 patients.

Funding: NIDDK Support, Clinical Revenue Support

PO0003
Deciphering the Impact of Cytokine Storm on APOL1 Expression in Primary Human Glomerular Endothelial Cells
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Background: High Risk (HR) Apolipoprotein L1 (APOL1) genotypes are associated with collapsing glomerulopathy in the context of interferons (IFNs), HIV, systemic lupus erythematosus (SLE), and SARS-CoV-2 infection. Elevated circulating inflammatory cytokines, commonly referred to as “cytokine storm” are believed to play causal role in disease pathogenesis. Although the role of IFN and TNF in APOL1 induction has been described, it is unknown if other components of “cytokine storm” implicated in COVAN and lupus glomerulopathy also induce APOL1 expression. In vitro and animal studies show that expression of variant APOL1 is sufficient to cause glomerulopathy in dose-dependent manner. Therefore, it is important to establish if other components of “cytokine storm” regulate APOL1 expression in human glomerular compartment.

Methods: We evaluate the direct effect of cytokines implicated in the above diseases on APOL1 expression in primary human glomerular endothelial cells, a cell type with known significance in lupus and COVAN. We also screened these select cytokines using peripheral blood monocytes (PBMCs) from patient with SLE and HR APOL1 genotype.

Results: IFNα (β-γ/u) are the strongest drivers of APOL1 expression. Importantly, we also found that IL-6 increased APOL1 expression by 7 fold compared to control (p=0.01) in glomerular endothelial cells. Treatment with composite of all cytokines induced the most robust APOL1 expression. However, Jak 1/2-specific inhibitor, baricitinib, markedly attenuated this effect, with reduction in APOL1 expression from 800 fold down to 4 fold. Additionally, in PBMCs of a lupus patient with HR APOL1, IL-18 also showed significant upregulation of APOL1 expression.

Conclusions: Our data suggest that other cytokines beyond IFNα may be important in the pathogenesis of COVAN, HIVEAN, and APOL1-associated lupus collapsing glomerulopathy. Also, baricitinib may be a promising novel therapeutic in these cytokine-mediated APOL1 nephropathies.

Funding: Other NIH Support - Common Fund (DP2, NIH Director New Innovator Award)

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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Results: We mined the available scRNA-seq dataset of human adult kidneys (GSE19078, GSE131882), and identified a proximal tubule subgroup. PTv cells, is susceptible to SARS-CoV-2 infection. PTv cells are highly enriched of a variety of factors associated to viral infections (such as ACE2, DPFP, ANEP, CTSB, TMPRSS2 etc.). Through cell communication and gene regulatory network analysis, we inferred that PTv cells are more active than other PT cells in terms of repairment, fibrosis, development, and reabsorption. Further by analysis in the datasets GSE139061 and GSE126085, we found that the proportion of PTv increased during acute kidney injury, suggesting that PTv could be used to predict the progression of kidney injury. Analyzing human kidney organoids and scRNA-seq data (GSE140989, GSE151096, GSE108379, GSE147863, GSE119561, GSE114802, GSE136314, GSE118184), we identified that the PTv widely present in kidney organoids, indicating that kidney organoids can be used in SARS-CoV-2 related research.

Conclusions: We revealed the characteristics of the PTv, a gateway cell for SARS-CoV-2 in kidney, and provided a molecular basis for the feasibility of renal organoids to study the renal tropism of SARS-CoV-2.

PO0006

Longitudinal Proteomic Characterization of AKI in Hospitalized COVID-19 Patients


Background: Acute kidney injury (AKI) is a known complication of COVID-19 associated with increased in-hospital mortality.

Methods: We longitudinally measured serum levels of 4,497 proteins (Somasean) in 437 COVID-19 patients at multiple timepoints along their hospital course and identified associations with AKI. Using single cell transcriptomic data from healthy human kidney specimens, we identified cell-specific kidney intracellular markers and quantified their leakage in sera from AKI patients. We also investigated whether serum proteomics improves AKI prediction.

Results: We identified 408 upregulated and 107 downregulated proteins in COVID-AKI (144 cases, 293 controls, FDR<0.05, Fig 1A). Downregulated proteins included coagulation cascade inhibitors (protein C, heparin cofactor 2) and platelet dysregulation markers (Fig 1B), including platelet factor 4 (PF-4). Given the role of PF-4 in induced thrombocytopenia (HIT), we then retrospectively analyzed 4,035 COVID-19 hospitalizations and found a significant association of HIT suspicion with COVID-AKI (aOR = 12.6, p <0.001). Intracellular AKI associated proteins were enriched for markers of the Loop of Henle, descending vasa recta endothelium, and NK cells (Fig 1C), which all have low ACE2 (Fig 1D) and TMPRSS2 expression (SARS-CoV2-receptor and activator respectively), suggesting bystander damage within the kidney, not direct viral invasion likely drives COVID-AKI. Finally, a random survival forest model incorporating protein levels improves AKI prediction.

Conclusions: The COVID-AKI serum proteome is characterized by dysregulated platelets with clinical evidence of HIT, improves prediction of incident AKI in a machine learning model and suggests inflammation mediated renal cell death, rather than direct viral invasion via the renal ACE2 receptor.

PO0007

TIMP-2*IGFBP7 and N-Gal are Strongly Associated with the Development of AKI in Patients with Severe Pneumonia Caused by SARS-CoV-2


Background: The cut-off points for the urinary kidney biomarkers (BM): TIMP2*IGFBP7 (Tissue Inhibitor of Metalloproteinase-2 * Insulin-Like Growth Factor Binding Protein-7) and Neutrophil Gelatinase associated lipocalin (NGal) in patients with AKI by SARS-CoV-2 are not defined.

Methods: Between May-August 2020 prospectively included patients with severe pneumonia caused by SARS-CoV-2 without AKI at the moment of enrollement. Fresh urine was collected at admission of critical care and was immediately frozen at -80 degrees Celsius. NGal and TIMP-2*IGFBP7 were measured in urine. We derived cutoffs based on sensitivity (S) and specificity (E) for predicting AKI using K-DEQ criteria for urinary kidney BM and some serum BM. The best cut-off of N-Gal and TIMP-2*IGFBP7 were used to construct Kaplan Meier curves to assess differences in the risk of AKI. We performed a logistic regression model for significant variables to AKI. The analysis was conducted by SPSS V25.

Results: We included 51 patients, 20 AKI and 31 matched controls. Hypertension in the AKI group was 50% vs 12.9% p=0.009. Mortality in the group with AKI was 8 (15.7%) vs 2 NO-AKI (3.9%) p=0.013. Table 1 shows AUC of urinary and serum clinical BM for predicting AKI. TIMP2*IGFBP7 cut-off point of 0.2 ng/ml had S= 50%, E= 90%, and N-Gal 45 ng/ml had S=70.5%, E 80.6%. Survival curves for AKI were constructed after stratifying TIMP-2 IGFBP7 >0.2 vs <0.2 and N-Gal >45 vs <45 ng/ml, cut-off <0.2 of TIMP2*IGFBP7 had lower risk for AKI during (Log-rank test p = 0.002), lower risk for AKI was also observed with the cut-off <45 ng/ml for N-Gal (Log-rank test p = 0.001). Multivariat analysis indicated risk factor for AKI was higher when TIMP2*IGFBP7 >0.2 (ng/ml)/1000 (OR 10.29, 95% CI=1.26-83.60, p=0.029); and higher N-Gal >45 ng/ml (OR 5.75, 95% CI 1.00-30.87, p=0.038).

Conclusions: TIMP2*IGFBP7 and NGal in urine are excellent predictors of AKI in patients with severe pneumonia caused by SARS-CoV-2.

Funding: Government Support - Non-U.S.

Prediction of AKI using urinary and serum clinical biomarkers

<table>
<thead>
<tr>
<th>Urinary Biomarker</th>
<th>AUC</th>
<th>p</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMP-2*IGFBP7</td>
<td>0.697</td>
<td>0.012</td>
<td>0.537-0.853</td>
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<tr>
<td>NGal</td>
<td>0.789</td>
<td>0.001</td>
<td>0.640-0.929</td>
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<tr>
<td>Creatine (mg/dl)</td>
<td>0.680</td>
<td>0.012</td>
<td>0.549-0.811</td>
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<tr>
<td>Procalcitonin (ng/l)</td>
<td>0.752</td>
<td>0.005</td>
<td>0.613-0.884</td>
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<tr>
<td>Troponiny (ng/l)</td>
<td>0.742</td>
<td>0.007</td>
<td>0.555-0.889</td>
</tr>
</tbody>
</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

Figure 1

Figure 1

AUC= Area under the curve

PO0008

AKI in a Mouse Model of COVID-19: Therapeutic Potential of a Novel ACE2 Variant

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Background: We have previously shown that in the ischemia reperfusion model of AKI kidney ACE2 activity decreases and that the administration of a shorter soluble ACE2 variant markedly attenuates AKI in terms of GFR and kidney histiography (Shirazi et al, ASN 2019). Here, we report the effect of a novel ACE2 variant designed to prevent/treat SARS-CoV-2 in transgenic k18-hACE2 mice infected with a lethal viral dose.

Methods: In a BSL-3 facility, transgenic k18-hACE2 mice were infected intranasally with 2x10^6 PFU SARS-CoV-2. ACE2 1-618-DDC-ABD was administered intranasally and intraperitoneally 1 hour prior to viral challenge as well as 24 and 48 hours afterwards for a total of 3 doses. Infected control animals received PBS at the same time-points. Kidneys were removed from all animals and examined by light microscopy (LM) histologically and for apoptosis, using PAS and TUNEL staining, respectively.

Results: In mice infected with SARS-CoV-2, variable degrees of AKI were found by LM with the following features seen in the few most severe cases: proximal tubule brush border loss (black arrows, figure 1A and B), cytolysis (red arrow, figure 1A), tubular basement membrane disruption (blue arrows, figure 1A and B) and apoptosis (white arrows, figure 1A, B, D and E). In animals treated with ACE2 1-618-DDC-ABD, survival was near 100% and proximal tubular kidney injury was absent or markedly attenuated with less proximal tubule injury (figure 1C) and minimal apoptosis (figure 1F). Glomeruli appeared ischemic (figure 1B, green arrow) but otherwise normal without evidence of thrombosis.

Conclusions: Kidneys from a transgenic mouse susceptible to SARS-CoV-2 infection, like patients with COVID-19, displays variable degrees of proximal tubular injury suggesting that this model can be useful to study AKI in COVID-19. Mice that received soluble ACE2 1-618-DDC-ABD protein were essentially protected from AKI suggesting a potential preventative/therapeutic role for soluble ACE2 in this otherwise pharmacologically untreatable devastating disease.

Funding: Private Foundation Support
Kidney Injury Molecule 1 Is a Receptor for SARS-CoV-2 in Lung and Kidney

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Background: Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 was first reported in Wuhan in 2019 and reached pandemic proportions. SARS-CoV-2-related respiratory failure and acute kidney injury (AKI) are major complications of infection. Kidney Injury Molecule-1 (KIM-1) is a scavenger receptor expressed by kidney epithelial cells and was previously reported to be a receptor for Hepatitis virus A. We hypothesized that KIM-1 is a receptor for SARS-CoV-2 and may play an important role in COVID-19 lung and kidney injury.

Methods: Human lung and kidney autopsy samples were immunostained and analyzed. Liposomal nanoparticles displaying the SARS-CoV-2 spike protein on their surface (virus-like particles) were generated. Virome uptake by A549 lung epithelial cells, mouse primary lung epithelial cells and human kidney tubuloids (3D structures of kidney epithelial cells) was evaluated in the presence or absence of anti-KIM-1 antibody or TW-37, a small molecule inhibitor of KIM-1-mediated endocytosis that we discovered. Protein-protein interaction characteristics between purified SARS-CoV-2 spike protein and purified KIM-1 were determined using microscale thermophoresis. HEK293 cells expressing human KIM-1 but not angiotensin-converting enzyme 2 (ACE2) were infected with live SARS-CoV-2 or pseudovirions expressing the SARS-CoV-2 spike protein.

Results: KIM-1 was present and expressed in lung and kidney epithelial cells in COVID-19 patient autopsy samples. Human and mouse lung and kidney epithelial cells expressed KIM-1 and endocytosed spike virions. Both anti-KIM-1 antibodies and TW-37 inhibited uptake. Enhanced KIM-1 expression by human kidney tubuloids increased virome uptake, whereas TW-37 was less effective. Using microscale thermophoresis, the EC50 for interaction between KIM-1 and SARS-CoV-2 spike protein and the receptor binding domain were 56.2 ± 3.10 nM, and 9.95 ± 3.10 nM, respectively. KIM-1-expressing HEK293 cells without ACE2 expression had increased susceptibility to infection by live SARS-CoV-2 and pseudovirions expressing spike protein compared with control cells.

Conclusions: KIM-1 is a receptor for SARS-CoV-2 in the lung and kidney and thus, KIM-1 inhibitors such as TW-37 can be potential therapeutics and/or prophylactic agents for COVID-19.

Funding: NIDDK Support, Other NIH Support - NCATS, Government Support - Non-U.S.

Plasticity of Neutrophil Subsets in ANCA Vasculitis and COVID-19

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Background: A population of granulocytes appear in the PBMC layer of dense separated blood and are termed Low Density Granulocytes (LDGs). These are seen in many conditions including cancer, sepsis, autoimmunity and pregnancy. We previously identified LDGs in acute and remission ANCA vasculitis (AAV) and hypothesised that these LDGs are also present in COVID-19 (C-19) and our aim is to phenotype these cells and determine whether LDGs are a disease specific cellular response to inflammation. Of particular interest is the expression of intracellular Arginase 1 (Arg-1), an enzyme linked to T cell suppression in many disease situations.

Methods: LDGs were isolated using a modified percoll preparation and analysed by both traditional and imaging flow cytometry, in patients with active and remission AAV vasculitis, in patients with severe moderate and mild C-19 and in healthy controls. The phenotyping panel included CD14, CD15, CD16, CD33, CD62l. Intracellular Arg-1 was stained following permeabilisation with saponin.

Results: We identified extensive populations of LDGs in both AAV and Covid-19 peripheral blood. LDG levels are associated with disease severity. Arg-1 is differentially expressed in neutrophil populations from AAV and C-19. In C-19 Arginase levels are correlated to disease severity suggesting that Arginase release may be associated with favourable outcome. Interestingly, all neutrophil fractions show lower levels of Arginase in C-19 patients whereas in AAV only LDGs have lower levels. Healthy controls have high Arginase expression.

Conclusions: Neutrophil subsets display disease specific responses in C-19 and AAV demonstrating their plasticity in inflammatory settings and warrant further investigation.

Funding: Government Support - Non-U.S.

Plasma TNFRI1 Predicts Major Adverse Kidney Events in Hospitalized Patients with COVID-19

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Background: Patients hospitalized with COVID-19 are at risk for major adverse kidney events (MAKE). Predicting which patients will experience progression of disease and poor outcomes remains elusive. We sought to develop a biomarker-based risk model for predicting MAKE in patients hospitalized with COVID-19.

Methods: We applied least absolute shrinkage and regression methodology (LASSO) to a prospectively enrolled cohort of 432 patients admitted with COVID-19 who had

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Underline represents presenting author.
blood specimens collected (median 2 days [IQR 2-4 days] from admission) from March 2020 to June 2021, at three large academic medical centers. Clinical variables and 26 plasma biomarkers were used as candidate features in the prediction models for the outcome of MAKE, defined as KDIGO stage 3 AKI, dialysis-requiring AKI, or in hospital mortality. Cross-validation was used for optimal shrinkage parameter selection and model tuning by optimism-corrected using bootstrapping.

Results: MAKE occurred in 85 (20%) patients within 60 days of admission. Application of LASSO to the 26 biomarkers selected IL-12, IL-13, IL-6, TIE2, FLOT1, NGAL, MCP1, YKL40, Ang1, Ang2, and TNFR1, which yielded an AUC of 0.88 (95% CI 0.79-0.97). A cutoff of TNFR1 at 3005 pg/ml had a sensitivity of 69%, PPV of 60% and NPV of 92% for occurrence of MAKE over 60 days.

Conclusions: In this multi-center cohort study, plasma TNFR1 by itself produced a robust prediction for MAKE in patients hospitalized with COVID-19 that did not improve when combined with multiple clinical variables and was equivalent to combined inputs of 10 other plasma biomarkers.

Funding: NIDDK Support

PO0014


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Background: Incidence of Acute Kidney Injury (AKI) among COVID-19 patients is 35%. Requirement for Renal replacement therapy (RRT) is estimated to be 15%-20%. We aimed to identify risk factors associated with mortality and need for RRT in COVID-19 patients with AKI. We also estimated burden of the pandemic on inpatient hemodialysis (HD) unit.

Methods: Inpatients over 18 years, diagnosed with COVID-19 on RT-PCR between March-June 2020 were included in the study. AKI was defined using KDIGO guidelines. Data collected included demographics, serum creatinine, time to AKI, AKI comorbidities, all-cause death, and HD initiation. All inpatient HD sessions from January 2020 to June 2020 were included to estimate burden of COVID-19. CVVHD, PI RRT and PD were excluded. Statistical analysis included logistic regression, ANOVA, z-test for proportions and Chi-square test. Interrupted time series analysis using Auto Regression Integrated Moving Average (ARIMA) was used to predict proportion of bedside HD sessions from January 2020.

Results: 1991 patients positive for COVID-19 on RT-PCR were included. 683 (34.2%) were found to have AKI. 185 patients (27.1%) required RRT. Mortality among AKI patients was 64.7%. Age (OR=1.04; CI 1.03 to 1.06), AKI after 1 week (OR=2.15; CI 1.06 to 4.35), albuminuria (OR=2.57; CI 1.11 to 5.93), for need for RRT (OR=2; CI 1.26 to 3.19) and intratubulation (OR=4.6; CI 2.71 to 7.75) were the mortality risk factors. Albuminuria (OR=2.97; CI 1.04 to 8.46), CKD (OR=3.5; CI 1.67 to 7.34) and intratubulation (OR=7.8; CI 5.14 to 11.91) were the risk factors for RRT. Diabetes and hypertension did not increase mortality or the need for RRT. To estimate the burden of pandemic, 24086 HD sessions between Jan. 2016 to June 2020 were analyzed. Proportion of bedside HD was significantly higher in 2020 when compared to previous years (p<0.01) due to isolation requirement showed an extra burden of 870 nurse-hours with March-April accounting for 73.1% of the extra burden.

Conclusions: Age, AKI after 1 week and intratubulation are significant predictors of mortality among COVID-19 patients with AKI. To estimate burden of pandemic, ARIMA model was used to predict proportion of bedside HD sessions from January 2020.

Funding: Veterans Affairs Support

PO0016

Comparison of Mortality in Hospitalized COVID-19 Patients with AKI vs ESRD

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Background: Patients hospitalized with COVID-19 illness are at high risk for developing acute kidney injury (AKI) and have high mortality rates. Chronic kidney disease (CKD) and end stage renal disease (ESRD) are independent risk factors for COVID-19 disease severity and mortality. Our study compares mortality rates of hospitalized patients with COVID-19 illness who develop AKI with baseline renal function, 2 develop AKI with baseline moderate-to-severe CKD stages 3 or 4, and 3 have ESRD.

Methods: Consecutive patients admitted with COVID-19 illness referred to Nephrology with AKI or ESRD on dialysis were included. Retrospective data collected included: Demographics, medical history including CKD stage, labs, O2 therapy, AKI diagnosis (KDIGO), and renal replacement therapy (RRT). Chi-square test was used to evaluate the unadjusted association between AKD stage and mortality. Multivariate logistic regression models were used to estimate associations between CKD stage and mortality adjusting for potential confounders.

Results: 166 patients were analyzed: 87 patients had AKI with baseline normal renal function (GFR > 60 ml/min (AKI-N), 41 patients had AKI on CKD Stage 3 or 4 (AKI-CKD3/4), and 38 patients had ESRD. Mechanical ventilation was used in 33(27.9%) AKI-N, 20(48.8%) AKI-CKD3/4, and 10(26.3%) ESRD patients, p = 0.069. Three [3.5] AKI-N received iHD, and 9[10.3%] received CRRT/PI RRT. Six [14.6%] AKI-CKD3/4 received iHD and 7[17.1%] received CRRT/PI RRT. Of all AKI patients, 55.5% had CKD stage 3/4 or ESRD. Compared to AKI-N, both AKI-CKD3/4 and ESRD had significantly increased odds of mortality (OR=2.59, p=0.006) and decreased odds of mortality for ESRD patients (OR=0.5, p=0.001), compared to AKI-N.

Conclusions: COVID-19 patients with ESRD had less mortality than AKI-N, while AKI-CKD3/4 had higher mortality than both ESRD and AKI-N patients. Prospective studies to determine specific criteria for early initiation of RRT in COVID-19 AKI patients are warranted, as it may decrease mortality especially in those with baseline CKD 3/4.

PO0017

Association with COVID-19: Differences Between Previously Healthy Kidney Individuals and CKD Patients

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Background: Renal injury associated with COVID-19 has an incidence of 3-9%, ranging from urinary abnormalities to acute kidney injury (AKI-COVID19), which is mainly observed in critical care patients. The main risk factors for AKI-COVID19 appearance are: oncologic disease, sepsis, heart failure. However, it has not described if there are differences between AKI-COVID19 patients in previously healthy kidney (AKI-COVID19) and those with baseline kidney disease (AKI-CKD), thus we decided to explore it in patients who were assisted during the first pandemic wave (2020) in Clínica de la Costa, Barranquilla, Colombia.
Methods: 572 patients with confirmed diagnosis of COVID-19 (PCR) were evaluated. Our study included patients and their epidemiological data, serum parameters, and functional status were recorded. Statistical analysis and comparison between AKI-NRF and AKI-CKD patients were performed.

Results: From 720 individuals evaluated at the emergency room for suspicion of COVID-19, 572 of them were admitted with confirmed SARS-CoV-2 infection. Most of them were male (59%), median age 55 years, with hypertension (36%), obesity (23%), diabetes (18%), heart disease (5%), and COPD (9%). Almost all patients were robust (97%). 188 COVID-19 patients developed AKI (33%), although 149 (26%) presented a previous normal renal function (AKI-NRF), while 39 (7%) had CKD (AKI-CKD). Most of CKD patients (91%) developed AKI. There was a predominance of male gender, old age (a 60 years), frailty status (CFS ≥ 4), diabetes mellitus, obesity, COPD in AKI group (AKI-NRF and AKI-CKD subgroups) respect to NO AKI group (n: 380). The prevalence of hypertension and cardiac disease was significantly higher in AKI-CKD respect to AKI-NRF, and even higher respect to NO AKI. However, there was a tendency of higher mortality rate in AKI-NRF (69%) compared to AKI-CKD (56%). Even though, this trend did not reach statistical significance (p=0.09), mortality rate in AKI compared to NO AKI (16%) (p<0.0001) did. D-dimer was slightly higher in AKI-NRF compared to AKI-CKD (p=0.06).

Conclusions: There was a trend to higher mortality rate and D-dimer levels in AKI-NRF individual compared to AKI-CKD patients.

PO0018

AKI in Inpatients with COVID-19: Risk Factors and Mortality

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Background: AKI in hospitalized patients with COVID-19 is a common adverse complication. Our aim was to investigate risk factors associated with AKI and whether AKI in this setting is independently associated with in-hospital mortality at 30 days.

Methods: All adult patients admitted with a positive SARS-CoV-2 PCR between 3/2021 to 1/2021 to nineteen hospitals who had a COVID-associated billing diagnosis and no history of ESKD or kidney transplant were included. AKI was defined according to the Kidney Disease Improving Global Outcomes guidelines. Risk factors associated with AKI were determined using bivariant and multivariable logistic regression, and mortality was evaluated using Kaplan-Meier and Cox Proportional Hazards models.

Results: The study cohort included 9,681 patients, of which 3,666 (38%) met criteria for AKI. Compared with patients without AKI, patients with AKI were older (mean (SD) age 67 (16) vs. 60 (18) years), more likely to be male (58% vs. 47%), and more likely to be black (21% vs. 15%). Patients with AKI were also more likely to have diabetes mellitus (52% vs. 32%), hypertension (78% vs. 57%), CKD (55% vs. 17%), and coronary artery disease (20% vs. 11%). Patients with AKI were also more likely to be on ACEI/ARB on admission (51% vs. 37%), require mechanical ventilation (21% vs. 3.2%) or have higher WBC, hs-CRP, ferritin, D-dimer, and cardiac troponin. P-values were <0.01 for all of the aforementioned comparisons. Risk factors significantly associated with AKI in the multivariable model included age, sex, race, hypertension, CKD, diabetes, ACEI or ARB on admission, mechanical ventilation, WBC on admission, hs-CRP, ferritin, d dimer, and troponin. Death occurred more frequently in patients with AKI (22%; n=811) than in those without (5%; n=178). Patient with AKI had higher mortality risk as compared to those without AKI, hazard ratio (HR) 3.08 (95% CI 2.56-7.1), that remained significant even after controlling for all variables associated with AKI, such as age, sex, race, comorbidities, inflammatory biomarkers, elevated troponin, and COVID-related treatments, HR 1.64 (95% CI 1.34-2.01).

Conclusions: Patients with COVID-19 who develop AKI have a higher mortality. We found that associations of AKI in the setting of COVID-19, and the increased mortality risk associated with AKI in COVID-19 is independent of these factors.

PO0019

Burdens of AKI and CKD Among COVID-19 Survivors

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Background: COVID-19 is known to be associated with increased risk of acute kidney injury (AKI) during the acute phase of the infection. However, the burden of AKI and chronic kidney diseases (CKD) after the first 30 days of COVID-19 infection is not clear.

Methods: 181,384 COVID-19 patients from the United States Veterans Health Care System who survived the first 30 days of infection were enrolled and compared with 4,397,509 non-infected controls on burden of AKI and CKD at 6 months. Adjusted comparisons were conducted across severity of infection measured based on intensity of care received, and by subgroups based on age and pre-existing health conditions.

Results: With a median follow up of 150 (interquartile range: 115; 221) days, the adjusted excess burden of AKI due to COVID-19 was 6.07 (95% confidence interval: 5.46, 6.69) and excess burden of CKD was 7.19 (5.78, 8.55) per 1000 persons at 6 months. The excess burden of AKI increased with the severity of acute infection/excess burden 1.28 (0.68, 1.86), 28.11 (25.94, 30.26) and 73.18 (67.53, 79.02) per 1000 persons at 6 months for COVID-19 patients without hospitalization, hospitalized and admitted to intensive care units, respectively. The excess burdens of CKD were 1.66 (0.19, 3.30), 36.41 (31.71, 41.11) and 82.55 (71.93, 93.78) for those not hospitalized, hospitalized and admitted to intensive care units, respectively. The burden of AKI and CKD increased with increased age (≥60, 60-70, >70 years) and increased pre-existing health conditions (Charlson comorbidity index of 0, 1-3 and >3) (Table).

PO0020

Association Between BMI and Risk of AKI in Hospitalized Patients with COVID-19

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Background: Acute Kidney Injury (AKI) is a frequent complication in ICU patients with a negative impact on patient outcomes. High body mass index (BMI) is reported to be associated with a higher risk of AKI in critically ill patients. Obesity is also a risk factor for developing COVID-19 and for severe illness requiring hospital admission, mechanical ventilation and is associated with mortality.

Methods: A multicenter retrospective cohort study was conducted on 2,716 electronic health records (EHR), (n=1,719 in first surge dates of 3/1/20 until 7/16/20, (n=997 in second surge dates of 10/15/20 until 2/26/21 with COVID-19. Patients without a recorded BMI value were excluded. AKI at admission was defined as the difference between first measured creatinine and nadir creatinine within the first 7 days of admission that was greater than 0.3 mg/dl[1]. The Chi-squared test was used to compare BMI as a categorical variable between AKI and non-AKI groups at admission. The Mann–Whitney U test was used for the same comparison when BMI was treated as a continuous variable.

Results: BMI was dichotomized to < 25 kg/m² and ≥ 25 kg/m² (80.2% vs. 73.7%, p = 0.0108). BMI was not found to be associated with either peak CRP or peak D-Dimer among AKI patients in both surges.

Conclusions: A direct relationship between BMI and AKI is well known, mostly from data that included surgical patients with multiple comorbidities and did not account for peri operative stress[5]. The proinflammatory state in obesity may lead to endothelial damage. In CKD and ESRD, obesity is paradoxically associated with a better prognosis. Few studies have shown an inverse relationship between BMI and AKI risk. High levels of lipoproteins in obesity is thought to lead to endothelial protection in the kidney vasculature. A ‘pre-conditioning’ effect of obesity attenuating against abrupt bursts of hyperinflammation on renal vasculature has been shown. Also adipokine and cytokine profiles produced by adipose tissue can exert protective effects by decreasing inflammation. We describe here the first study showing an inverse relationship between BMI and developing AKI at hospital admission in COVID-19.

PO0021

Association Between Inflammation Markers in Patients with SARS-CoV-2 and the Development and Severity of AKI

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Background: Acute Kidney Injury (AKI) is a common complication associated with SARS-CoV-2 infection. Sepsis, direct cellular injury due to the tropism of the virus, and systemic inflammation are mechanisms involved in its development.

Methods: Prospective Cohort from March-2020 to March-2021 including 200 patients ≥18 years with SARS-CoV-2 RT-PCR. All patients with development of AKI (KDIGO classification) during their hospitalization were registered. Age, gender, hospitalization time, oxygen use, SOFA, APACHE II, BRESICA, PAFI, Leukocytosis, creatinine (Cr) and inflammation markers (procalcitonin, ferritin, RCP, DLH, D-dimer) were registered.

Results: The incidence of AKI was 40%, 77% were male, 64% had AKI 1 and 36% were AKIN in 2 y 3. The use of higher supplemental oxygen, APACHE, BRESICA, D-Dimer and procalcitonin at day 9 and 12 were associated with AKI. In a logistic regression analysis, risk factor to AKI was septic shock (RR; 1.7-117; p=0.013). Other results are shown in Table.
PO0022

Impact of COVID-19-Associated AKI on Subsequent Development of CKD
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Background: There is paucity of data about post-hospital discharge kidney-related outcomes in individuals with COVID-19-associated acute kidney injury (CoV-AKI) during the pandemic. We hypothesized that patients who survive a hospital admission due to COVID-19 and AKI are at risk for acquiring residual chronic kidney disease (CKD) thereafter.

Methods: We conducted a retrospective observational study examining records of patients hospitalized at Ochsner Medical Center over a 3-month period (March-May 2020) with COVID-19 and diagnosis of AKI by KDOQI. We examined the rate of full recovery of AKI (serum creatinine value back to within 10% of baseline or < 1.2 mg/dL) at 9 months post-hospital discharge. Factors associated with recovery were assessed.

Results: Among 916 admissions due to COVID-19 within the study [220 (24%) to an intensive care unit], there were 226 (26%) cases of AKI, 9% of them (43%) with AKI requiring dialysis (AKI-RRT). Patients with CoV-AKI who had a median age of 67 (34-99) and 58% were men. Self-identified black race accounted for 65% of the cohort. Among those with CoV-AKI, there were 111 in-hospital deaths (49%). Of 115 patients with CoV-AKI who were discharged alive, 9-month follow-up data were retrieved in 97 (missing data in 18). Full recovery of kidney function was achieved by 76 (78%). Among those who progressed to residual CKD, 11 (11%) patients were declared to have end-stage kidney disease (ESKD) requiring dialysis. Baseline CKD stages 3-5 was associated with lower rate of full renal recovery [23/76 (30%) vs. 14/23 (61%); RR: 2.01, p=0.004].

Conclusions: Full recovery from CoV-AKI was observed in ¾ of those who remain alive post-hospital discharge. About 1/10 of patients with CoV-AKI reached ESKD at intermediate-term follow-up. Preexisting CKD is associated with lower rate of recovery in CoV-AKI. These data do not seem to suggest that CoV-AKI is associated with greater risk of development of CKD compared to other forms of in-hospital AKI.

PO0023

Predictors of Recovery of Kidney Function Following AKI During Hospitalization for COVID-19
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Background: Studies have shown that COVID-19 hospitalization is associated with severe AKI. However, determinants of kidney function recovery for these patients are not well studied.

Methods: We conducted a retrospective analysis of patients admitted to our institution from March 2020 to April 2021 with diagnoses of COVID-19 and AKI. Recovery of kidney function was defined as a discharge creatinine less than 0.3 mg/dL above baseline. Data on patients’ demographics, comorbidities, AKI stage, ICU admission, and laboratory values were collected by chart review. Univariate analysis and a multivariate logistic regression model were used to identify factors associated with kidney recovery. Results: Of 216 patients, the average age was 66.3 years and 56.0% were men. 62% of patients had recovery of kidney function by discharge. Univariate analysis identified increased severity of illness (ICHF, p < 0.063), AKID (p < 0.001), AKI stage (p < 0.001), ICU admission (p < 0.001), and lower albumin (p < 0.040) as correlates of non-recovery at discharge. In the multivariate logistic regression model ([AUC: 0.732, 95% CI (0.644-0.808)], CHF (p = 0.010), AKI-2 (p < 0.011), AKI-3 (p = 0.001), and ICU admission (p = 0.006) remained associated with non-recovery (Table 1). Follow-up data, at a median of 64 days post-discharge, was available for 61% of the cohort (n = 131). Of these patients, 14% had new recovery after discharge, while 18% had no improvement compared to discharge. At 60 days post-discharge, 8.4% had new CKD. At discharge, 3% of patients were dialysis dependent. Baseline CKD (p = 0.030) and CHF (p = 0.037) were associated with non-recovery at 60 days post-discharge.

Conclusions: Inflammatory markers (d-Dimer and procalcitonin) were associated with the development and severity of AKI but only septic shock was predictive of the development of AKI.

Comparison of socio-demographic in patients with SARS CoV-2 and AKI

PO0024

Recovery from AKI Requiring Kidney Replacement Therapy in Critically Ill Patients with COVID-19
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Background: Acute kidney injury (AKI) requiring kidney replacement therapy (KRT) occurs in as many as one in five critically ill patients with COVID-19. Expanding on previous work by this group, we examined the association of clinical factors at the time of KRT initiation with the outcome of kidney recovery at hospital discharge, accounting for the competing outcome of death.

Methods: We used data from the Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19 (STOP-COVID), a multicenter cohort study that enrolled adults with COVID-19 admitted to ICUs at 68 hospitals across the US from March 4 to June 22, 2020. Among those who acutely required KRT, the outcome of kidney non-recovery (continued dialysis dependence at hospital discharge) was explored with multimonial logistic regression, with kidney recovery (independence from dialysis at discharge) as the reference outcome and death as an alternate outcome. Exposures of interest included demographics, baseline medical status, and markers of illness acuity at the time of KRT initiation.

Results: Of 876 patients with AKI-KRT, 588 (67%) died, 95 (11%) survived to discharge and remained dependent on KRT, and 193 (22%) survived to discharge without KRT dependence. Patients with lower baseline eGFR had greater odds of kidney non-recovery, with OR 8.58 (95% CI: 3.03-24.28) among patients with eGFR ≤60. Reduced urine output on the day of KRT initiation was also associated with kidney non-recovery, with OR 4.23 (95% CI: 1.61-11.15) for urine output <50 mL/day vs >500 mL/day (Figure).

Conclusions: Among critically ill patients with COVID-19 with AKI requiring KRT, lower baseline kidney function and reduced urine output at the time of KRT initiation are associated with kidney non-recovery.

Funding: NIDDK Support.
PO0025

Critically Ill Patients with COVID-19 and AKI: Clinical Characteristics and Outcomes

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Background: Acute kidney injury (AKI) is a well-recognized complication of COVID-19. In this retrospective cohort study, we describe the clinical characteristics and outcomes of patients with severe COVID-19 in 8 intensive care units (ICUs) during the first wave of the pandemic.

Methods: Demographic, clinical, laboratory characteristics, and outcome data, including need for renal replacement therapy (RRT), mechanical ventilation, mortality, and RRT dependence at discharge and at 3 and 6 months, were extracted from the electronic medical record (EMR) between March and July 2020. Using nadir-to-peak serum creatinine, AKI and its stages were defined by the KDIGO consensus. Group comparisons were performed using ANOVA and chi square tests.

Results: After excluding 20 patients with end-stage kidney failure, 479 patients with severe COVID-19 were included. Table 1 displays the characteristics and outcomes of the cohort stratified by AKI. 409 (89.2%) patients developed AKI, with 194 (42.3%) developing stage-3 AKI. Male gender, white race, obesity, and COPD were associated with higher stages of AKI severity. 83 patients (18.1%) required RRT of which 27 (32.5%) survived, and 12 (44.4%) remained dialysis-dependent at hospital discharge. Follow up at 3-months and 6-months indicated dialysis dependence in 5 (45.5%) and 4 (36.4%) of 11 patients (1 died), respectively.

Conclusions: AKI is highly prevalent in our cohort and peak serum creatinine occurs within 3 days of intubation. Long-term dialysis dependence is of concern and merits further study. Multivariable analyses are under way to identify factors that are associated with severe AKI, need for RRT and in-hospital death.

PO0026

Increased Markers of Disease Severity in COVID-19 Patients with Hospital-Acquired vs. Community-Acquired AKI

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Background: The etiology of AKI in COVID-19 correlates strongly with age, comorbidities, and laboratory markers of disease severity. Outpatients with COVID-19 have different exposures that may cause AKI than hospitalized patients; thus, the etiology of AKI occurring before hospitalization [community-acquired AKI (CA)] may differ from those with hospital-acquired AKI (HA).

Methods: Excluding ESKD and hospital transfers, all COVID-19 PCR-confirmed cases admitted to 4 hospitals from 3/01/20 to 5/31/20 had data collected electronically through 7/31/20 including readmissions. Baseline C-EPI eGFR was determined by chart review for the period of 6 months prior to 5 months post-admission. AKI and recovery from AKI were scored using KDIGO staging. CA was defined as AKI with the highest level of creatinine (Cr) on admission, rising Cr on admission, or RRT started within 48 hours of admission without a subsequent AKI event after recovery. All AKI occurring > 48 hours was considered HA. To test which laboratory values correlated with CA or HA, we used a model adjusted for demographics, BMI, Elixhauser comorbidity index (ECI), and CKD stage.

Results: The table shows patients with HA and CA had similar demographics with only the ECI differing significantly. CA had less severe AKI, improved recovery to baseline, and lower mortality than HA. The lower mortality in CA was directly related to the lower stage of AKI. Within a given stage of AKI, mortality was not different between CA and HA. Recovery of renal function was significantly better in CA stage 1 vs. HA (5% vs. 26%, p = 0.001) but was not different for stage 2 or 3. In an adjusted model, higher
Temporal Patterns in Incidence of AKI Associated with COVID-19 Using the National COVID Cohort Collaborative (N3C) Database

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Background: Acute kidney injury (AKI) is a common complication of patients hospitalized with coronavirus disease 2019 (COVID-19), however, the epidemiological studies are limited by single or few centers and short duration. How the incidence of COVID-19-associated AKI has changed over the last 18 months since start of the pandemic is not known.

Methods: We used the N3C enclave to collect data from 42 centers from all geographical regions of the United States of patients hospitalized with COVID-19 from December 2019 to May 2021. Unique patient visit occurrence ID data across various hospitalizations for each center was harmonized to uniformly collect information on serum creatinine (Cr), acute dialysis, end-stage kidney disease (ESKD) and transplantation. From a total of 127,223 patients hospitalized with COVID-19, 3,662 patients with pre-existing ESKD and 20,091 with ≤ 2 measures of Cr were excluded. AKI and AKI stages were defined by KDIGO criteria. Baseline Cr was defined from the outpatient values before hospitalization when available or lowest inpatient value if not available. We analyzed how the incidence of in-hospital AKI changed over time (every 4-month period). Mann-Kendall Test was used to test for monotonic trends of the AKI incidence.

Results: Of the 103,471 patients hospitalized with COVID-19, 31,634 (30.6%) were diagnosed with AKI (mean age 63.3 years, 43.7% female, 32.4% non-white, and 19.5% Hispanic). 14,129 (13.7%) patients were diagnosed with AKI-1, 7,996 (7.7%) had AKI-2 and 9,509 (9.2%) patients had AKI-3. AKI-3 without dialysis and 3,224 (3.1%) had AKI-3 with dialysis. The incidence of ‘all AKI’ decreased from 38.8% in Dec 2019-March 2020 to 26.2% in March-May 2021 (p-value for trend = 0.086) and the incidence of AKI-3 declined from 15.5% to 6.5% (p = 0.086). This is the largest and most nationally representative cohort of patients hospitalized with COVID-19 with the highest number of cases of AKI and of AKI-3 reported thus far. The incidence of COVID-19-associated AKI has shown a non-statistically significant decline during the past 18 months of the pandemic.

AKI Prediction and Recovery in Hospitalized Patients with COVID-19

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Background: AKI is a complication in patients hospitalized with COVID-19 and is associated with poor outcomes. We aimed to develop predictive models for AKI development and recovery in patients hospitalized with COVID-19.

Methods: Patients with a positive SARS-CoV-2 PCR admitted to 19 Texas hospitals from 3/13/2020-1/1/2021 were included. AKI presence and stages were determined using KDIGO guidelines. Individuals with AKI present on admission (POA) were excluded from the predictive models. Patients were followed for 90 days to evaluate for renal recovery (serum creatinine ≤1.1 times baseline). Baseline models for AKI were built using logistic regression: Model 1 included age, sex, race, smoking status, presence of hypertension (HTN), diabetes (DM), chronic kidney disease (CKD), coronary artery disease (CAD), and chronic heart failure (CHF), and use of ACEI/ARB. Model 2, added admission WBC, hs-CRP, and hemoglobin; Model 3, added ferritin and D-Dimer to Model 2 to assess for accuracy improvements. 10-fold stratified cross validation was done to evaluate model performance.

Results: Of 83,982 patients, 2,702 (32%) had AKI, of which 2281 (84%) recovered by 90 days: 92% of stage 1, 75% of stage 2, and 40% of stage 3 AKI, p for trend <0.001. After excluding AKI-3 at present on admission, 776 of 5671 developed AKI during the hospitalization. Percentages of AKI stages 1, 2, and 3 were 67%, 8%, and 25%. Overall, 152 (20%) of 776 required RRT. Patients with AKI were older, more likely to be male, black, and have hypertension, diabetes, coronary artery disease, congestive heart failure, and CKD. The interval improvement of each AKI predictive model was statistically significant, with last model AUC of 78.1 (95% CI 76.3%-79.9%) and all p <0.001. The final model had improvement in all metrics when compared to Models 1 and 2, with a sensitivity of 69%, specificity 76%, positive predictive value 32%, negative predictive value 94%, positive likelihood ratio 3.02, and negative likelihood ratio 0.40.

Conclusions: AKI is common among patients hospitalized with COVID-19, but a large proportion recover renal function by 90 days. Recovery rate is lower based on stepwise higher stages of AKI. Additionally, inflammatory biomarkers to demographics and medical comorbidities can improve prediction of AKI in this patient population.
PO0030
Clinical Characteristics and Outcomes of COVID-19 Patients with AKI at Community-Based Hospital
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Background: The disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and later called Covid-19 has resulted in significant morbidity worldwide. The virus can cause various complications and affect many organ systems. Preliminary reports have shown that Acute Kidney Injury (AKI) is common in patients with Covid-19, however, outcomes of kidney injury in hospitalized patients, especially at the community-based hospitals are not well described. The aim of this study was to describe the incidence, severity, and outcomes of Covid-19 patients with AKI at the community-based hospital.

Methods: This was a single-center, retrospective observational cohort study. All patients (age ≥18) with positive by polymerase chain reaction testing for Covid-19 who required hospitalization were included in the study. Patients with End-Stage Renal Disease and kidney transplants were excluded. We compared outcomes of patients with and without AKI. We used univariable and multivariable Cox regression model to evaluate the relationship between AKI and in-hospital mortality.

Results: 220 patients were included in the study. 89 (40%) patients developed AKI, of whom 67% required kidney replacement therapy (KRT) and 131 (60%) did not develop AKI. In-hospital mortality of patients with AKI was markedly higher than patients without AKI. Among the patients with AKI, 59 (43.8%) experienced in-hospital death while in patients without AKI, 23 (17.5%) died (P<0.001). Unadjusted HR was 2.01 (1.23-3.14; P<0.001). The risk of in-hospital death remained significantly high following adjustment for baseline demographics and comorbidities with adjusted HR 1.8 (CI 1.50-2.74, P=0.015). The median hospital length of stay of patients who were discharged alive differed based upon AKI status. Patients with AKI-KRT had the longest median length of stay (15.5 days IQR 8.5-23.7), followed by patients with AKI non-KRT (7 days, IQR 5-14) and patients without AKI (6 days, IQR 4-10).

Conclusions: AKI is a common condition among patients hospitalized with Covid-19 and is associated with an increased risk of in-hospital mortality. It is important to consider this complication in the management of Covid-19 patients.

PO0031
Risk Factors for AKI and Mortality in COVID-19 in Western Mexico
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Background: Acute kidney injury (AKI) in COVID-19 is associated with disease severity. The aim of this study was to identify risk factors associated with the development of AKI and its clinical impact, such as need for RRT and mortality.

Methods: This is an ongoing prospective study of 161 survivors of KDIGO stage 2 or 3 AKI who were admitted at Stony Brook Medicine (SBM) for COVID-19 between March-June 2020. ‘CKD’ was defined as patient’s final outpatient serum creatinine (SCr) value remaining >10% or 50% above baseline (defined as the lowest SCr during hospitalization) and final GFR < 60 ml/min/1.73m². CKD was divided into ‘incident’ and ‘progressive’ based on baseline CKD status. We also investigated the readmission rate with and without AKI and post-discharge mortality. A comparison cohort of 66 AKI survivors concurrently admitted to SBM who tested negative for COVID-19 were also analyzed for all outcomes.

Results: COVID-19 AKI survivors were more likely to be non-White, Hispanic, have a lower prevalence of baseline CKD and greater severity of illness (mechanical ventilation, acute respiratory distress syndrome, vasopressor use and greater length of hospital stay) during hospitalization compared to COVID-19 negative survivors (p < 0.01). COVID-19 negative AKI survivors were more likely to have re-hospitalization (p =0.03), although no difference was noted in re-hospitalization with AKI among the 2 groups. 29 out of 161 (18%) of COVID-19 positive AKI survivors died after their discharge from COVID-19 hospitalization as compared to only 1 out of 66 patients (1.5%) of the COVID-19 negative AKI survivors (p=0.001). 42 (26.1%) of COVID-19 positive and 17 (25.8%) of the COVID-19 negative patients had a SCr and eGFR measure > 90 days after discharge.

Conclusions: COVID-19 positive survivors of Stage 2 or 3 in-hospital AKI were more likely to have greater severity of illness during hospitalization and greater post-discharge mortality compared to COVID-19 negative AKI survivors. We did not find a difference in the rates of incident or progressive CKD at 10 months follow-up.

PO0032
Follow-Up Study of Survivors of Stage 2 or 3 In-Hospital AKI with or Without COVID-19
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Background: Acute kidney injury (AKI) is a hallmark of hospitalized patients with Coronavirus Disease 2019 (COVID-19) and associated with in-hospital mortality. Recent data suggests glomerular filtration rate (GFR) continues to decline after discharge in COVID-19 AKI survivors, but there are very few reports describing the long-term post-discharge outcomes.

Methods: This is an ongoing prospective study of 161 survivors of KDIGO stage 2 or 3 AKI who were admitted at Stony Brook Medicine (SBM) for COVID-19 between March-June 2020. ‘CKD’ was defined as patient’s final outpatient serum creatinine (SCr) value remaining >10% or 50% above baseline (defined as the lowest SCr during hospitalization) and final GFR < 60 ml/min/1.73m². CKD was divided into ‘incident’ and ‘progressive’ based on baseline CKD status. We also investigated the readmission rate with and without AKI and post-discharge mortality. A comparison cohort of 66 AKI survivors concurrently admitted to SBM who tested negative for COVID-19 were also analyzed for all outcomes.

Results: COVID-19 AKI survivors were more likely to be non-White, Hispanic, have a lower prevalence of baseline CKD and greater severity of illness (mechanical ventilation, acute respiratory distress syndrome, vasopressor use and greater length of hospital stay) during hospitalization compared to COVID-19 negative survivors (p < 0.01). COVID-19 negative AKI survivors were more likely to have re-hospitalization (p =0.03), although no difference was noted in re-hospitalization with AKI among the 2 groups. 29 out of 161 (18%) of COVID-19 positive AKI survivors died after their discharge from COVID-19 hospitalization as compared to only 1 out of 66 patients (1.5%) of the COVID-19 negative AKI survivors (p=0.001). 42 (26.1%) of COVID-19 positive and 17 (25.8%) of the COVID-19 negative patients had a SCr and eGFR measure > 90 days after discharge.

Conclusions: COVID-19 positive survivors of Stage 2 or 3 in-hospital AKI were more likely to have greater severity of illness during hospitalization and greater post-discharge mortality compared to COVID-19 negative AKI survivors. We did not find a difference in the rates of incident or progressive CKD at 10 months follow-up.

PO0033
Comparing COVID Acute Respiratory Distress Syndrome Patients on Extracorporeal Mechanical Oxygenation (ECMO) to Non-COVID Patients: Incidence and Effects of AKI
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Background: AKI has historically plagued those with ARDS and during the pandemic especially so with large resultant mortality rates. During the past year those centers so equipped offered ECMO to treat severe COVID pneumonia. We compared the
non COVID ARDS requiring ECMO with patients with COVID pneumonia requiring ECMO. The aim of the study was to understand the difference in the renal outcomes and its effects of mortality and thereby help in prognostication.

Methods: This is a single center retrospective study where patients with COVID pneumonia needing ECMO in between March 2020 to April 2021 were compared with non COVID ARDS patients needing ECMO between April 2013 to April 2021. The 2 groups were compared and risk ratio calculated for the incidence of AKI, the need for Renal replacement therapy (RRT) and the mortality associated with it.

Results: After excluding the patients who did not meet the criteria, 26 COVID patients treated with ECMO were compared with 22 patients with non COVID ARDS treated with ECMO. The median age of COVID group was higher (48 years vs 36 years) and the median number of days needing ECMO for the COVID group was higher (13 days vs 31 days). Incidence of AKI and the AKI needing RRT were similar in the 2 groups. The overall mortality in patients with COVID pneumonia was higher. Patients with COVID who developed AKI had 1.32 times the risk of mortality, which increased to 1.62 when RRT was needed.

Conclusions: This is a first study comparing the renal outcomes of COVID ARDS requiring ECMO and non COVID ARDS requiring ECMO. Even though the median age and the median number of the days on ECMO were higher for the COVID group, surprisingly the incidence of AKI and those needing RRT were similar. But there was a significantly higher mortality when patients on ECMO developed AKI and even higher for those on RRT. This could be attributed to the cytokine storm seen with COVID, causing a multiorgan dysfunction which can manifest in the form of AKI. Presence of AKI needs to be identified early and can be used for the prognostication in COVID pneumonia.

P00035
Association of Endotoxemia with AKI in Critically Ill Patients with SARS-CoV-2 Infection
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Background: AKI is frequently complicated by sepsis. Endotoxin (lipopolysaccharide), a component of the outer wall of gram-negative bacteria, has been investigated and acknowledged as one of the triggers of lethal shock during sepsis and drivers of cytokine storm. In studies, septic shock was present in 6.4% patients with severe COVID-19, but blood cultures and respiratory cultures were negative in 76%. Initial cohort study of COVID-19 patients from China showed 4.5% developed AKI, subsequent reports showed higher prevalence. While these data suggest that patients with COVID-19 are at risk for septic shock and AKI, mechanisms mediating these processes in the setting of severe coronavirus 2 (SARS-CoV-2) infection remain unclear.

Methods: We conducted a single-center, cross-sectional study in critically ill patients with COVID-19 to test the prevalence of endotoxemia and whether endotoxemia is associated with the development of AKI. Patients were recruited using criteria: Age ≥ 18y, MODS ≥ 9, sepsis and intensive care unit admission, excluded if pregnant, requiring chronic dialysis or chronic immunosuppressive medications. Blood endotoxin activity (EA) measured in patients who met the criteria using the FDA-approved Endotoxin Activity Assay (EAA). EAA is a chemiluminescence bio-assay based on the oxidative burst reaction of activated neutrophils to complement coated LPS-IgM immune complexes. Patients divided into low (0.0 – 0.39 EA units), intermediate (0.40 – 0.59 EA units), high (≥ 0.60 EA units), and non-responder (NR) (patients whose neutrophils do not have the ability to respond to preformed immune complexes in the EAA) group based on measurements from the EAA.

Results: In this study, endotoxemia observed in 24/32 (75%) of our critically ill patients with COVID-19, despite only 2 patients having positive blood cultures for gram-negative organisms. The incidence of AKI was higher in the high EA group (7/14, 50%) as compared to intermediate EA group (1/10, 10%), p=0.01. The need for renal replacement therapy (RRT) was higher in the elevated EA group (4/14, 29%), with none of the patients in the intermediate group requiring RRT, p=0.008.

Conclusions: This study demonstrates the high prevalence of endotoxemia in critically ill patients with COVID-19, regardless of presence of bacteraemia. We also observed that high EA was associated with AKI and the need for RRT.

P00036
AKI in Extracorporeal Support
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Background: Acute kidney injury (AKI) is common in critically ill patients receiving extracorporeal membrane oxygenation (ECMO). Use of continuous renal replacement therapy (CRRT) with ECMO may help optimize fluid balance and correct electrolyte abnormalities but may also worsen outcomes. The relationship between AKI, CRRT, and survival in ECMO patients remains poorly defined. The aim of this study was to evaluate AKI outcomes in the setting of ECMO support. We assessed factors that may influence AKI severity, as well as the safety of combined CRRT with ECMO.

Methods: We performed a retrospective analysis of patients that received ECMO from 2018-2021 at a tertiary hospital, using a prospectively maintained database. All patients requiring CRRT received continuous veno-venous hemodialfiltration (CVVHDF). Data collected includes demographics, ECMO and CRRT parameters, anticoagulation, baseline kidney disease, baseline serum creatinine (sCr), ECMO and CRRT duration, hospital length of stay (LOS), complications (patient and device-related), and outcomes.

Results: To date, 16 ECMO patients with AKI have been analyzed. Mean age was 48.6 ± 15.6 years. Eleven (68%) were male, and 50% were African American. ECMO indication included respiratory failure due to COVID-19 (43%), followed by respiratory failure from sepsis (19%). Initial ECMO modality was VV- in 75% and VA- in 25%. Mean baseline sCr and sCr at CRRT initiation were 1.3+/-1 mg/dL and 3.93+/-.1 mg/dL, respectively. Mean ECMO duration was 30+/-.37 days, and mean CRRT duration was 26+/-.21 days. Elevated plasma hemoglobin (mean peak 103 mg/dL) levels occurred in 14 (88%) patients. Of 10 (63%) patient surviving to discharge, 3 (30%) were dialysis dependent. sCr at CRRT start did not influence CRRT duration: for sCr<4 mg/dL, mean CRRT duration was 37 days, and for sCr>4 mg/dL, mean CRRT duration was 20 days (p>0.21). Mean creatinine at discharge was 1.78+-.1 mg/dL.

Conclusions: Our results suggest that CRRT can be safely combined with ECMO to achieve satisfactory patient outcomes. Dialysis independence seems attainable in most patients; however, additional patient enrollment is underway to support this concept with a greater degree of confidence.
PO0037

RAAS Inhibition and Risk of AKI in COVID-19
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Background: Direct viral invasion of the kidney via ACE2 has been hypothesized as a mechanism of AKI in COVID-19 (COVID). The impact of RAASi on the risk of AKI in COVID is not known. We hypothesized that active use of RAASi preceding admission would be associated with a greater proportional risk of AKI in COVID than influenza (flu).

Methods: In this retrospective cohort, we compared the AKI incidence by RAASi status in 11,898 hospitalized Veterans with COVID or flu between Oct 1, 2019 and Sept 30, 2020. To control for confounding, propensity score weighting balanced baseline conditions, labs, and co-therapies in 4 exposure groups: RAASi users with COVID, non-users with COVID, RAASi users with flu, and non-users with flu. Weighted logistic regression estimated the main effects of RAASi and COVID, and their interaction.

Results: In flu, 7% of RAASi users had a stage 2-3 AKI vs 5% of non-users, a 2% increase (p<0.03). In COVID, 16% of RAASi users had a stage 2-3 AKI vs 12% of non-users, a 4% increase. While the absolute increase in AKI incidence for RAASi users vs non-users was greater in COVID patients vs flu, the difference was not statistically significant (p=0.66) and the RAASi association was proportionally smaller in COVID (see interaction in Table). Similar absolute differences were observed in stage 1-3 AKI (Table), and the interaction was also not statistically significant (p=0.66).

Conclusions: COVID was associated with a greater incidence of AKI than flu. RAASi was associated with an increased incidence of Stage 2-3 AKI in patients with COVID or flu. The proportional effect of RAASi was similar in COVID and flu patients. These findings do not support a disproportionate risk of AKI among RAASi users with COVID.

Funding: Veterans Affairs Support Study

AKI Incidence Rates and Odds Ratios in COVID and Flu by RAASi Status

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<tr>
<th>IR: Incidence Rate</th>
<th>OR: Odds Ratio</th>
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<tr>
<td>Stage 1-3</td>
<td>Stage 2-3</td>
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<td>No-RAASI</td>
<td>No-RAASI</td>
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IR: Incidence Rate, OR: Odds Ratio.
Rates and Stage 1-3 ORs are based on the entire weighted cohort. Stage 2-3 ORs are in the subset of Stage 2-3 and no AKI patients.

PO0038

Dexamethasone Reduces AKI in Critical COVID-19 Patients

Background: More than 50% of severe COVID-19 patients develop acute kidney injury (AKI) and a high percentage of them will require renal replacement therapy (RRT). The aims of this study were to identify AKI prevalence and associated factors in patients with COVID-19 and invasive mechanical ventilation (IMV).

Methods: Prospective cohort analysis of all COVID-19 patients with IMV, admitted to our Institute in Mexico City (Mar 2020 - Jan 2021). AKI was defined according to KDIGO guidelines. Patients with CKD stages 4 or 5 were excluded. Demographic, clinical, laboratory, and treatment variables were registered. AKI development was analyzed by uni- and multivariate logistic regression, mortality by survival analysis.

Results: Of 552 COVID-19 patients, AKI was detected in 196 (35.5%). Among AKI; 80 (40.8%) were Stage 2, and 116 (79.2%) Stage 3. The incidence of each AKI stage was lower in patients treated with dexamethasone (DEXA, Fig. 1A) and decreased the requirement of RRT (30 vs 16, p=0.05). For the multivariate analysis, AKI was grouped into no AKI/Stage1 and Stage 2-3 AKI. DEXA treatment was associated with less AKI incidence (OR 0.34, 95%CI 0.23-0.51) and lower mortality in the adjusted Cox-regression analysis (Fig. 1B).

Conclusions: AKI is associated with increased mortality in COVID-19 patients with IMV. The use of DEXA is associated with lower AKI severity and lower mortality.

PO0039

Volume Balance and AKI in Critically Ill Patients with SARS-CoV-2
Samantha Grumling, Ashley La, Anthony Hung, Daniel S. Rubin, Jay L. Koyner. University of Chicago Division of the Biological Sciences, Chicago, IL.

Background: Evidence from the management of critically ill patients suggests restrictive volume management strategies and avoidance of volume overload improve ICU outcomes. Restrictive practices have been applied to the management of patients with SARS-CoV-2 (COVID-19), but data describing volume management and its associated outcomes in those with and without acute kidney injury (AKI) in this setting are lacking.

Methods: We conducted a single-center retrospective cohort study of ICU patients with COVID-19. 7-day cumulative volume balance from ICU admission in excess of 5% (negative balance) or +5% (positive balance) of ICU admission weight as well as AKI based on KDIGO guidelines were identified. Associations between volume balance, AKI and clinical outcomes (dialysis, mechanical ventilation, and inpatient mortality) were explored.

Results: 194 of 374 ICU admissions (51.9%) had AKI with 60 of 374 (16.0%), 30.9% of those with AKI requiring dialysis. 110 of 374 (29.4%) developed negative balance and 40 of 374 (10.7%) developed positive balance. Inpatient mortality was higher in those with AKI and negative balance (28%) and positive balance (35%) compared to those with neutral balance (16%) (p=0.039). Of the subjects with negative balance (Table), despite no difference in their net volume balance, inpatient mortality was significantly higher in those with AKI compared to those without AKI (p=0.048). Using the Kaplan-Meier estimator, patients with no AKI had no difference in inpatient survival when compared on the basis of volume balance (p=0.69). However, in those with AKI, inpatient survival was significantly lower for positive and negative volume balance compared to neutral balance (p=0.01).

Conclusions: Negative and positive volume balance are associated with higher inpatient mortality particularly in patients with AKI. Future research must investigate the impact of negative balance on morbidity and mortality in patients with and without AKI.

Outcomes of ICU Patients with Negative Balance by AKI Status

<table>
<thead>
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PO0040

Urinary Findings Reveal Dominant Tubular Injury in Hospitalized Patients with COVID-19
Avital Angel-Korman, Adi Leiba. Samson Assuta University Hospital, Ashdod, Israel; Ben Gurion University, Faculty of Health Science, Beer-Sheva, Israel.

Background: Renal manifestations during infection with SARS-CoV-2 are prevalent and include proteinuria and hematuria as well as acute kidney injury (AKI). Possible mechanisms of renal involvement with COVID-19 are acute tubular injury (ATI) due to cytokine storm, direct virus-induced tubulopathy or glomerular injury related to podocytopathy. However, a kidney biopsy or urine studies including direct urine microscopy have rarely been performed. Our aim was to examine the urinalysis, level of...
protein excretion and microscopy findings in urine collected from hospitalized COVID-19 patients in order to better elucidate the nature of COVID-19 related kidney involvement.

Methods: We collected fresh urine samples from 92 patients admitted to the COVID-19 ward at Samson Assuta University Hospital in Israel. Urine samples were collected randomly, regardless of renal function or prior medical history. Urinalysis and urine chemistry were performed in addition to direct urine microscopy analyzed by an experienced nephrologist.

Results: Urine samples were collected from 55 men and 37 women, most of whom (64%) had severe COVID-19 at the time urine samples were obtained. AKI at different levels of severity was diagnosed in 37 patients (40%). Proteinuria and hematuria were present in 43% and 38% of urinalysis samples, respectively, suggesting glomerular involvement. Urine protein to creatinine and albumin to creatinine ratios were measured in 76 patients (83%). Median urinary albumin to protein ratio (UATPR) was very low --0.16, indicative of a tubular origin of the proteinuria. Direct urine microscopy was performed on 58 samples, of which granular casts were detected in 43% (25 samples) and in 5 of them granular casts were spotted without evidence of AKI. Additionally, uric acid crystals and amorphous urate were found in 19 (33%) of microscopy samples. Median urine pH was 5.5 which likely contributed to precipitation of uric acid. Notably, urine sediment clues of either nephrotic or nephritic syndrome were absent in all examinees.

Conclusions: Urinary sediment findings and a very low UATPR support ATI as the main mechanism for kidney injury in COVID-19 patients. Acidic urine and uric acid crystals may have resulted from viral related ACE2 down regulation, enhanced angiotensin II and aldosterone mediated urinary acidification. Further studies are needed to shed light on COVID-19 related kidney involvement.

PO0041

Urinary Epidermal Growth Factor as a Protector in COVID-19 Patients with AKI

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Background: Acute Kidney Injury (AKI) in hospitalized patients with infection by SARS-CoV-2 (COV-AKI) is a multifactorial syndrome with immune and inflammatory responses. Knowing the cytokine profile will help to understand the pathogenesis.

Methods: Single center, prospective study at the National Institute of Respiratory Diseases (INER), Mexico. Between May-August 2020 we included patients with severe pneumonia by Sars-CoV-2. We collected urine for cytokines quantification with a Human Cytokine Magnetic 30-plex panel by Luminex, TIMP-2 and IGF-BP7 by ELISA and N-Gal by Architect®. Clinical and laboratory data were gathered from medical file. We evaluated for AKI defined by the 23rd AKIN consensus with [TIMP2][IGFBP7] >0.3. We used χ2 and Mann Whitney-U test to compare groups. We calculated the area under the curve (AUC) for EGF, determined the best accuracy cut-off point and correlated EGF with NGAL, [TIMP2][IGFBP7] and GFP with a Spearman-rho. We did a univariate and multivariate logistic regression.

Results: We included 51 patients with 53 years-old median age and 58.8% men. Hypertension and D-dimer were higher in the AKI group. In the urinary cytokines there were differences for RANTES as risk factor and EGF as protective factor. The analysis was consistent considering all the values and taking out the outliers. The AUC for EGF was 0.788 (p<0.01, 95% CI: 0.59-0.97), with the best accuracy cutoff of 4600 pg/mL. EGF showed correlation with NGAL p=0.62 (p<0.01), [TIMP2][IGFBP7] p=0.71 (p<0.01) and CKD-EPI GFR p=0.74 (p<0.01). EGF shows protective effects with statistically differences in the univariate and multivariate logistic regression (Table 1).

Conclusions: Patients without AKI had more expression of uEGF, this cytokine could be involved in the renal protection against the development of COV-AKI. EGF has an inverse correlation with NGAL and [TIMP2][IGFBP7] and a positive correlation with the GFR.

Funding: Government Support - Non-U.S.

Univariate and multivariate analysis for AKI

PO0042

The Assessment of Bronchoalveolar Lavage (BAL) Fluid Composition in Critically Ill Patients with and Without COVID-19 and AKI

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Background: Recent reports identified enrichment of T cells and monocytes in the BAL fluid of patients with COVID-19 pneumonia, in contrast to neutrophilia in patients with non-COVID-19 pneumonia, which suggests a distinct immunopathology. We evaluated whether AKI, an independent risk factor for adverse outcomes, modifies BAL cell composition in critically ill patients.

Methods: We retrospectively analyzed BAL specimens from 710 critically ill patients undergoing evaluation for pneumonia at an academic medical center from 3/2018-11/2020. Kruskal-Wallis tests compared distributions of BAL fluid % cell counts by COVID-19 and AKI status. Multivariable linear regression models tested the associations of COVID-19 status with the BAL fluid % cell counts. We tested for effect modification by AKI status. AKI was defined by the K/DOQI criteria.

Results: Mean age was 60±15 years and median baseline serum creatinine was 0.8 [0.6-1.1] mg/dl. COVID-19 was positive in 34.5% and AKI occurred in 42.8% of patients. Figure 1A shows differences in BAL fluid cell composition by COVID-19 and AKI status. Highest % of neutrophils were in COVID-19(-) AKI(-) patients and lowest in COVID-19(+) AKI(-) patients. Macrophages, monocytes, and lymphocytes were highest in COVID-19(+) AKI(-) patients and lowest in COVID-19(-) AKI(+) patients. COVID-19(+) patients had a significantly lower % of neutrophils and a higher % of monocytes- and lymphocytes after multivariable adjustment (Figure 1B). Patients who were AKI(+) had decreased % of neutrophils when COVID-19(-), while the opposite effect was noted for COVID-19(+) (P for interaction=0.007).

Conclusions: AKI may differentially modify the cell BAL fluid cell composition among patients with suspected pneumonia based on their COVID-19 status.

Funding: Private Foundation Support

PO0043

Clinical Outcome and Antibody Response in COVID-19-Positive Pediatric Kidney and Liver Transplant Recipients

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Background: The COVID-19 pandemic has profoundly impacted transplantation activity worldwide. Nevertheless, data on the clinical and laboratory features of SARS-CoV-2 infection in pediatric recipients of solid organ transplant (SOT) recipients are scarce.

Methods: We describe clinical and laboratory manifestations, including serologic response, and short-term outcomes of 25 pediatric recipients of SOT who tested positive for SARS-CoV-2 during the first nine months of the epidemic in Israel.

Results: The mean age was 15.2±4 years; 14 (56%) were kidney and 11 (44%) liver transplant recipients. Twenty-three (92%) of the patients were symptomatic. The most common symptoms were fever (44%), headache (44%), cough (40%), and fatigue (36%). Most (84%) had a mild disease. Two patients (8%), both kidney transplant recipients with additional comorbidities, had severe respiratory disease and required adjustments in their immunosuppression therapy. None were admitted to the pediatric intensive care unit or died, and all the patients fully recovered after a median of 27 [interquartile range 21-41] days. Significant longer virus shedding time was observed among kidney and pancreas transplant recipients than among liver transplant recipients (35.1±9.8 vs.19.6±4.7 days, p=0.0005). Following a median of 7 (5-10.5) weeks after COVID-19 diagnosis, 3 (22%) reported residual symptoms, mainly fatigue; 22/23 (96%) had positive antibody responses.

Conclusions: Our study demonstrated that while the majority of pediatric recipients of SOT developed a mild disease with a positive serologic response, a relatively high percentage (8%) developed a severe disease. This enhances the need for close monitoring of this particular population, especially those with comorbidities.
COVID-19 Seropositivity in New York ESKD Patients
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Background: Patients on hemodialysis (HD) with COVID-19 infections have increased emergency room visits, hospitalization, and mortality. We evaluated COVID-19 seroprevalence in a dialysis association in NYC.

Methods: We collected data on patients undergoing maintenance HD in four different units in Manhattan, New York. Data was collected regarding demographics, cause of kidney failure, time on dialysis, and insurance. Covid antibody was tested using the elecsys Anti-SARS-CoV-2 immunoassay. We performed univariate analysis using Chi square test and multivariate linear logistic regression models to identify variables associated with COVID-19 seropositivity.

Results: Seropositivity was detected in 108 (20.2%) out of the 535 patients tested. In univariate analysis, age, HD unit, race, institutionalized status, time on dialysis, and type of insurance were associated with seropositivity. In multivariate analysis, race, age, time on dialysis were not associated with COVID seropositivity. Patients uninsured, or those covered by medicare, had a significantly higher likelihood of testing positive for COVID antibodies than patients covered by private insurance (OR, 8.02, P=0.005). In reference to the Chinatown unit, patients receiving treatment at the 34th Street unit (OR, 4.90, p=0.002) and the Lower Manhattan unit (OR, 3.42, p=0.02) were more likely to test positive. Institutionalized patients were almost eleven times more likely to test positive for the antibodies than those not institutionalized (OR, 10.97, p<0.001). Race was not significantly associated with antibody positivity.

Conclusions: Our study showed increased prevalence of COVID-19 antibodies in Institutionalized and uninsured/Medicaid patients but no association with race suggesting socioeconomic status, is more important than race in determining the risk of COVID-19 infection in patients on maintenance dialysis.

Prevalence and Dynamics of SARS-CoV-2 Nucleocapsid IgG in Kidney Transplant Recipients
Yorg Al Azzi, Pablo Loarte Campos, Cindy T. Pynadath, Omar Alani, Harith Racees, Luz E. Liriano-Ward, Maria Ajaimy, Enver Akalin. Montefiore Medical Center, Bronx, NY.

Background: We aimed to investigate the prevalence and dynamics of SARS-CoV-2 IgG in kidney transplant recipients in the Bronx, New York, one of the epicenters of the pandemic.

Methods: Between March 16 and May 5, 2021, 255 patients tested positive for SARS-CoV-2 RT-PCR. From May 3 to May 5, 1,164 patients were screened for SARS-CoV-2 IgG antibodies and 199 (17.1%) were tested positive (Figure).

Results: 62 of the 199 patients were previously diagnosed COVID-19 by RT-PCR, while the remaining 137 did not have significant symptoms and had not been previously tested by RT-PCR. Overall prevalence of COVID-19 diagnosis by RT-PCR and/or SARS-CoV-2 IgG in 1,348 patients tested was 29%. Seventy-one RT-PCR+ patients were screened for SARS-CoV-2 IgG antibody and 62 (87%) were positive at a median 106 days (81-188). A total of 50 patients of 199 who were previously tested positive for SARS-CoV-2 IgG (30 diagnosed with IgG and 20 with RT-PCR) were retested at a median time of 112 days (IQR: 81-121). Twenty-six patients (52%) became seronegative at a median time of 105 days (IQR: 84-141) from their first positive IgG. Nine of 20 (45%) patients who were diagnosed by RT-PCR became seronegative at a median time of 108 days (IQR: 81-168) from their first positive IgG. While 17 of 30 (57%) patients who were initially diagnosed by a positive IgG became seronegative at a median time of 121 days (IQR: 90-145) from the date of diagnosis.

Conclusions: In summary, 35% of kidney transplant recipients were asymptomatic or mildly symptomatic and developed SARS-CoV-2 IgG without requiring testing by RT-PCR. However, half of the patients who initially developed antibodies lost them over time raising the questions of lasting immunity against SARS-CoV-2 and how effective are RT-PCR. However, half of the patients who initially developed antibodies lost them over time raising the questions of lasting immunity against SARS-CoV-2 and how effective are RT-PCR.
Renal biopsy performed on four patients demonstrated acute tubular necrosis. Fifty-two (22.5%) patients received KTR, most commonly with CKRT in 26 (50%) or combination of CKRT and HD in 17 (32.7%). Median hospital day for initial dialysis was 5.0 [2.0 - 10.0]; mechanical ventilation 0.0 [1.0 - 4.0]. ECMO 1.0 [0 - 4]. LOC was significantly longer for AKI patients over 8.7 [4.5 - 17.5]; No AKI 7.7 [4.0 - 12.7], AKI 15.0 [7.1 - 27.2] days p <0.01. Most common comorbidities were Type 2 diabetes and hypertension. D-dimer, LDH, CRP, procalcitonin and IL-6 were significantly higher. Upon discharge, 138 (59.7%) were discharged without KRT, whereas 12 (5.2%) patients required KRT. Nine (3.9%) went hospice, and 72 (31.2%) died. One patient was still admitted to the hospital.

Results: We identified 48 kidney transplant recipients who were diagnosed with Coronavirus-19 infection during the study period. Eighteen KTRs among these hospitalization for symptoms of fever and respiratory distress. Four patients died of Coronavirus-19 infection related complications and were excluded from the study. The 14 remaining patients in the study were predominantly black (78%), with a median time since transplant of 4 years. 64% of the patients developed AKI, with an average peak serum creatinine of 2.64 mg/dl and GFR of 34. The mean serum creatinine and GFR of the group were 2mg/dl and 44 at baseline (prior to infection). This represented an increase in their serum creatinine and GFR of 34% and 29% respectively. The median follow-up post infection was 7.5 months. Median serum creatinine and GFR related to AKI, in 48 and 43 at months, and 2.2 mg/dl and 40 at 6 months post infection. New onset proteinuria was noted in 5 out of the 14 patients (36%), with complete resolution of same in all at 3 months follow up. 75% patients with AKI had complete recovery at 3 month follow-up. The mean baseline GFR of patients who had incomplete recovery was 32. There was only 1 graft loss and this was in a patient who had chronic rejection and had a baseline Cr of 3.8 mg/dl at time of coronavirus-19 infection.

Conclusions: AKI is common among KTRs that are hospitalized with Covid-19 infection. Most of these recover, although we noted that patients with baseline lower kidney function (GFR <32) and existing proteinuria had a lower recovery rate.
PO0052
Associations of Dialysis Modality and Setting with Incidence of COVID-19 Diagnosis and Hospitalization
Eric D. Weinhandl,1,2 David T. Gilbertson,1 James B. Wetmore,1 Kirsten L. Johansen,1 Hennepin Healthcare Research Institute, Minneapolis, MN; 1University of Minnesota Twin Cities, Minneapolis, MN

Background: The novel coronavirus 2019 (COVID-19) pandemic has resulted in substantial morbidity and mortality among patients undergoing maintenance dialysis. Patients performing home hemodialysis (HHD) or peritoneal dialysis (PD) may be able to minimize exposure to the community, thus lowering risk of COVID-19 infection. We assessed whether HHD and PD were associated with lower risks of COVID-19 infection and hospitalization, compared to in-facility hemodialysis (IHD).

Methods: We analyzed Medicare Parts A and B claims accrued during 2020. For each epidemiologic week from week 12 (beginning March 15) to week 37 (September 6), we identified patients with a Medicare-covered outpatient dialysis treatment during the preceding 7 days. We stratified patients into cohorts of IHD, HHD, and PD, we limited the IHD cohort to patients without residency in a skilled nursing facility during the 28 days preceding the epidemiologic week. During each week, we estimated the incidence of COVID-19 infection and COVID-19 hospitalization, per Medicare claims with ICD-10-CM diagnosis code U07.1. Using logistic regression with adjustment for demography, comorbidity, and state, we estimated odds ratios of outcomes during weeks 12-22, 23-33, and 34-37.

Results: Incidence of COVID-19 infection (figure) and COVID-19 hospitalization peaked twice: during weeks 14-16 and weeks 29-30. During weeks 12-22, adjusted odds ratios (AORs) of COVID-19 infection for HHD versus IHD and PD versus IHD were 0.55 (95% CI, 0.43-0.71) and 0.52 (0.46-0.58), respectively. During weeks 23-33, corresponding AORs were 0.63 (0.50-0.78) and 0.63 (0.57-0.69).

Conclusions: Both home dialysis modalities were associated with similarly lower risks of COVID-19 infection and hospitalization. Nephrologists and dialysis provider should consider counseling patients about potentially lower risk of infectious respiratory disease with home dialysis.

Funding: NIDDK Support

PO0053
Understanding Dialysis Patient COVID-19-Related Mortality
Alvin H. Moss,1 Annette Aldous,2 Glenda Harbert,1 Amanda C. Nicklas,3 Dale Lupu,1,2,3 West Virginia University Health Sciences Center, Morgantown, WV; 3The George Washington University Milken Institute of Public Health, Washington, DC; 4The George Washington University School of Nursing, Ashburn, VA

Background: Reported COVID mortality in dialysis patients is high and ranges from 15-25%. We reviewed data from a prospective 14-month study of seriously ill (SI) dialysis patients pre-COVID (May 2019-January 2020) and during COVID (February 2020-June 2020) to better understand COVID-related mortality in SI and not SI patients.

Methods: We recruited 10 dialysis centers (6 in NYC, 3 in Denver, CO, and 1 in Dallas, TX) with 1,507 patients. Dialysis staff screened patients monthly with the surprise question (SQ)—Would I be surprised if this patient died in the next 6 months?—and recorded outcomes. Those with a “No” response were identified as SI. A SQ “No” response is known to identify older patients with multiple comorbidities and an increased risk of early mortality. In this rolling population, we calculated the monthly mortality risk prior to and during COVID and determined the relative risk of death (RR) for SI compared to not SI during both periods. We also compared the increased mortality risk during COVID between patients dialyzed in NYC vs. Denver and Dallas and used logistic regression to determine whether COVID-19-related mortality differed by geographic region.

Results: Over 14 months, dialysis centers screened a monthly average of 1,342/1,507 (89.1%) patients and identified 274 (18.2%) as SI, with more consistent screening pre-COVID than during COVID (98.6% vs. 71.2%). Pre-COVID, the monthly mortality rate for SI patients was 2.8% and for not SI patients 0.4% (RR 7.02, 95% CI, 4.76-10.44). During COVID, the monthly mortality rate for SI patients increased to 4.8% and for not SI to 1.5% (RR 3.19, 95% CI, 2.28-4.44). The absolute increase in monthly mortality risk from pre-COVID to COVID was greater for SI than for not SI patients, 2.0% vs 1.1%. The excess monthly mortality was higher in NYC (2.3% for SI and 1.2% for not SI) than in Denver and Dallas (1.3% for SI and 0.7% for not SI), but the difference was not significant (p = .12).

Conclusions: A “No” response to the SQ identified SI dialysis patients whose 5-month mortality risk during COVID increased to 23.9% (annualized rate 57.4%). For not SI, the 5-month mortality rate during COVID increased to 7.5% (annualized rate 18%). These findings underscore the importance of advance care planning not only for SI patients but also for all dialysis patients, who are particularly vulnerable to concurrent infections such as COVID-19.

Funding: Private Foundation Support

PO0054
Temporal Trends in Mortality and Hospitalization Related to SARS-CoV-2 in Dialysis Patients in Québec (Canada)
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Background: In Canada, Quebec province was the most severely hit region during the first year of the SARS-CoV-2 pandemic. We aimed to compare characteristics and outcomes of dialysis patients during the first and second SARS-CoV-2 transmission surges in this province.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO0055
COVID-19 Outcomes in Hospitalized Patients with CKD

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Background: Current research revolving around Coronavirus Disease 2019 (COVID-19) has identified that patients with co-morbid illnesses are at risk for worse outcomes.

Methods: This is a retrospective study comprising an observational dataset of 149 hospitals that included hospitalized patients (n=9366) aged 18 and above with a Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Polymerase Chain Reaction (PCR) positive result between January 1st, 2020 and May 29th, 2020. Main outcomes and presentations, treatments, and outcomes of COVID-19 among hospitalized patients with AKI, dialysis-dependent end-stage kidney disease (ESKD-D) or kidney transplantation (KTX) at an urban, Midwestern tertiary center (3/19/2021–3/25/2021). Results: Among 184 patients, 91 had AKI (49%), 51 CKD-D (28%), and 42 patients were KTX recipients (23%). Monthly cases ranged from 6 in March to 35 patients in December 2020. Among the cohort, 61% were Black (including 50% AKI, 82% ESKD-D, and 57% KTX). Overall, 35% required mechanical ventilation, with highest use in the AKI group (54%). 48% of ESKD-D patients required renal replacement therapy (RRT) and 9% treated with ECMO. Mechanical ventilation was lower among KTX recipients (12%) and 9% required RRT. The most common medical treatment was dexamethasone (48%). Mortality was 46% in the AKI and 23% in CKD-D groups, but 2% among KTX recipients.

Conclusions: We observed high mortality associated with COVID-19 among hospitalized patients with kidney disease, especially in those with AKI. Public health and therapeutic studies should focus on mitigating COVID-19 disease transmission and optimizing outcomes in this vulnerable population.
PO0057

Decision-Making During Uncertain Times: A Qualitative Study of Kidney Patients, Care Partners, and Nephrologists During the COVID-19 Pandemic

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Background: Older adults faced treatment decisions for kidney failure during the COVID-pandemic, despite high risk of hospitalization, intensive care, and death. Given heightened uncertainty, clinicians needed to adapt communication about risks, benefits, and treatment decisions during the COVID-19 pandemic. Understanding how to support decision-making during uncertain times can guide clinicians in future public health crises.

Methods: Qualitative study using semi-structured interviews (August-December 2020) with CKD stage 4-5 patients, age 70+, carepartners, and clinicians in Boston, Portland, Maine, San Diego, and Chicago. Thematic analyses were conducted.

Results: Among 76 participants (39 patients, 17 carepartners, 20 clinicians) 13 patients (33%) identified as Black, and 7 (18%) were receiving dialysis. Four themes characterized treatment decision-making during the COVID-19 pandemic: Dificultly communicating risk: balancing hope with caution; Clinicians’ increased support for home dialysis; Patient confidence in chosen modality; and Coping with uncertainty and isolation in CKD. Clinicians struggled to balance discussion of COVID-19 risks while preserving hope. Black patients reported fewer conversations about COVID-19 risks than White patients and had more unaddressed questions. Clinicians reported being more open to home dialysis than pre-COVID-19. While some patients expressed interested in conservative management, few clinicians offered conservative management as an option. All patients who had initiated treatment prior to COVID-19, irrespective of modality, believed that their treatment was safest and optimal during the pandemic. With few clinical conversations incorporating COVID-19-specific risks, patients and carepartners struggled to cope, finding both in-person and telehealth visits safe but isolating.

Conclusions: Although clinicians struggled communicating about COVID-19 leaving patients with unaddressed concerns, patients across modalities felt safe and confident in their treatment. Clinicians developed an openness to home dialysis, though few offered conservative management despite patient preferences. Research should examine optimal approaches to enhance communication and shared-decision making to prepare for future systemic challenges.

Funding: Private Foundation Support

PO0058

Risk Factors for In-Hospital Mortality Among Patients Hospitalized with COVID-19 and ESKD

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Background: End Stage Kidney Disease (ESRD) has been shown to be a risk factor for poor outcomes in the setting of COVID-19 infection. Our study aims to identify risk factors for mortality in ESRD patients hospitalized with COVID-19.

Methods: We conducted a retrospective analysis from March 1st, 2020 to January 31st, 2021 at Loma Linda University Medical Center. Inclusion criteria included patients admitted with diagnosis of COVID-19 and history of ESRD prior to admission. Risk factors for hospital mortality were identified with univariate and multivariate logistic regression methods.

Results: A total of 92 patients (age 59.9±13.7) were included in the analysis, of which 88 (28%) were deceased. Multivariable regression analysis (Figure 1) demonstrated that age greater than 70 had adjusted odds ratio (OR) with 95% confidence interval (CI) for mortality 1.10 (95% CI: 1.01, 1.20, p=0.03). An Ejection Fraction of less than 50% had OR=1.13 (95% CI: 1.03, 1.23, p<0.001), AKI-injury stage had OR=1.25 (95% CI: 1.14, 1.37, p=0.001), positive D-dimer levels had OR=1.18 (95% CI: 1.07, 1.30, p=0.001) and diabetes had OR=1.12 (95% CI 1.03, 1.22, p=0.01), all significant risk factors for mortality. In addition, Hispanics had a higher risk of mortality with OR=1.20 (95% CI 1.09, 1.33, p<0.001) when compared to Caucasians.

Conclusions: Diabetes, age greater than 70, Hispanic background, Heart failure with reduced ejection fraction, AKI-injury stage, and positive D-dimer level are identified as risk factors associated with higher mortality amongst patient admitted with COVID-19 and AKI.

PO0059

Risk Factors for In-Hospital Mortality Among Patients Hospitalized with COVID-19 and AKI

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Background: Coronavirus disease-2019 (COVID-19) has the highest mortality in patients with advanced age and those with pre-existing chronic medical conditions. Limited data, however, is available with regard to COVID-19 mortality in acute kidney injury (AKI). We aimed to identify risk factors associated with mortality in patients hospitalized for COVID-19 with AKI.

Methods: This is a retrospective cohort study conducted at Loma Linda University Medical Center (LLUMC) from March 1st, 2020 to January 31st, 2021. Inclusion criteria included patients admitted to LLUMC with diagnosis of COVID-19 and AKI during the admission based on the Risk Injury Failure Loss ESIRD (RIFLE) criteria. Univariable and multivariable logistic regression models were utilized to explore risk factors associated with in-hospital mortality.

Results: A total of 320 patients (age 66.5 ± 14.4) were included in the analysis, of which 88 (28%) were deceased. Multivariable regression analysis (Figure 1) demonstrated that age greater than 70 had adjusted odds ratio (OR) with 95% confidence interval (CI) for mortality 1.10 (95% CI: 1.01, 1.20, p=0.03). An Ejection Fraction of less than 50% had OR=1.13 (95% CI: 1.03, 1.23, p<0.001), AKI-injury stage had OR=1.25 (95% CI: 1.14, 1.37, p<0.001), positive D-dimer levels had OR=1.18 (95% CI: 1.07, 1.30, p<0.001) and diabetes had OR=1.12 (95% CI 1.03, 1.22, p=0.01), all significant risk factors for mortality. In addition, Hispanics had a higher risk of mortality with OR=1.20 (95% CI 1.09, 1.33, p<0.001) when compared to Caucasians.

Conclusions: Diabetes, age greater than 70, Hispanic background, Heart failure with reduced ejection fraction, AKI-injury stage, and positive D-dimer level are identified as risk factors associated with higher mortality amongst patient admitted with COVID-19 and AKI.
PO0060
Outcomes of COVID-19 Infection in Dialysis vs. Kidney Transplant Patients: A Nationwide Cohort Study from Qatar

Background: COVID-19 infection carries a high burden and poor outcomes in patients who are immunocompromised like kidney transplant or on dialysis. Our aim is to compare outcomes between dialysis and kidney transplant patients infected with COVID-19 in the State of Qatar.

Methods: Retrospective cohort study reviewing medical, laboratory and radiographic data of all dialysis and kidney transplant recipients’ patients in our national registry (between February and August 2020). Data collected from a national-based electronic medical record.

Results: 76 patients on dialysis patients had COVID19 vs 43 kidney transplant (p<0.01). Kidney transplant patients with COVID19 tended to be younger than dialysis patients (52 vs. 58 years old, p=0.007), has less hypertension and more history of deep venous thrombosis. Clinical presentation did not differ between both groups with more asymptomatic in dialysis patients compared to kidney transplant patients (14.5% versus 2.3%, p=0.03). More patients died from COVID19 in the dialysis patients vs. kidney transplant patients (11 (14.5%) vs. only 1 (2.3%), p=0.034). Inflammatory markers were significantly higher in dialysis patients (IL6 peak and Ferritin) compared to kidney transplant patients.

Conclusions: Our national study showed similar incidence and severity of COVID19 in dialysis compared to kidney transplant in Qatar. Mortality and inflammatory markers were higher in dialysis patients.

PO0062
Mortality in COVID-19 Patients with CKD with and Without Kidney Replacement Therapy in Western Mexico

Background: COVID-19 is a new disease of pandemic proportions. Currently, there are no reports on clinical outcomes in patients with CKD with and without KRT in the Mexican population. Our aim was to describe the clinical outcomes in patients with CKD.

Methods: Retrospective cohort study of hospitalized adult patients COVID-19 confirmed with RT-PCR, from April to December 2020 in a second-level hospital in Western Mexico. Information was obtained from medical records.

Results: 1012 patients were included, of which 130 patients (12.8%) had CKD (65.3% men), with a mean age of 53.8 years, 43.8% with Diabetes Mellitus and 82.3% with Hypertension. 84 patients (64.6%) were on KRT, within which 47 patients were on hemodialysis, 31 on peritoneal dialysis and 6 with a kidney transplant. 46 patients had no KRT, in stages ranging from KDIGO 3b to 5. 78.4% of 14 patients (10.7%) required mechanical ventilation. In our study, mortality among patients with normal kidney function was 30.6%. Regarding patients with CKD, patients on hemodialysis had a mortality of 25.5% (OR 0.74, 95% CI 0.39-1.5), patients on peritoneal dialysis had a mortality of 54.8% (OR 2.75, 95% CI 1.33-5.66), patients with CKD and no KRT had a mortality of 43.5% (OR 1.74, 95% CI 1.15-3.17).

Conclusions: In our population, an increased mortality was found in patients with CKD with and without KRT highlighting the mortality of patients on PD.

PO0061
One-Year Experience of COVID-19 Disease of 700 Chronic Dialysis Patients from Ecuadorian Highlands

Background: In December 2019, first Covid-19 disease cases were reported. The pandemic spread with 114,217,365 cases and 2,533,014 deaths worldwide in March 2021, with 286,155 cases and 15,811 deaths in Ecuador. The aim of this work was to share COVID-19 disease was more frequent in men and has added up to asymptomatic if no symptoms. Hospital-stay, time until negative PCR, mortality and laboratory findings were collected.

Results: A total of 205 patients (29%) presented COVID-19 symptoms; 115 tested positive (16%), 60% were men (p=0.03), 25 subjects died (22%). Mortality was related with age above 64 years old, saturation < 90%, severe disease (p=0.03), previous pulmonary pathology and hospitalization (p=0.01). Hospitalization was needed in 74 patients (64%) with hospital stay 11 days (4-15), days until death during hospitalization of 12 days (4-19) and time until negative PCR 20 days (10-25). Symptomatic time was 16 days (11-26).

Conclusions: COVID-19 disease was more frequent in men and has added up to 22% of extra mortality to chronic dialysis population. Patients older than 64 years old, previous pulmonary pathology, LOS at presentation are at higher risk of mortality. Health care burden due to COVID-19 is high in dialysis population suggesting that vaccination programs must include dialysis patients and staff involved in their care to diminish mortality, infections and health care burden.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
African Americans Have Lower COVID-19 Mortality Risk Than Caucasians in CKD

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Background: In the general population, African Americans have increased mortality risk with COVID-19. This has not been well-studied in CKD population.

Methods: We analyzed a national Veteran cohort using data from the VA COVID-19 Shared Data Resource for COVID-positive patients (N=196,269) from 3/1/2020 - 3/9/2021. Diagnosis of COVID-19 was defined as a confirmed positive laboratory test result. Date of diagnosis was defined as the date of first positive COVID-19 test or the first negative test for patients who never tested positive for COVID-19. Baseline eGFR was defined as at least one outpatient serum creatinine measurement obtained within two years before the index date or the average of the two closest serum creatinine measurements obtained within two years before the index date. We identified 58,743 patients with valid eGFR measurements. Of this cohort, 51,002 were African American or Caucasian. Mortality data were available for 50,830 patients. We used Cox regression models to compare COVID-19 mortality in African Americans versus Caucasians based on pre-COVID eGFR stratification.

Results: Of the COVID-positive patients with available eGFR and mortality data, baseline mean age was 60 ± 17 years, 24% African American, 76% Caucasian, and 21% with eGFR <60. There were 627 deaths among African Americans and 2,480 deaths among Caucasians. Average follow-up duration was 0.5 ± 0.3 years in African Americans and 0.4 ± 0.2 years in Caucasians. While there was no difference in mortality risk between African American and Caucasian Veterans without CKD, African Americans had lower mortality risk when compared to Caucasians in the CKD subgroup (Table 1).

Conclusions: In the CKD subgroup, African Americans have lower COVID-19 mortality risk than Caucasians. The reasons for this observation are unclear.

Funding: NIDDK Support, Other NIH Support - NHLBI, Veterans Affairs Support

PO0065

COVID-19 Among a Population of Predominantly American Indian and Hispanic American Kidney Transplant Recipients

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Background: COVID-19 leads to higher mortality among organ transplant recipients when compared to the general population.

Methods: In this study, 52 renal transplant recipients with COVID-19 were followed through 90 days from the date of initial diagnosis. We analyzed basic demographics, therapies used, and clinical outcomes among patients who survived and those who did not.

Results: Of the entire cohort, 53.8% were Hispanic Whites, 38.5% American Indian, and 5.8% were non-Hispanic. However, 86% had COVID-19. There were 15% of deaths attributed to complications secondary to COVID-19. All those who died were either American Indian or Hispanic. Comorbidities among the non-survivors included hypertension (100%), chronic kidney disease (67%), diabetes (78%), and either obesity (BMI >30) or obese (100%). 89% had acute kidney injury and 56% required renal replacement therapy. Gender, blood type, and panel reactive antibody prior to transplant did not correlate with disease severity. There was no improvement in mortality during the fall/winter surge compared to the spring/summer surge, though therapies improved during the pandemic. None of the patients who received monoclonal antibody progressed to severe disease or died.

Conclusions: In conclusion, mortality with SARS-CoV-2 infection remains high among kidney transplant recipients, especially from ethnic minority groups. However, therapy with monoclonal antibody was associated with a reduced progression to severe disease and better outcomes. Therefore, it should be considered as a therapy in this high-risk group of patients if they satisfy the eligibility criteria listed by the Food and Drug Administration. Finally, further studies are needed to corroborate the findings from this study.

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PO0066
Patients on Chronic Maintenance Hemodialysis with and Without COVID-19 Infection: Comparison of Baseline Characteristics and Mortality
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Background: The COVID-19 pandemic has impacted nearly all aspects of the care of patients, particularly those with chronic conditions. There is a need for higher quality of evidence to better identify populations at risk, in various clinical situations. We analyzed the difference in demographic characteristics in patients with end stage kidney disease (ESKD) who were started on hemodialysis (HD) in 2020 and contracted COVID-19, with those who remained free of the infection in a large multicenter cohort.

Methods: We performed a retrospective multi-center cohort study using TriNetX Research Network database, a federated medical records network, to identify 7405 unique adult patients ≥ 18 years from 37 healthcare organizations (HCOs), mostly in the United States, for whom maintenance HD was initiated for ESKD between 1/1/2020 and 12/31/2020 (study period). From this group, we then identified patients who had a confirmed diagnosis of COVID-19 infection during the study period. We calculated the odds ratio (OR) and 95% confidence interval (CI) of mortality in the first three months of initiation of HD for the COVID group.

Results: 903 patients (33 HCOs) had a confirmed diagnosis of COVID-19 infection. Patients in the COVID-positive group were less likely to be white (p=0.019), and more likely to: — be of Hispanic/Latino ethnicity (p<0.0001), — have had a previously failed kidney transplant (p<0.0001) — have diabetes mellitus (DM) (p<0.0001), and — have a BMI above 31 (p=0.003). A total of 628 patients died during the study period. After propensity matching, COVID exposure was associated with higher odds of mortality (OR: 2.32; CI: 1.16, 3.24). The survival probability at the end of 3 months was 84.4% for the COVID group, compared with 92.5% for the no-COVID group (p<0.0001).

Conclusions: During the study period, among the patients who were started on HD for ESKD, those who contracted COVID-19 infection were more likely to be Hispanic/Latino, less likely to be white, more likely to have a previously failed kidney transplant, more likely to have DM, and to have a BMI above 31. The COVID-positive group also had a higher mortality and a less-3 month survival probability compared to the control group.

PO0067
Kidney Transplant Patients with and Without COVID-19 Infection: Comparison of Baseline Characteristics and Outcomes
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Background: The COVID-19 pandemic has been associated with enormous impact on morbidity and mortality, particularly among individuals with chronic conditions and among patients on chronic immunosuppressive therapy. There is a need for higher quality of evidence to better identify populations at risk, in various clinical situations. We analyzed the difference in kidney transplant (KT) rejection, kidney transplant failure and mortality in patients who received a KT in 2020 and contracted COVID-19 with those who remained free of the infection, in a large multicenter cohort.

Methods: We performed a retrospective multi-center cohort study using TriNetX Research Network database, a federated medical records network, to identify 3773 unique adult patients ≥ 18 years, who had received a kidney transplant (KT) between 1/1/2020 and 12/31/2020 at 34 healthcare organizations (HCOs), mainly in the United States. From this group, we then identified patients who had a confirmed diagnosis of COVID-19 infection after KT. We calculated the odds ratio (OR) and 95% confidence interval (CI) of mortality, KT rejection, and KT failure in the two groups during the first 3 months after KT (study period).

Results: A total of 590 patients from 27 HCOs had a confirmed diagnosis of COVID-19 infection. Patients in the COVID-positive group were less likely to be white (p<0.019), and more likely to: — be of Hispanic/Latino ethnicity (p<0.0001), — have had a previously failed kidney transplant (p<0.0001) — have diabetes mellitus (DM) (p<0.0001), and — have a BMI above 31 (p=0.003). A total of 628 patients died during the study period. After propensity matching, COVID exposure was associated with higher odds of mortality (OR: 2.32; CI: 1.16, 3.24). The survival probability at the end of 3 months was 84.4% for the COVID group, compared with 92.5% for the no-COVID group (p<0.0001).

Conclusions: During the study period, among the patients who were started on HD for ESKD, those who contracted COVID-19 infection were more likely to be Hispanic/Latino, less likely to be white, more likely to have a previously failed kidney transplant, more likely to have DM, and to have a BMI above 31. The COVID-positive group also had a higher mortality and a less-3 month survival probability compared to the control group.

PO0068
Characteristics and Outcomes of Patients with COVID-19 Infection Requiring Extracorporeal Membrane Oxygenator with and Without Continuous Renal Replacement Therapy: A Single-Center Study
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Background: Up to 1-in-3 cases of severe COVID-19 infection can cause respiratory failure sometimes necessitating extracorporeal membrane oxygenation (ECMO) support. Acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT) is a common complication, yet risk factors & outcomes in these patients are not well studied.

Methods: A retrospective single-center study included 40 patients who received ECMO support for severe COVID-19 infection from Jan 20 to April 21. We extracted demographic, clinical, & laboratory variables on all patients. Primary outcome was hospital mortality; other recorded outcomes were total length of stay, ventilator, ECMO, & CRRT days, dialysis dependence at discharge. Group comparisons with & without CRRT were made by 2-sample Wilcoxon test for continuous variables & Fisher’s exact test for categorical variables. Association of CRRT use & primary outcome was assessed by multivariable logistic regression (odds ratio (OR), 95% confidence interval (CI)).

Results: Overall cohort was 62.5% male, 32.5% black, with a median age of 51 years & BMI of 39.4. Thirty percent were diabetic & 42.5% were hypertensive. Of the 40 ECMO patients, 36 were on veno-venous, 2 on arterio-venous, & 2 utilized both veno- and arterio-venous circuits. 19/40 (47.5%) of ECMO patients required CRRT for AKI (3/19 patients CRRT was connected through the ECMO circuit). The median CRRT days were 20. Compared to those without CRRT, ECMO with CRRT patients needed a median of 19 ventilation days vs 15, ECMO days vs 11, & 28 hospital days vs 32. Overall mortality was 50% (68.4% ECMO+CRRT vs 33.3% in others; p-value 0.0562). Logistic regression indicated that CRRT use in ECMO was associated with increased adjusted odds of death (6.37 OR, 1.12-36.19 95% CI). Of those who did not experience hospital mortality in the ECMO+CRRT group, 83% were dialysis-dependent at discharge.

Conclusions: Overall, extracorporeal support offers a meaningful bridge until organ recovery in severe COVID-19 infection. Despite necessitating ECMO, 50% of patients were able to be liberated from ECMO & survived. However once renal failure ensued, all patients required CRRT, which in turn predicted poor outcomes.

PO0069
Hypertension After Multisystem Inflammatory Syndrome in Children (MIS-C)
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Background: MIS-C is an inflammatory condition in children associated with previous SARS-CoV-2 infection that has significant morbidity. Yet, long-term consequences of MIS-C remain unknown. The objective was to determine the prevalence of hypertension (HTN) and pre-HTN during the inpatient and post-hospitalization period in children diagnosed with MIS-C.

Methods: A retrospective study of children ≤18 years of age admitted to a tertiary center with MIS-C between 3/1/2020-2/28/2021 was performed. Children with a minimum of three documented outpatient blood pressure (BPs) were included. All available BPs were averaged and indexed (SBPi/DBPi) to the 95%ile for age, sex and height for the inpatient stay and post-hospitalization period. HTN was defined as mean SBPi or DBPi >95%ile for age, sex and height. Data were analyzed using paired tests and logistic regression.

Results: Among 66 children with MIS-C (mean age 9.4±4.6 years, 59.1% male, 21.2% Black, BMI z-score 0.48±2), 1.5% were hypertensive while hospitalized compared to 18.2% with post-hospitalization HTN (p=0.001). 4.5% were prehypertensive while hospitalized compared to 21.2% of MIS-C children post-hospitalization (p=0.003). Mean SBPi (0.91±0.13 vs. 0.86±0.06, p<0.03) and DBPi (0.87±0.13 vs. 0.77±0.09, p<0.0001) were significantly greater post-hospitalization compared to during hospitalization. In a multivariable model, Black race (OR 10.9 CI 1.6-75.2, p=0.02) and greater BMI z-score (OR 2.9 CI 1.2-7, p=0.02) were significantly associated with post-hospitalization HTN. Acute kidney injury (21.2%), inpatient steroids (86.4%), outpatient steroids (3%), vasoactive support (36.4%) and other clinical/demographic variables were not associated with post-hospitalization HTN (all p>0.05). After hospitalization, no MIS-C patients were started on antihypertensives for the management of HTN. No left ventricular hypertrophy was noted on echocardiography at six months post-hospitalization in those with HTN.

Conclusions: MIS-C appears to be associated with the development of post-hospitalization pediatric HTN and pre-HTN. Follow-up of children who have recovered from MIS-C requires careful BP monitoring and consideration of antihypertensive medication.
The Role of Hypertension in Incidence and Morbidity of COVID-19: A One-Year Review in US Veterans

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Background: The discovery that ACE2 was a co-receptor of COVID-19 as well as early clinical findings induced interest in the role of hypertension (HTN) and its treatment with angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) with regard to COVID-19 incidence and morbidity. We examined the effect of demographic and common risk factors of HTN and treatment with ACEI, ARBs, calcium channel blockers (CCB) and beta blockers (BB) in patients with COVID-19.

Methods: The VA COVID resource data combines hospital data, administrative and clinical record search results. The prevalence of HTN was defined by its presence in the last 2 years prior to COVID-19 testing. New event (incidence) was determined as occurrence within 60 days thereafter. ACEI and ARB, and CCB and BB were combined, basic demographic and risk factors were categorized for comparisons. Data sets were propensity matched, statistical analysis (SAS enterprise guide 7.1) used frequency distributions (chi square). The data was limited to the first year of collection.

Results: Of 1,305,466 veterans, we found positive tests (18.1%), HTN (56.9%), ACE or ARB (33.7%), and CCB or BB (15.4%). HTN and treatment had no effect on COVID-19 incidence (OR HTN 1.08, ACE/ARB 1.01, CCB/BB 0.94). Male, white patients aged over 60 years predominated, Age, race, and smoking had no effect on incidence, but DM2 (OR 1.2) and higher BMI (OR 1.4) did. We then examined demographics and risk factors in the COVID-19 positive population. Male gender (5.4%), age > 60 years (7.5%), race non-white (1.6%), BMI >30 (2), smoker (2.8), and DM2 (11.8). In turn, these factors at most affected outcomes (OR) such as all-cause mortality (7.9), admissions (2.1), ICU admissions (2.5), and ventilator use (2.7) with the exception of BMI which was associated with improved outcomes (0.6). ACE or ARB had no effect (<1.1) while CCB or BB had a small effect (1.26) on outcome.

Conclusions: In conclusion, HTN and anti-hypertensive treatment had no effect on COVID-19 incidence. HTN is associated with age, race, smoking and a diagnosis of DM2. Treatment with ACEI or ARB has no effect on morbidity while CCB or BB had a small effect that deserves further evaluation.

Funding: Veterans Affairs Support

Initial Blood Pressure (BP) and COVID-19 (C19) Mortality

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Background: For C19 to infect epithelia, serine proteases cleave the spike protein to enhance its binding to ACE2 and entry into the epithelia. Since viral replication highjacks components of the renin-angiotensin system, investigators speculate that hypertension (HTN) is a risk factor for severe infection; however, it is uncertain whether high BP at time of hospitalization affects the mortality of stage 1 (33/271; 12.18%) and/or stage 2 (24/150; 16.00%) SBP cohorts without C19. Mortality of C19(+) was 4.5-fold greater than C19(-) patients. Though infected patients had a small effect (1.26) on outcome.

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Funding: Commercial Support - XORTX Therapeutics Inc.

SIAHD with COVID-19-Induced Hemophagocytic Lymphohistiocytosis: A Case Report

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Introduction: The effects of COVID-19 on the body are still being unraveled as we learn more about this disease. Here we report a case of hypoxanemia secondary to Syndrome of Inappropriate Antidiuretic Hormone secretion (SIAHD) from COVID-19 induced hemophagocytic lymphohistiocytosis (HLH).

Case Description: A 47-year-old female with hypertension was admitted with COVID-19 infection. She had persistent fever, elevated inflammatory markers (ferritin: 6694 ng/mL, C-reactive protein: 217.1 mg/L, LDH 614 unit/L), and liver tests (ALP 275 unit/L, ALT 106 unit/L) and was thus diagnosed with COVID-19-associated HLH. Patient was treated with dexamethasone with resolution of fever but still had elevated CRP, ferritin, and LDH. She was discharged on a dexamethasone taper but returned just over a week later with malaise, brain-fog, and poor oral intake. Patient was then found to have severe hyponatremia with a serum sodium (Na) of 119 mmol/L and the following lab data: urine osmolality: 503 mOsm/kg, urine Na: 46, serum osmolality: 262 mOsm/Kg. Moreover, she had no edema on exam, nor did she display any signs of orthostatic hypotension. This was consistent with SIAHD. Her medication list didn’t include any medications that can cause SIAHD. No hormonal disturbances were detected. She was given high dose steroids again and Intravenous Immunoglobulin for persistent fever and lack of clinical improvement. Meanwhile, despite treatment with urea and fluid restriction, her Na stayed in the low 120’s. The decision was then made to start Interleukin-1 antagonist therapy. 1 day after the Interleukin-1 antagonist therapy was started, sodium started rising again by around 2 med day till it normalized.

Discussion: HLH has a wide range of causes including viruses but all can lead to a hyperinflammatory state. SARS-CoV-2 is known to cause a cytokine storm. Cases of COVID-19 associated HLH have been reported. The proposed mechanism of SIAHD is related to the surge of interleukins associated with inflammation due to HLH induced COVID-19. Particularly, IL-6 is increased with both HLH and COVID-19. IL-6 can cause the release of ADH by stimulating the hypothalamic-pituitary-adrenal axis. Thus, hyponatremia can be found in patients with COVID-19. One way of addressing that is through Interleukin receptor antagonism. More data is needed to prove the efficacy of that therapy.

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**PO0074**

**Association of Sodium Abnormalities with Outcomes in Hospitalized Patients with and Without COVID-19**

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**Background:** Several reports of serum sodium (Na) abnormalities have been reported in patients hospitalized with COVID-19. However, the association of Na abnormalities with hospital outcomes have not been well-described in patients with COVID-19 (C19 +) vs. especially in comparison to those who tested negative (C19 -).

**Methods:** This is a retrospective analysis of the first surge of COVID-19 (C-19) in patients who presented to our ED from December 2019–June 2020, with a systemic viral illness. There were 5,289 patients from the Covid19 data set, 1,703 COVID+ patients and 3,586 Covid- patients. Based on a nasal swab PCR patients were divided into two groups: C19 + and C19 -. Na levels at the time of hospitalization were used to divide patients into three groups: hyponatremia(hypON) (<135), normonatremia (normON)[135-145] and hypernatremia(hyperN)>145). In C-19 patients, hypON and hyperN were compared to normON using multivariable (MV) models adjusting for comorbidities to calculate odds/ risk (OR) ratios for outcomes.

**Results:** C19 + patients, had significant increased incidence of HypoN (26.7% vs 16.2%); and HyperN (4.2% vs 1.3%) compared to C19 - (Figure 1). Non MV analysis, among C19 + patients, found both HypoN and HyperN were significantly associated with mortality compared to normON. HypoN (compared to normON) was also associated with higher admission rate to the ICU, acute respiratory distress syndrome (ARDS), and intubation (Figure 2a & 2b).

**Conclusions:** Among patients admitted with acute viral illness, Na abnormalities on admission were more prevalent in patients with COVID-19 compared to those who tested negative (C19 -). Patients with higher admission rate to the ICU, acute respiratory distress syndrome (ARDS), and intubation had significantly increased incidence of HypoN (26.7% vs 16.2%); and HyperN (4.2% vs 1.3%) compared to C19 - (Figure 1). Non MV analysis, among C19 + patients, found both HypoN and HyperN were significantly associated with mortality compared to normON. HypoN (compared to normON) was also associated with higher admission rate to the ICU, acute respiratory distress syndrome (ARDS), and intubation (Figure 2a & 2b).

**Funding:** Private Foundation Support

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**PO0075**

**Association of Obesity with 3-Month COVID-19-Related Mortality in ESKD Patients**

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**Background:** In the general population obesity is associated with increased risk of mortality. However, in ESKD patients obesity is associated with lower risk of mortality, particularly in dialysis patients (i.e. the obesity paradox). In COVID-19 patients, obesity exhibits a similar association with mortality as observed in the non-COVID-19 general population. Given the obesity paradox, we questioned the association of obesity with mortality in ESKD patients with COVID-19.

**Methods:** Data from the European Renal Association COVID-19 Database (ERACODA) were analysed. Association of BMI (kg/m²), divided into: <18.5 (lean), 18.5-24.9 (normal weight), 25-29.9 (overweight), 30-49.9 (obese I) and ≥ 50 (obese II), with 3-month mortality was investigated using Cox proportional-hazards regression. Results were investigated for the total population and, dialysis patients and kidney transplant recipients separately.

**Results:** In 3160 ESKD patients (mean age: 65 years, male: 61%), 99 patients were lean, 1151 normal weight (reference group), 1160 overweight, 525 obese I and 225 obese II. During follow-up of 3 months, 28%, 20%, 21%, 23% and 27% of patients died in the lean, normal weight, overweight, obese I and obese II category, respectively. In fully adjusted model, the HRs for 3-month mortality were 1.65 (95% CI:1.10, 2.47), 1.07 (95% CI:0.89, 1.28), 1.17 (95% CI:0.93, 1.46) and 1.71 (95%CI:1.27, 2.30) in lean, overweight, obese I and obese II vs normal weight patients (Figure). Results were similar among dialysis patients and transplant recipients (p-interaction=0.99).

**Conclusions:** In ESKD patients with COVID-19, dialysis patients or kidney transplant recipients, obesity is associated with an increased risk of mortality at 3 months. This is contrary to obesity paradox generally observed in dialysis patients. There is need to investigate why in dialysis patients with COVID-19 the survival benefit of obesity is lost.

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**PO0076**

**Prevalence and Association of Dysnatremia with Outcomes in Hospitalized COVID-19 Patients**

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**Background:** Studies have reported both hypo and hypernatremia in patients hospitalized with COVID-19. We sought to examine the prevalence and association of dysnatremia with clinical outcomes among hospitalized COVID-19 patients at the Mount Sinai Health System.

**Methods:** We included 5,712 patients with COVID-19 who were a18 years old and hospitalized for ≥24 hours in the Mount Sinai Health System. Patients with ESKD, who received dialysis within the first 24 hours were excluded. We evaluated the association between serum sodium on admission (first level within 24 hours from admission) and the lowest serum sodium during hospitalization with AKI, IMV requirement, and in-hospital mortality using multivariable logistic regression models.

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Results: The median age of patients was 67 (55-78) years, 57% were male, and median serum creatinine was 1.0 (IQR, 0.7-1.4) mg/dL. On hospital admission, 6% had moderate/severe hypernatremia (<130 mEq/L), 18% had mild hypernatremia (130-134 mEq/L), and 8% had hypotremia (>145 mEq/L). After adjustment for demographics, comorbidities, and admission lab values, the adjusted OR for moderate/severe hypernatremia, mild hypernatremia, and hypotremia on admission, compared to normal serum sodium, for in-hospital mortality were 1.59 (1.16-2.19), 1.42 (1.14-1.76) and 2.91 (2.16-3.93), respectively (Figure 1A). Dysnatremias during hospitalization were also associated with all three outcomes, except IMV requirement was not significantly associated with hypotremia. (Figure 1B).

Conclusions: Both hypo- and hypernatremia on hospital admission and during hospitalization for COVID-19 were independently associated with AKI, IMV requirement, and in-hospital mortality. It is highly likely that dysnatremias are a marker for severity of illness and not causal for the adverse outcomes in COVID-19.

PO0077
The Role of CKD on Incidence and Morbidity of COVID-19: A One-Year Review in US Veterans
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Background: The Coronavirus disease 2019 (COVID-19) pandemic has greatly impacted the global community. With approximately 15% of the United States (US) population having chronic kidney disease (CKD), it is important to understand how COVID-19 interacts with CKD.

Methods: We used the VA COVID-19 resource data to examine the role of CKD on incidence and morbidity of COVID-19. The database combines standard hospital data, administrative and clinical record search results. CKD is defined in this system as having occurred at any time in the 2 years prior to the COVID-19 test, while new results (incidence) refer to 60 day period after positive test. Patients with chronic kidney failure (CKF2yrs) were excluded. We examined the effect of basic demographics and common risk factors on all-cause mortality, ICU admissions, ventilator use, and dialysis. Statistical analysis (SAS enterprise guide 7.1) used frequency distributions (chi square). The data was limited to the first year of collection.

Results: The population consisted of 1,305,466 veterans. Of these, 235,857 tested positive (18.1%) and 140,143 (11.4%) had CKD. White, male patients aged over 60 years predominated (60.7%, 81.2%, 53.3%). These demographics had no significant effect on COVID-19 incidence. Hypertension (HTN), diabetes mellitus type 2 (DM2), and smoking were taken as risk factors. These were found to have little effect (OR 0.86 – 1.22) while BMI had more weight (1.41). In the positive population CKD was recorded in 28,420 (12%). In these patients, significant differences were associated with CKD, such as higher death rate (OR 4.05), ICU admission and ventilator use when compared to the total population (OR 1.24, 2.88 vs 1.25, 3.13). Need for acute dialysis was disproportionately greater(OR 36.75).

Conclusions: CKD had no effect on incidence of COVID-19. Once present it was associated with higher rates of ICU admission, ventilator use, need for dialysis and all-cause mortality. This calls for increased vigilance in our patients with CKD to prevent COVID-19 infection.

Funding: Veterans Affairs Support

PO0078
Association of the COVID-19 Pandemic with ESKD Incidence
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Background: How the COVID-19 pandemic altered ESKD incidence, dialysis initiation, and preemptive kidney transplantation is unknown.

Methods: Using Centers for Medicare & Medicaid Services data, we investigated the incidence of ESKD, dialysis initiation, and preemptive kidney transplantation by week during the first half of 2020. Using Poisson regression, we compared findings in 2020 to a forecast of 2020, had 2017-2019 historical trends continued, overall and by strata of age and race.

Results: Mean weekly counts of patients with new ESKD are shown in the Figure. Incidence of ESKD dropped dramatically in 2020 compared with the expected incidence, particularly during epidemiologic weeks 15-18 (April; incidence rate ratio [IRR] 0.75, 95% CI 0.73-0.78), before approaching pre-pandemic levels in weeks 23-26 (June; IRR 0.93, 0.90-0.95). Across age groups, the decrease was most pronounced during weeks 15-18 among individuals aged 45-74 years (IRR 0.69, 0.66-0.73), compared with individuals aged 45-64 years, IRR 0.80, 0.77-0.84). In terms of race, the decrease was least notable among non-Hispanic Blacks (IRR 0.85, 0.81-0.89) and Hispanics (IRR 0.73, 0.69-0.78). Dialysis initiation reached a nadir during weeks 15-18 (IRR 0.76, 0.74-0.78), and preemptive kidney transplantation decreased even more strikingly during this period (IRR 0.56, 0.46-0.67).

Conclusions: During the first wave of the COVID-19 pandemic in 2020, the number of patients starting treatment for ESKD fell to a level not observed since 2011. Changes in ESKD incidence and utilization of treatment modalities may reflect differential access to care.

Funding: NIDDK Support
P00080
COVID-19 and CKD: An Overview of Reviews to Inform the World Health Organization Scientific Brief
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Background: The World Health organization (WHO) declared COVID-19 as a global pandemic in March of 2020. Many studies have assessed the association between different comorbidities and COVID-19 outcomes. In this overview of reviews, we aim to summarize the association between CKD and different COVID-19 outcomes.

Methods: We performed a systematic search through Embase, PubMed, Epistemomikos, and Cochrane as well as preprint databases from January 1, 2020 to January 5, 2021. After searching systematic reviews, we updated the search by identifying primary studies published after August 2020, which was the date of last search in the reviews. We focused on systematic reviews and large primary studies. We followed the GRADE methodology to assess the certainty in effect estimates. Data was pooled based on random effects model.

Results: We included a total of 69 systematic reviews and 66 primary studies in our overview. We did not identify any systematic reviews that directly reports on CKD and the risk of contracting COVID-19. There was no convincing difference on the risk of acquiring COVID-19 infection in patients with and without CKD in primary studies (OR = 1.00, 95% CI 0.76-1.33). CKD is associated with higher risk of COVID-19 related mortality pooled hazard ratio (HR) 1.48 (95% CI 1.33-1.65) and pooled odds ratio (OR) 1.77 (95% CI 1.54-2.02)(moderate certainty), hospitalization pooled risk ratio (RR) 1.63 (95% CI 1.03-2.58) (moderate certainty) and disease severity pooled RR 1.56 (95% CI 1.3-1.86) (moderate certainty). Notably, the risk of COVID-19 attributed hospitalization and mortality were higher in patients with more advanced CKD stage.

Conclusions: Evidence consistently demonstrated an increased risk of mortality, hospitalization, and disease severity in patients with CKD and COVID-19 infection. The results highlight the importance of recognizing patients with CKD as a high-risk group and of prioritizing these patients for COVID-19 prevention strategies including vaccination.

P00081
Virtual Pediatric Systems: AKI in Pediatric COVID-19 Among North American Intensive Care Units
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Background: There is a dearth of large-scale studies assessing the extent of Acute Kidney Injury (AKI) in pediatric COVID-19 patients. We aim to identify the epidemiology and associated risk factors of AKI in the pediatric COVID population through the Virtual Pediatric Systems (VPS) database.

Methods: We performed a retrospective analysis on 2,597 COVID-19 pediatric patients (± 24 years) in the VPS COVID-19 database including both males and females with a positive status of SARS-CoV-2 infection, ICU admission, and AKI diagnosis for the AKI group using ICD-10 codes. Variables included in the analyses covered demographics, diagnosis, lab order/results, treatment modalities, length of stay, and mortality. Categorical variables were summarized as percentages while continuous variables as medians. We utilized univariate analysis and multivariate linear regression to assess the differences between the patient group with AKI and those without.

Results: An AKI incidence of 10.7% (297/2757) was found within the pediatric cohort. The AKI group had a significantly higher median hospital length of stay (9.1 days vs. 5.1), PM2 and PM3 probability of death (1.2 vs. 0.96 and 0.99 vs. 0.78, respectively), and proportion of mortality (7.5% vs. 1.6%) in comparison to the non-AKI group. Similarly, the AKI group experienced higher rates of interventions in comparison to the non-AKI group such as vascular access (67.0% vs. 29.8%), airway/respiratory support (55.9% vs. 43.8%), renal support (5.4% vs. 0.4%), and cardio-respiratory support (2.9% vs. 0.8%).

Conclusions: AKI is a severe complication of COVID-19 in children and adolescents. Our study suggests a 4.7-fold increase in mortality in the COVID-19 AKI group. Pediatric COVID-19 patients should be monitored for AKI development and necessitate analyses on manifestations of COVID-19 to improve health outcomes.
Dialysis facility COVID-19 related resources, practices, and outcomes, as reported unit manager at each participating site

PO0084


Background: The objective of this study was to evaluate the impact of the COVID-19 pandemic to help conceptualize how patient care delivery, pharmaceutical representative interactions, conferences, and dialysis care may evolve.

Methods: Data was conducted between March 20, 2020 - March 31, 2021, providing coverage on the quickly evolving COVID-19 outbreak via online surveys. 50 nephrologists, neurologists, dermatologists, rheumatologists and gastroenterologists participated in each wave (total 250+) for 16 waves of research.

Results: Practice operation dynamics have changed due to the COVID-19 pandemic. Prior to 2020, 40% of practices were offering telemedicine, now nearly all (99%) offer virtual services. This migration has not come without challenges: 36% of physicians would prefer not to do telemedicine due to issues with patient access (60%), technology (53%) and their own reluctance to conduct new patient visits virtually (44%). The pandemic has created a high burnout among nephrologists compared to other specialties and nearly 20% would reevaluate their career choice if they could go back. Along with patient care, sales representative interactions have declined due to closed-door policies, with 51% of physicians reporting substantially lower or no engagements (virtual or in-person) compared to pre-COVID. Physicians are looking forward to resuming traditional in-person conferences, with 61% of vaccinated physicians planning to attend in-person if the option is available. COVID-19 has also significantly impacted HD patient care, with 66% of nephrologists reporting an outbreak among HD patients and/or staff. However, despite the obvious advantages of home care during the pandemic, only 34% of nephrologists indicated they were more likely to start a patient on a home modality due to the pandemic in March 2021 – versus 30% in March 2020. Despite their hesitancy, 80% of physicians agree the use of telemedicine will continue after the COVID-19 crisis has passed and estimate that ~20% of weekly visits will be virtual.

Conclusions: The pandemic has changed the delivery of patient care, evolving towards a more virtual model where possible – potentially creating physician burn out and interfering with the physician-patient relationship. The focus is now on the "new normal" post-COVID and the ongoing changes that will have on physicians.

PO0085

Analysis of the COVID-19 pandemic in Home and In-Center Dialysis Populations

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Background: While dialysis patients have a high risk of complications from COVID-19, in-center hemodialysis (ICH) patients show lower SARS-CoV-2 reproduction rates when compared to the general population (Cherif, JASN 2021), possibly related to lifestyle and interventions to prevent SARS-CoV-2 spread. Here we expand the research to study the prevalence of COVID-19 in both home (PD/HHD) and ICHD patients.

Methods: We analyzed COVID-19 cases in PD/HHD and ICHD patients from the U.S. Fresenius Kidney Care (FKC) network, from March 1 to November 27, 2020. Patients were tested for SARS-CoV-2 (confirmed by RT-PCR) when showing symptoms compatible with COVID-19 or exposed to an infected person. We perform statistical analysis for inter-intra-modalities, with continuous and categorical variables being expressed as the mean (standard deviation) and absolute (relative, %), respectively.

Results: We studied 263,223 patients (age 62.8±14.5 years, 57.7% males) receiving dialysis in the FKC network (87.3% ICHD; 12.7% PD/HHD). In the FKC network, 21,175 (8.05%) were infected with SARS-CoV-2. COVID-19 infection was more prevalent among ICHD (8.56%) vs. PD/HHD (4.49%) patients. Black had a significantly higher risk than other races for both ICHD (9.10%, p < 0.0001) and PD/HHD (5.13%, p = 0.0038), without a difference between modalities (p = 0.1827). While white ICHD patients did not have a different risk compared to others (8.52%, p = 0.4105), they had
PO0087
Feasibility of Infection Control Measures in Hemodialysis Units to Prevent Outbreaks of COVID-19: A Descriptive Study from Quebec

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Background: In-center hemodialysis (HD) units pose the perfect conditions for COVID-19 transmission yet limited space and resources are obstacles to infection prevention and control (IPAC) measures. We aimed to describe IPAC measures implemented and document the infection rates within HD units during the first year of the pandemic.

Methods: We invited leaders of Quebec’s HD units to collect information on IPAC measures from March 1th to June 30th 2020 and HD unit characteristics. Participating units were contacted again in March 2021 to collect information about the total number of patients, and the cumulative infection rate of each unit was compared to the regional cumulative infection rate using a standardized infection ratio (SIR).

Results: Data was obtained from 38 units, representing 90% of Quebec’s HD patients. 30% of units were perceived as crowded, and this was associated with objective distance measures between stations, which was much more likely to be <2m in units considered crowded (83.3% vs 19.2% p<0.001). IPAC measures regarding general prevention, screening procedures, physical distancing, and PPE use were implemented in 50% of units by 3 weeks and the remainder by 6 weeks. Data on cumulative infection rate was obtained in 26 units providing care to 3942 patients. The cumulative infection rate was disproportionally elevated in HD units compared to regional rates (Median SIR:2.68 IQR:1.58; 4.45)(Figure 1). No difference was noted in the SIR related to specific IPAC measures or to the physical characteristics of the units.

Conclusions: Hemodialysis units throughout Quebec were able to rapidly implement modified IPAC measures. Despite this, infection rates were disproportionally elevated.

PO0086
Perception of COVID-19 Risk Among In-Center Hemodialysis Patients

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Background: Dialysis patients are at high risk for severe complications related to COVID-19. The present study examined perception of risk of COVID-19 and its impact on behavior modification and emotional well-being among in-center hemodialysis (ICHd) patients during the recent COVID-19 pandemic.

Methods: In-depth, semi-structured telephone interviews were conducted between May and July 2020 with adult ICHD patients dialyzing at a large dialysis organization (LDO). Responses were analyzed using inductive thematic analysis. The reliability of categories was examined by an independent coder.

Results: A total of 41 LDO patients were interviewed. The median age was 63 years and 54% were female. Satisfactory inter-rater reliability was achieved for all identified themes (kappa = 0.70 - 0.99). We found that the COVID-19 pandemic caused a high level of worry among ICHD study subjects; 78% of those interviewed felt that they are at high risk of COVID-19. Consequently, subjects reported a high level of compliance with appropriate protective behaviors during the pandemic, such as wearing a mask, sheltering at home, social distancing, and frequent handwashing. The perception of the actual likelihood of contracting the virus during a hemodialysis session was relatively low (M = 3.38 on a 0 to 10 risk scale). The pandemic had no impact on self-reported anxiety to dialysis treatment schedules, medications, or diet. However, subjects reported dominating emotions of frustration, fear, stress, depression, and anxiety.

Conclusions: The study subjects were aware of the risk of COVID-19 and seemingly increased compliance with protective behaviors as a consequence. It appears that the pandemic had a strong negative impact on the study subjects’ emotional well-being and that additional support in this area might be beneficial.
PO0088

Safety and Efficacy of the Anti-COVID-19 Vaccination Practiced During the Hemodialysis Session
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Background: CKD patients represent a population at high risk of mortality from Covid-19. For 3 years, our hospital has been running a complete intradialytic vaccination project (HBV, Hemophylus, Pneumococcus, Influenza) for hemodialysis patients during dialysis treatment. This study aims to evaluate the safety and the serological response of intradialysis anti-Covid19 vaccination.

Methods: 217 hemodialysis patients from 5 centers were vaccinated with Moderna (Fig. 1). Patients with a previous infection received only one dose. 30 patients (4.6%) refused the treatment. The administration took place one hour after the start of the dialysis session, and therefore with the session still in progress. 44 vaccinated patients, with no history of previous Covid19 infection, out of a total 80 dialysis patients, were selected on voluntary basis, in our HD-center, to measure and titrate the anti-RBD S1 antibodies of the virus spike antigen 14 days after the second dose.

Results: Of the 217 patients, 64.3% were male, with a mean age of 70 ± 14 years. 19 patients (8.7%) had mild adverse reactions at site of vaccine-inoculation. Neither serious adverse events nor intradialytic complications were recorded. Table 1 shows the characteristics of the 44 patients whose antibody titration was performed. Seroconversion was achieved in 41 patients (93.18%), anti-RBD S1 titer was 936,6 ± 661,7 UI/mL.

Conclusions: Our preliminary data from our study shows that intradialytic vaccination for Covid-19 is safe and effective and solves logistic problems in prophylaxis’s management. This approach should be preferred in hemodialysis patients. We are planning to extend anti-RBD S1 antibodies monitoring of the Sars-Cov2 virus in all HD Centers involved in the study and to include Peritoneal Dialysis’ patients.

PO0089

Assessing the Impact of a Renal Care Management Program on Disease Progression Prior to and During the COVID-19 Pandemic
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Background: The transition to dialysis among chronic kidney disease (CKD) patients marks a significant change in health accompanied by increases in morbidity and healthcare costs. Delaying this transition means extending the patient’s quality of life and cost savings. The effects of renal care management on the transition to dialysis and whether having access to the program impacts the risk of transitioning to dialysis as well as the timeline of transitioning to dialysis is necessary to study given the increased role of case management programs with the advent of the COVID-19 pandemic. Understanding the role of disease management programs provide direction for management programs across the globe.

Methods: The design is a retrospective, cohort study of patients in the US drawn from a national claims database who were identified as having CKD 4 or 5 on July 1, 2018. The data was analyzed to determine whether program access affected the rate of transition to dialysis and the likelihood of transitioning to dialysis from 2018 to 2020.

Results: We followed the cohort of 7,992 participants (3,561 with access to Kidney Resource Services and 4,431 without access to Kidney Resource Services) during a two year period from 2018 to 2020. Those with access to Kidney Resource Services transitioned to dialysis later than those without access to the program. Further, after controlling for patient risk and characteristics, patients with access to the program had a 22 percent reduced risk of initiating dialysis compared to those without access.

Conclusions: Patients with stage 4 or 5 CKD who have access to renal care management have a reduced risk of transitioning to dialysis as well as a later transition to dialysis compared to CKD patients without access to renal care management. Further research is needed given the increased need for education during and post the COVID-19 pandemic to address social and clinical determinants of health.
PO0091

COVID-19 Vaccine Hesitancy and Uptake Amongst a Multiethnic Hemodialysis Population


Background: Broad adoption of vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is key to fighting the spread of Covid-19. Hemodialysis patients are at increased risk of exposure to SARS-CoV2 and associated with high morbidity and mortality if they contract Covid-19, therefore attaining high vaccination rates in dialysis patients is of utmost importance. The aim of this study was to establish the prevalence of vaccine hesitance across the multi-ethnic population of dialysis patients in North East London, and to assess whether vaccine uptake could be improved by offering vaccination in a familiar setting by trusted healthcare professionals.

Methods: Prior to the initiation of the hemodialysis vaccine programme, a survey was conducted of 837 in-centre haemodialysis patients to identify those willing to accept the vaccine. The vaccine was then offered to all haemodialysis patients during their dialysis attendance, by their dialysis team of nurses and nephrologists.

Results: Of 674 responses, 476 (71%) patients reported willingness to accept the vaccine. However only 41% of the 232 patients of Black ethnicity stated that they would accept the vaccine with 59% undecided or declined, compared to acceptance of 77% and 82% of the Asian and White patients respectively (p=0.0001). The actual acceptance rate was significantly higher in all ethnic groups than that predicted by the survey (82.2% uptake in total), with 71.5%, 86.0% and 89.3% in Black, Asian and White cohorts respectively (p=0.0001). In total, 59.1% of patients who responded ‘no’ in the initial survey, accepted the vaccine when offered on the unit.

Conclusions: Though vaccine hesitancy remains a concern, even in this particularly vulnerable patient group, our data show that uptake can be improved by offering Covid-19 vaccination in a familiar environment by a trusted healthcare team.

PO0092

Navigating Vaccine Hesitancy in a Hemodialysis Clinic

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Background: Pre-vaccination, SARS-CoV2 infected 20% of our hemodialysis clinic with a 48% mortality. Vaccine access and hesitancy are significant barriers to vaccination among minority groups. Over 90% of our patients self-report as Black or African American, thus we created a multidisciplinary vaccine navigation program to optimize COVID-19 vaccination.

Methods: We surveyed the patients’ vaccination attitudes before the vaccine was available. All care team members: patient care technicians, nurses, social worker, dieticians, and nephrologists were educated to provide the patients with the efficacy and optimal care delivery for patients with or at-risk for CKD are needed. Here, we describe risk factors and access to care surrogates (area deprivation index-ADI) for clinical outcomes among SARS-CoV-2-tested patients in the CURE-CKD Registry.

Results: We formed a COVID-19 Sub-Registry within CURE-CKD (1/1-6/30/2021; N=171,988) of patients with CKD, diabetes (DM)/pre-DM, or hypertension (HTN) with SARS-CoV-2 testing at UCLA Health (UCLA; N=17,884) and Providence St Joseph Health (PSJH; N=154,104). Statistical analyses and fitted multivariable logistic regression models were adjusted for age and sex. The UCLA cohort included analyses for acute kidney injury (AKI), ADI (for poor housing, education, income), Charlson Comorbidity Index (CCI), and severe COVID-19 disease.

Conclusions: Although many patients had vaccine hesitancy, the growth curves show the rapid adoption of the vaccine. The main barrier to the vaccine was access. Multidisciplinary care in the hemodialysis clinic can facilitate access to care and may be a model for navigating kidney transplantation.
PO0094
Beliefs About and Impact of the COVID-19 Pandemic on a Population of Inner City Kidney Transplant Recipients (KTRs)
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Background: The COVID-19 pandemic was especially stressful for indigent people with multiple health conditions. We examined beliefs and behaviors at the height of the pandemic in a population of inner-city KTRs.

Methods: 40 KTRs followed at our Center were surveyed by telephone including questions about behaviors, knowledge and attitudes regarding COVID-19 using yes/no or Likert scale answers as well as the Stress and Social Support and Health Beliefs Questionnaires.

Results: Mean age was 57±1.8yrs, with 22 males and 18 females, 27 (77%) Black, (4) White 11% and 8 (23%) other. Time since transplant 7.75±1.0yrs. 35% (9/26) felt difficulties were piling up so high that they could not overcome them.13% (4/31) reported it was more difficult to pay for medications and were more likely to skip doses to make them last longer (r=0.473, p=0.008). 75% (23) were afraid of COVID-19. 51% (17/33) were afraid of catching it from a family member, 54% (18) from a friend, 84% (26) limited any in person interactions, 44% (19) avoided leaving home for any reason and 45% (15) avoided going to any public spaces. 57% who reported being more afraid of COVID-19 were more likely to report poor health (r=0.39, p=0.032), to report being afraid to leave their home (r=0.48, p=0.006), were more likely to have contacted their provider more than 4-6 times in the past two months (p=0.034), to state that their health was poorer (r=-0.39, p=0.032), and to say that their condition keeps them from working (r=-0.52, p=0.027). They also believed that eating Chinese food could increase COVID-19 risk (r=0.37, p=0.039).

Conclusions: In our population of inner-City KTRs: 1. Two thirds were afraid of COVID-19, including catching it from a friend or family member, and limited leaving their home. 3. They were also more likely to report poor health. contact their healthcare provider multiple times, as well as state their condition made it impossible to work and believe that one could catch COVID-19 from Chinese food. 4. Over 10% were financially stressed and skipped doses of medication to make them last longer and a third felt it difficult to cope overall. 5. Follow up will be necessary as the pandemic subsides to examine if there was a detrimental effect on graft survival due to multiple stressors that could affect adherence in this population.

PO0095
Barriers and Facilitators to Emotional Well-Being and Healthcare Engagement in COVID-19: A Qualitative Study Among Patients with Kidney Disease and Their Caregivers
Jia Hwee Ng,1 Candice Halinski,1 Devika Nair,2 Michael A. Diefenbach.1
1Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Kidney Disease and Their Caregivers Barriers and facilitators to patients’ and caregivers’ emotional well-being and healthcare engagement have not been deeply described, leaving a gap in interventions during future crisis settings.

Methods: We conducted a qualitative study among patients with CKD (stages 4-5), kidney failure, kidney transplantation, and their caregivers. Interviews were guided by Leventhal’s Model of Self-Regulation that emphasized individual interpretations and emotional responses to health threats as determining factors of health behaviors. Interviews were audio-taped, transcribed, and analyzed thematically.

Results: Twenty-eight patients (median age 63, self-reported race: White 57%, Black 18%, Asian 1%, others 14%) and 14 caregivers were interviewed over six months. Barriers and facilitators related to patients’ emotional well-being included 1) negative emotional responses (feelings of increased vulnerability, anxiety, social isolation, and depression); 2) coping behaviors (adaptive coping via self-preservation and emotion regulation; maladaptive coping via alcohol and unhealthy eating); and 3) the need for caregiver support for daily tasks. Barriers and facilitators to healthcare engagement included: 1) continued trust in the medical community (“I put my faith in [my doctor’s] knowledge”); and 2) technology (telehealth was a facilitator to access for some but inadequate for multidisciplinary care “[my] transplant evaluation was stopped…we could not go to the cardiologist”). Caregivers reported higher burden compared to before the pandemic.

Conclusions: Patients and caregivers widely reported negative emotional reactions to enforced pandemic-related social isolation. Coping efforts were partially successful. Telehealth provided adequate access to kidney health services for some but was insufficient for those requiring multidisciplinary care. Lessons learned from the COVID-19 pandemic suggest that patients with kidney disease may benefit from psychosocial and multi-modal structural supports to offset social isolation, reduce caregiver burden, and bolster access to multidisciplinary care during future crisis settings.
PO0097
Clinical, Functional, and Mental Outcomes in Hemodialysis Patients 3 Months After COVID-19 Diagnosis
Marc H. Hemmeler,1 Marlies Noordzij,2 Priya Vart,3 Kitty J. Jager,3 Rafael Duivenvoorden,2 Alfesio C. Abrahams,4 David A. Arroyo,5 Yuri Bartaglia,6 Robert Eckart,7 Francesca Mallamaci,8 João Oliveira,3 Andrea M. Groeneveld,1 Sylvester Nivnick,1 Lillian Abreu,1 Casper F. Fransen,1 Luuk Hilbrands,2 Ron T. Gansevoort2 on behalf of the ERACODA Collaborators
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Background: There is overwhelming evidence that hemodialysis (HD) patients are at high risk of death in the first month after developing COVID-19. However, less is known about their long-term mortality risk and functional and mental outcome. We aimed to assess these outcomes in a large cohort of HD patients 3 months after COVID-19 diagnosis.

Methods: From ERACODA, we included adult HD patients who presented with COVID-19 from February 1, 2020-January 31, 2021 and with complete data on vital status and hospitalization. Recovery of functional and mental status was estimated by the treating nephrologist. Logistic regression was used to calculate odds ratios (OR) with 95% confidence interval (95%CI) for the likelihood of reaching the pre-COVID-19 status.

Results: A total of 2,249 HD patients (mean age 67.5 ± 14.4 years) were included, of whom 1,087 (44%) were not hospitalized, 1,165 (48%) were hospitalized but not admitted to an ICU, and 197 (8%) were hospitalized and ICU-admitted. In these 3 groups, the survival probability at day 28 was 90%, 75% and 47%, and at 3 months 90%, 73% and 40%, respectively. For 854 patients who survived 3 months after COVID-19 diagnosis, data on functional and mental status was available: 743 (87%) reached their pre-COVID-19 functional status within 3 months. 111 patients had not yet reached this, but it was expected that 58% of them would do so within 1 year. Higher age (adjusted OR: 0.97; 95%CI: 0.96-0.99), higher frailty score (0.81; 0.70-0.93) and ICU admission (0.11; 0.05-0.26) were associated with a lower likelihood of reaching pre-COVID-19 functional status. Pre-COVID-19 mental status was reached by 803 (94%) patients. Higher frailty score (0.76; 0.65-0.89) and ICU admission (0.27; 0.11-0.67) were associated with lower likelihood of reaching prior mental status. For 56% of the 51 patients who had not yet reached their prior status, it was expected that they would do so within the coming year.

Conclusions: Three months after a COVID-19 diagnosis, most HD patients who were not admitted to the ICU were still alive. Furthermore, a vast majority had already reached their pre-COVID-19 functional and mental status at that time point.

Funding: Commercial Support - The ERACODA project receives unrestricted grants from Baxter and Sandoz., Private Foundation Support

PO0099
Hand Sanitizer Overdose in the Era of COVID-19
Neelharika Mettupalli, Ashton N. Breithaupt, Alice Chedd. The University of Tennessee Health Science Center College of Medicine, Memphis, TN.

Introduction: Isopropyl alcohol is a common ingredient in hand sanitizers. Ingestion should be suspected if patient presents with high osmolar gap & pseudo renal failure without metabolic acidosis.

Case Description: A 4 y/o female with h/o of HTN & hypothyroidism, brought to the ED following altered mental status. 2 bottles of hand sanitizers were found empty next to her. She was drowsy, unable to provide any further history. Vitalis T: 36.7 C, HR 91, BP 124/84, RR 14, SaO2 97 on RA. Physical exam was unremarkable. Initial labs on admission: Serum creatinine 2.47, i-stat creatinine at 0.7, bicarb 24, AG 8, serum osmolality 341, osmol gap of 57. Ethanol level was negative. Table1 outlines the patient's labs. Given normal bicarb, normal AG with very high osmol gap, isopropyl alcohol ingestion was suspected. IV fomepizole was started, as some hand sanitizers contain methanol. Fomepizole was continued until osmolar gap closed. No dialysis was required. Methanol level was undetectable. Acetone level high 176. Isopropanol level high 49. Patient’s mental status improved with supportive measures.

Discussion: Isopropanol ingestion presents with normal bicarb, normal AG with very high OG. Treatment is usually supportive. Clinicians should be aware of falsely elevated serum or if measured via colorimetric method due to acetone’s interference. Our case presents a new challenge added to numerous challenges physicians are facing in the COVID Era.

Labs

PO0100
Federated Learning for AKI Prediction in COVID-19 Patients

Background: Predictive models are trained on single-center data and are non-generalizable, and multi-center data pooling raises privacy concerns. Federated learning (FL) trains models by updating parameters from a central aggregator without sharing raw data. We used FL to predict acute kidney injury (AKI) in COVID-19 patients within 3 (AKL) and 7 (AKL) days of admission as a use case.

Methods: We selected 4035 COVID-19 patients admitted to 5 hospitals in New York city, after excluding patients with AKI, to train logistic regression and logistic regression with L1 regularization (LASSO) models through 3 approaches: local data, pooled data from all sites, and a FL method.

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**Results:** Federated models outperformed local models as measured by area under the receiver operating characteristic curve (Figure 1, Table 1). SHAP plots indicate differences in feature importance between LASSO models in AKI prediction (Figure 2).

**Conclusions:** FL has utility for developing accurate predictive models without compromising patient data.

**Funding:** NIDDK Support

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**Table 1.**

<table>
<thead>
<tr>
<th>Model</th>
<th>Area Under ROC Curve (AUC)</th>
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<tr>
<td>Local</td>
<td>0.72</td>
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<tr>
<td>Federated</td>
<td>0.77</td>
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</tbody>
</table>

**Figure 1A**

**Figure 1B**

**Figure 2.** SHAP plots of LASSO local and federated models in predicting AKI within 3 days of admission at Mount Sinai Hospital.

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**Introduction:** A 66-year-old man with history of hypertension, chronic obstructive pulmonary disorder, latent tuberculosis, and biopsy-proven giant cell arteritis (GCA) was admitted for fevers and intermittent headaches three weeks after receiving dose 2 of the Moderna COVID-19 vaccine.

**Case Description:** On admission, the patient was afibrile with normal vitals and unremarkable physical examination. He noted his GCA had been in remission off treatment for two years. Labs noted new-onset microscopic hematuria and proteinuria (1.5 g/24 hr) as well as serum creatinine (SCr) of 2.2 mg/dL from 1.4 ten days prior. His sedimentation rate and C-reactive protein were also markedly elevated (119 mm/hr and 105 mg/L). Given rapidly progressive glomerulonephritis, IV Solumedrol was given for 3 days (after infection was ruled out). A kidney biopsy showed pauci-immune, necrotizing, crescentic glomerulonephritis and small vessel vasculitis (Figure 1A & 1B). Serologies returned with positive p-ANCA and high-titer myeloperoxidase antibody, confirming the diagnosis of Microscopic polyangiitis (MPA). He was transitioned to oral Prednisone and given the first of two doses of IV Rituximab. One week post-biopsy his Scr was 1.8 mg/dL.

**Discussion:** Renal involvement by MPA in patients with GCA is rare but has been reported. This case is unique in its temporal relation to COVID-19 vaccination. There have been reports of crescentic IgA nephropathy as well as minimal change disease following COVID-19 vaccination but we are unaware of cases of de novo or recurrent vasculitis. While causality is difficult to prove, clinicians should closely monitor patients post-vaccination.

**PO0102**

**COVID-19 Pandemic Highlights Global Inequities in Chronic Hemodialysis Care: A DOPPS/ISN Survey**

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**Background:** Patients receiving chronic hemodialysis (HD) are highly vulnerable in all settings. It is unknown whether the COVID-19 pandemic has disproportionally affected the care of chronic HD patients in low (LIC) and low-middle income (LMIC) settings. This survey aimed to identify global challenges and inequities in HD care delivery during the COVID-19 pandemic.

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Methods: The Dialysis Outcomes and Practice Patterns Study (DOPPS) and the International Society of Nephrology (ISN) conducted a global online survey of HD units (HDU). Sample HDUs included DOPPS sites in China, a random sample stratified by region and HDU population, and an open invitation via ISN’s membership list. The survey assessed availability of COVID-19 diagnostics and personal protective equipment, the impact of COVID-19 on HD delivery and patient outcomes from COVID-19. Responses were stratified by country income according to World Bank classification.

Results: Responses were received from 412 HDUs across 78 countries (Table 1).

Conclusions: Striking global inequities were identified in access to COVID-19 diagnostics, infection prevention, and access to routine HD care during the pandemic. Higher apparent mortality in patients on chronic HD in LICs and LMICs is likely due to access to and use of dialysis, as well as greater disruptions to HD delivery. Urgent action is required to address these inequities, which disproportionately affect low-income settings, exacerbate pre-existing vulnerabilities and lead to worse outcomes.

Case Description: A 76-year-old female with DM, HTN, SLE (in remission) & COVID-19 was admitted with bilateral leg edema & generalized skin reaction 2 weeks post receiving 1st dose of Moderna vaccine. Skin manifestations included generalized macular & blistering lesions, painful ruptured vesicles & skin weeping. Skin biopsy revealed epidermal necrosis, neutrophilic spongiosis & negative DIF. The 2nd case was a 78-year-old male with DM & ESRD on PD who was admitted with inadequate PD due to membrane failure. Also complaint of itchy, painless maculopapular rash, which was initially localized following 1st dose of Moderna vaccine but became progressive & diffuse post 2nd dose. Biopsy was nonspecific with focal epidermal squamous atypia, overall negative DIF except C3 granular staining in basement membrane. Immunological tests failed to detect ab against infectious origin. Both cases denied oral or genital ulcers, new onset diarrhea, new medication, new sexual contact or recent travel. CBC were normal & other lab tests were negative for active immunological, autoimmune or other dermatological disease. Both cases had received 2 doses of Moderna vaccine. PD due to membrane failure was considered to be a potential adverse event. None of the patients received SARS-CoV-2 vaccination as per their nephrologist.

Discussion: The majority of studies looked at skin reaction to COVID19 vaccine were in non-renal disease population & reported minor, self-limited manifestations, our case report highlights a more severe & generalized skin manifestation in ESRD. Associated factors may be related to difference in vaccine response in renal patients, altered immune response in uricemic environment or progression due to delayed healing & concomitant presence of edema in setting of inadequate dialysis. Clinical trials for Moderna vaccine didn’t include participants with renal disease & hence insufficient to determine the pharmacology & side effect profile in this population.

PO0105

Glomerular Disease in Temporal Association to SARS-CoV-2 RNA Vaccination: A Series of 16 Cases

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Background: Vaccination is considered safe in patients with chronic kidney disease. However, given the ability to activate the immune system, vaccinations carry a risk of inducing inflammatory disease flares. The mass vaccination for SARS-CoV-2 provides a unique opportunity to investigate potential vaccine-associated glomerular diseases.

Case Reports: Kidney biopsies from patients who presented with acute kidney injury (AKI) and/or nephritic/nephrotic syndrome within three weeks of SARS-CoV-2 vaccination were included in the study (n=16). Kidney biopsies were reviewed at a single center and clinical information was provided from nephrologists for clinicopathologic correlations.

Results: Sixteen patients with a new onset of kidney disease or flare within 3 weeks of SARS-CoV-2 vaccination were identified and all had glomerular disease on biopsy. Eleven patients had two vaccine doses prior to symptom onset. The patient cohort included 6 males and 10 females, with a mean age of 58 years. Biopsy diagnoses included IgA nephropathy (n=7), minimal change disease (n=4), ANCA-associated glomerulonephritis (n=3), membranous glomerulopathy (n=1), and diffuse lupus nephritis (n=1). Thirteen patients had co-morbid medical conditions, including hypertension (n=10), diabetes (n=4), autoimmune disease (n=5), and chronic kidney disease (n=4). The most common clinical presentation was AKI with concurrent nephritic or nephrotic syndrome (n=9), followed by nephritic syndrome with preserved kidney function (n=5), nephrotic syndrome with preserved kidney function (n=1), and isolated hematuria (n=1). Three patients had undergone kidney biopsy prior to vaccination. A majority of patients had an elevated serum creatinine (mean 3.4 mg/dL, 14 had proteinuria (nephrotic range in 4), 11 had hematuria, and 10 had hypoalbuminemia (mean 2.9 g/dL). Six patients had antinuclear antibodies and 4 had a positive ANCA serology at the time of biopsy. Clinical follow-up is ongoing.

Conclusions: IgA nephropathy, minimal change disease, ANCA-associated glomerulonephritis, membranous glomerulopathy, and lupus nephritis were identified with temporal association with SARS-CoV-2 vaccination. The mass vaccination for SARS-CoV-2 is safe in patients with chronic kidney disease but with potential adverse events.

PO0106

Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposition (PGLMD) Associated with COVID-19

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Introduction: Renal disease in COVID-19 is often due to acute tubular injury but can include multiple glomerular lesions such as collapsing glomerulopathy. This is the first reported case of COVID-19-associated PGLMD.

Case Description: A 71-year-old woman with normal baseline creatinine (Cr) was admitted with COVID-19 and discharged on oxygen and dexamethasone (Dex). She improved but returned a month later with edema and rash. She was found to have nephrotic syndrome, hematuria, and AKI (peak Cr 8.5 mg/dL) requiring HD. PET kidney biopsy revealed PGLMD with clonal IgG3-kappa. SPEP, serum free light chains (sFLC), 24hr urine UPEP, bone marrow biopsy with flow cytometry, fat pad biopsy, and PET-CT

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were negative for monoclonal immunoglobulin (Ig) or cell line, amyloid, or malignancy. Though symptoms had long since resolved, she was still PCR-positive for SARS-CoV-2 on nasal swab. Upon discharge she was given cyclophosphamide (Cy). Her renal function improved (Cr 2.5) and she came off HD 2 weeks later. Her outpatient oncologist opted not to continue therapy. However, 2 months later she was readmitted with nausea, dyspea, and anaemia with recurrent AKI (Cr 6.7) and nephrotic syndrome. HD was restarted. Repeat kidney biopsy [Figure] was noted to be a "carbon copy" of the first. SLEP, spot UPEP, and sFLC were again negative. She was started on Cy, bortezomib, and DEX with similar partial response (Cr <2.5).

**Discussion:** PGNMD is a rare type of monocular gammopathy of renal significance (MGRS) that often has no detectable extrarenal monoclonal Ig or cell line. MGRS and PGNMD, though usually not postinfectious, have been reported with other viruses (e.g., viral hepatitis, parvovirus-B19). However, though causality is unclear, this is the first case of MGRS reported in association with COVID-19.  

**Case Description:** Routine labs 1 day prior to COVID-19 mRNA vaccine series were negative with serum creatinine (Cr) 0.8 mg/dl, urea protein creatinine ratio (UPCR) 0.42 mg/mg (65 mg/dl of protein), and serum albumin 4.8 g/dl. Thirty-one days after the second COVID-19 vaccine, routine labs were significant for nephrotic range proteinuria with UPCR >6:21 mg/mg (>2500 mg/dl of protein), hypoalbuminemia (1.7 g/dl), and proteinuria 4.3 mg/dl. Of note, he remained asymptomatic until 2 days prior to labs when noted to have periorbital and lower extremity edema associated with decreased urine output. Allograft biopsy revealed foot process effacement without definitive evidence of segmental sclerosis. Infectious workup including viral studies for SARS-CoV-2 were negative. He received methyldopa and 1 g IV for 3 days. His UPCR dropped to 375 mg/m2 weekly x2, and an oral prednisone taper. During week 4 of PP concurrent with prednisone taper, the patient appeared clinically well with noted improvement in labs: UPCR 0.55 mg/mg, Sc 0.57 mg/dl, and serum albumin 3.5 g/dl. He is currently receiving a tweak of PP and steroids.

**Discussion:** While there are isolated reports of new onset or exacerbation of proteinuric kidney disease after an mRNA COVID-19 vaccine, to our knowledge, this is the first report of FSGS recurrence in a kidney transplant recipient. Although causality is not proven, the temporal relationship strongly suggests an association between the vaccine and disease recurrence. Comparing our reports, our patient presented somewhat later, -1 month after dose #2 as compared to within 2 weeks after dose #1. Although the risk-benefit ratio of COVID vaccination for kidney transplant recipients remains favorable and vaccination is encouraged by national clinical guidelines, close monitoring after COVID vaccine for kidney transplant patients at risk for disease recurrence is warranted.

**Case Description:** 63-year-old Hispanic female with past medical history of hypertenion, psoriatic arthritis presented to the hospital with gross hematuria for 6 weeks starting 3 days after 2nd dose of Pfizer COVID vaccine. Her PCP had sent her to ER 5 days after onset of hematuria as had noted a creatinine (Cr) of 1.6 with >3+ protein and >20 RBCs on urinalysis suspicious for nephrotic syndrome. On review she had serum Cr of 0.5 about 4 months ago with no proteinuria or hematuria before. In the ER she was given antibiotics for urinary tract infection and outpatient referral for nephrology. She could not make the outpatient appointment and with continued gross hematuria for a month, she presented to the ER again where she was noted to have Cr of 10 mg/dl and urine protein ratio of 7.5 g/mg. Renal imaging including CT urogram was normal. Renal biopsy showed IgA nephropathy, M1SOET1C1 with a fibrocellular crescent and acute tubular necrosis likely secondary to lyzed red cells in setting of multiple RBC casts in the tubules. She was put on 250 mg Solumedrol for 3 doses followed by 1 mg/kg of Prednisone with eventual downtrend in Cr to 4.5 in 15 days.

**Discussion:** There have been 2 cases reported in literature with known IgA nephropathy who developed gross hematuria post COVID-19 vaccination. SARS-CoV-2 vaccines use nucleoside modified purified mRNA which does elicit higher neutralizing antibody titre and strong cluster of differentiation response leading to production of several proinflammatory cytokines. Thus, there is a concern that vaccines might exacerbate immune mediated glomerular diseases. IgA1 is involved in the pathogenesis of IgA nephropathy and patients with IgA nephropathy have higher than normal IgA1 levels. While studying the antibody response to other vaccines like influenza. Also while studying the antibody response to COVID-19 patients with IgA nephropathy are known to express higher IgA response compared to IgG and IgM along with reports of concurrent worsening of the glomerulonephritis. Nephrologists should closely follow patients with IgA nephropathy to establish the frequency of disease activation post vaccination.

**Case Description:** She was asymptomatic for urinary tract infection, neither was she menstruating. Her renal functions were normal with a creatinine of 0.93 mg/dL. Urinalysis showed hematuria with > 50 red blood cells (RBC) per high-power field (HPF) and 2+ protein on the dipstick. She again experienced gross hematuria with > 50 RBC/HPF on urinalysis and proteinuria of 2.23g after receiving the 2nd Pfizer vaccine, at which time she was referred to the Nephrology department for further evaluation. We examined urine sediment which was significant for dysmorphic RBCs and many casts. A renal biopsy showed that the majority of 14 glomeruli had global sclerosis on light microscopy, a diffuse increase of mesangium, and interstitial fibrosis with tubular atrophy. Immunofluorescence microscopy was positive for Immunoglobulin A (IgA), IgM, and C3, and negative for IgG, IgM. Electron microscopy revealed mesangial expansion and cellularity and peri-mesangial electron-dense deposits. These and other findings fit with the Oxford Classification of M1, S1, E0, T0, C0. Following

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the biopsy, we prescribed Lisinopril 5 mg daily for control of proteinuria. We did not prescribe steroids because of the mild nature of the disease and lack of significant inflammation. The patient continues to do well without symptoms. Her most recent labs show preserved renal function and spot proteinuria reduced to 1.3 g.**  

**Discussion:** The current case raises questions about the potential association of IgA Nephropathy with COVID-19. Recent studies suggest that the SARS-CoV-2 virus can interact with the ACE-2 receptor expressed in mesangial cells, podocytes, and proximal tubular epithelium of Bowman’s capsule, and the collecting ducts. Research suggests that the inflammatory environment from COVID-19 can activate or exacerbate immune mediated diseases in predisposed individuals. The mucosal immune response against COVID-19 may have contributed to the progression of IgAN in this patient. We plan on checking the SARS-CoV-2 anti-RBD IgA titer to see if there is a correlation between anti-RBD IgA levels and progression of kidney function. Also, the persistence of IgA antibody or memory B cells post-COVID-19 infections may have prognostic implications in advancing IgAN or even end-stage kidney disease. Although our patient has not been vaccinated, there have also been cases of patients with IgAN developing gross hematuria or even end-stage kidney disease. The mucosal immune response against COVID-19 includes aberrant mucosal immune response to the initial SARS-CoV-2 infection that she contracted in December 2020. This could have then predisposed her to IgA nephropathy after the administration of the vaccine. The virus’ spike protein or other factors may trigger an aberrant mucosal immune IgA response which can then lead to the onset and progression of IgA nephropathy. Further case series are needed to establish a more definitive association of the COVID-19 vaccine with IgA nephropathy.

**PO0111**

IgA Nephropathy Flare Following COVID-19 Vaccination

Mohammad Hanza, Kelly H. Beers. Albany Medical Center, Albany, NY.

**Introduction:** IgA nephropathy is the most common cause of primary glomerulonephritis in people of Asian origin. It is characterized by mesangial deposition of IgA which activates Lectin and Alternative pathways that cause glomerular damage which results in hematuria and proteinuria. Untreated disease can progress to chronic kidney disease, and even end-stage kidney disease.

**Case Description:** We describe a case of a 28-year-old male of Chinese descent who has a biopsy-proven diagnosis of IgA nephropathy (Oxford classification M1 E0 S1 T0 C1). Patient was maintained on Losartan 100 mg daily with proteinuria under 500mg per day. He presented to the nephrology clinic for an urgent visit after he experienced gross hematuria in his urine following the second dose of his COVID-19 vaccination (Moderna). His first shot of the same vaccination was 28 days ago. After receiving his second dose, patient experienced high-grade fever (TrmX of 39F) and chills. Next morning, he again experienced high-grade fevers and on the same night, he experienced gross hematuria. On his visit to the clinic, patient was feeling back to normal. His vital signs were within normal limits. Physical examination did not reveal any cracks in his lungs or lower extremity edema. Workup revealed elevated hemoglobin in his urine with 10-20 RBCs per high power field with no WBCs. Spot urine analysis revealed urine protein-creatinine ratio of 828mg/g. A 24-hour urine collection was performed which revealed urine protein excretion to be 925 mg/24hr. All these findings were consistent with a flare of his well-established IgA nephropathy. Since patient’s urine protein excretion was less than 1g/day, a decision was made to start the patient on steroids and instead closely monitor the patient on his usual dose of Losartan 100 mg daily. Patient had not had any further complaints. He is to regularly follow up at our nephrology clinic.

**Discussion:** IgA nephropathy is seen in individuals with recent mucosal infection or after administration of mucosal vaccination as these phenomena result in elevated IgA secretion that can then deposit in the mesangium. Our case is unique in the sense that a non-mucosal mRNA vaccination caused IgA flare. This could indicate a possible mucosal response to COVID-19 vaccination which can be a possible mechanism as to how the vaccine protects against COVID-19. Further investigations are necessary to examine the link between the two.

**PO0112**

IgA Vasculitis with Renal Manifestations in a College-Aged Individual After COVID-19 Infection

Samuel A. Lasoff, Tushar Chopra, Emaad M. Abdel-Rahman. University of Virginia, Charlottesville, VA.

**Introduction:** IgA Vasculitis is one of the most common causes of primary glomerulonephritis, however there are very few cases reported in association with COVID-19. Approximately 20-50% of patients present with renal manifestations, such as IgA Nephropathy (IgAN). Here we present a case of rapidly progressing crescentic IgAN presenting after COVID-19 infection.

**Case Description:** A 28-year-old male presented to the emergency department with elevated creatinine after being seen in the rheumatology clinic. A timeline of the patient’s symptoms is presented in Figure 1. The renal biopsy showed a rapidly progressing IgAN with acute tubular injury and RBC casts. The patient, a 19-year-old male presented to the emergency department with symptoms that included: high fever, chills, and myalgia. The patient had been diagnosed with COVID-19 via PCR test 2 weeks prior to presentation. He was positive for SARS-CoV-2. At presentation, his blood pressure was 100/50, HR 90, respiratory rate 24, and temperature 38.7°C. He was also started on prednisone, Cr level started getting better. In 3 weeks Cr level was down to 1.7.

**Discussion:** This is the first reported case of biopsy-proven IgAN flare-up after SARS-CoV-2 vaccination that caused AKI. Corticosteroid is an effective treatment, promptly improving Cr. IgAN exacerbation after SARS-CoV-2 vaccination should be closely monitored for frequency and consequence to further elucidate AEFI of the novel vaccine.
Impact of the COVID-19 Pandemic on Kidney Diseases Requiring Renal Biopsy: A Single-Center Observational Study

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Background: The coronavirus disease-2019 (COVID-19) pandemic impacted healthcare services for kidney disease patients. Lockdown and social distancing were mandated worldwide to avoid the clinical closure of medical centers. The diagnostic workup for kidney disease may have been delayed during the COVID-19 pandemic because non-urgent tests and visits were postponed due to closure of medical services during the lockdown.

Methods: We here report the impact of the COVID-19 pandemic on a total number of 299 native kidney disease patients requiring renal biopsy for diagnosis in a retrospective observational study from a tertiary hospital in Germany.

Results: The lockdown period in March and April 2020 primarily affected patients admitted to the normal medical ward with a compensatory increased rate of renal biopsies in May 2020. In addition, there was a shift towards more patients admitted with this virus with hemoglobinuria during the COVID-19 pandemic. This phenomenon of an increased number of patients with hemoglobinuria during the COVID-19 pandemic was specifically observed in a subgroup with hypertensive nephropathy requiring renal biopsy, not attributed to the COVID-19 lockdown period itself.

Conclusions: To our knowledge, this is the first report of identifying a subpopulation susceptible to closure of medical services during the COVID-19 pandemic and diagnostic delay of specific kidney diseases. Therefore, the COVID-19 pandemic should be regarded as a risk factor especially in patients with diseases other than COVID-19 primarily admitted to the medical ward.

Tip Lesion Variant of Focal and Segmental Glomerulosclerosis (FSGS): A Case Report in a Patient with COVID-19

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Introduction: Acute kidney injury (AKI) is a common complication of SARS-CoV-2 infection. Published cases report acute tubular injury as the most common pathological finding in these patients. Glomerular disease has been reported in a minority of patients, with collapsing focal segmental glomerulosclerosis being the most common. Nonetheless, the exact aetiology of injury is still unclear and inconclusive. The authors present a case of a patient diagnosed with a tip lesion variant of focal and segmental glomerulosclerosis (FSGS) and concomitant SARS-CoV-2 infection.

Case Description: A 43-year-old African woman, with no known past medical history, presented to the emergency department with a 6-day history of fatigue, dry cough, hypoaesthesia, myalgia, dyspnea, nausea and vomiting. Laboratory tests confirmed SARS-CoV-2 infection. Despite fluid therapy, there was an elevation of serum creatinine from 1.1 to 1.6 mg/dL and the urinalysis was positive for protein (4) and blood (2). The urinary sediment revealed 3 red blood cells per high-power field. The urinary protein/creatinine ratio was approximately 13 g, subsequently confirmed with a 24-hour urine collection (13445 mg/24hours). All immunological tests were negative with the exception of hepatitis B serology (positive for HBV past infection). Renal ultrasonography showed a right kidney of 130 mm and a left kidney measuring 99 mm with important reduction of corticomedullary differentiation. After cure criteria for COVID-19, the proteinuria was 1022 mg/24h. The kidney biopsy revealed a tip lesion variant of focal and segmental glomerulosclerosis (FSGS). Low dose angiotensin converting enzyme inhibitors were started but no corticosteroid due to spontaneous regression of proteinuria. The patient returned home 20 days later with normalization of creatinine levels and 24-hour urine protein decreased to 1.1 mg/dL and 1060 mg, respectively.

Discussion: To our knowledge, this is the first case report of a patient with tip lesion variant of focal and segmental glomerulosclerosis (FSGS) possibly associated with COVID-19 disease. More data from kidney biopsies will further elucidate about pathologic processes associated with kidney injury and glomerular involvement in SARS-CoV-2 infection.

Cause or Not: IgA-Dominant Infectious-Related Glomerulonephritis in a Patient Infected with COVID-19

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Introduction: IgA dominant infectious related glomerulonephritis (IGAD-IRGN) is an uncommon variant of IRGN. It has been mostly associated with S.aureus infections. In the COVID-19 Era, there has been one case of IGAD-IRGN related to COVID-19. This is a case of IGAD-IRGN in a patient infected with COVID-19.

Case Description: 51 y/o male with no previous medical history who presented with a 3 day history of generalized swelling. Patient had no known medical problems and was not taking any medications. He reported drinking 3 beers daily. Denied any recent illness or sick contacts. At ED, the patient was found with anasarca and uncontrolled blood pressure. Initial blood tests showed normal renal function with hypoalbuminemia (2.9g/dL). UA showed active sediments and nephrotic range proteinuria of about 4 g/day. Positive SARS-CoV-2 test, including serology workup. Labs were remarkable for elevated ESR (105), low C4 (12), normal C3 (95) and elevated RF (44). ANA, HIV, HCV, light chain ratio, cryoglobulins and ANCA were negative. UPIEP showed faint IgK lambda showing hazy intrarenal opacities with a perihilar distribution. Pre-biopsy COVID molecular testing came back positive. He was diuresed aggressively and received losartan for BP control. A kidney biopsy was performed and revealed MPGN pattern with IF strongly positive for IgA in addition to weaker staining for C3, and IgG. EM showed subendothelial humps with few mesangial and subepithelial deposits. The diagnosis of IgA-dominant immune complex-mediated glomerulonephritis consistent with IRGN was made.

Discussion: IGAD-IRGN is a rare variant of IRGN that has been mostly associated with S.aureus infections. It is believed that the recent COVID-19 pandemic could reasonably explain the finding of IGAD-IRGN on kidney biopsy. IGAD-COVID-related GN has been reported only once in the literature. Up until recently, most cases of COVID related kidney injury have been associated to ATN and collapsing FSGS. A recent biopsy with positive SARS-CoV-2 RNA in the nasopharyngeal specimen and mild multifocal pneumonia treated with meropenem and Remdesivir. Serologic work-up for nephrotic syndrome was negative. A skin biopsy demonstrated leukocytoclastic vasculitis. Renal allograft biopsy showed membrane proliferative and sclerosing glomerulonephritis with dominant IgA staining by immunofluorescence, consistent with IgA nephropathy. He received pulse dose steroids followed by tapering treatment in kidney, left function and reduction of his proteinuria to 0.6 g four months after steroid treatment.

Discussion: We postulated that our patient developed de novo HSP and nephrotic syndrome as a result of COVID-19 infection. Podocytopeny and nephrotic syndrome linked to viral infection have been well described, particularly in AA patients with high-risk APOL1 genotype. Key cytokines known to be elevated in COVID19 infection can drive autoimmune responses, such as interferon and IL-6. Cytokine release, uncontrolled activation of both innate and adaptive immune cells, along with genetic variants likely predispose patients to the development of glomerular disease mediated by various immune mechanisms. Published biopsy series consistently demonstrate acute tubular injury as the most common renal manifestation of COVID-19 manifestation, however, new onset autoimmune diseases such as IgAN may also be triggered by COVID infection. HSP can be a rare manifestation in COVID-19. Our case occurs post COVID-19 infection and systemic autoimmunity should be recognized as a complication of COVID-19, regardless of the presence or absence of pulmonary findings.
Discussion: kidney transplant recipients are more susceptible to infections, along with increased disease severity. At the same time their immunosuppressed state may reduce the inflammatory response following this type of infection. Decisions were based on stopping or attenuating the viral load and the systemic inflammation caused by this virus, but at the same time protecting against acute allograft rejection and the confection with other pathogens. Our findings suggest that the use of statins and antithrombotic prophylaxis in all hospitalized transplant patients may be beneficial to reduce the risk of mortality in patients with COVID-19 infection. Also, the maintenance of immunosuppressive therapy was not associated with worse outcomes.

PO0120
ANCA Vasculitis Presenting as Hemoptysis Post COVID-19 Infection
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Introduction: COVID-19 infection has been suggested to be a trigger for a de-novo autoimmune response. This case represents one of a few reported cases of ANCA-vasculitis developing after a COVID infection.

Case Description: A 41-year-old female with a history of chronic sinusitis (not vasculitis related), obesity, right pulmonary sequestration, and highest COVID-19 infection 1-month prior manifesting as only mild cough with loss of taste and smell, was admitted with a 2-week history of progressive cough productive of blood-tinged sputum and lower extremity neuropathy. CTA of her chest showed air space opacities in right lower lobe concerning for bacterial superinfection in a host with altered pulmonary architecture. She was treated for presumed community acquired pneumonia. A week later, she presented with worsening hemoptysis and respiratory failure requiring intubation, which escalated quickly to needing extracorporeal membrane oxygenation (ECMO). Extensive bilateral airspace infiltrates due to diffuse alveolar hemorrhage and a PR3-ANCA level of 175 U/ml were strongly suggestive of a new diagnosis of ANCA-vasculitis (granulomatosis with polyangiitis). Her renal function remained normal, and urine sediment had no findings to indicate an ongoing concurrent nephritic process. She was given high dose pulse intravenous steroids, recombinant factor VII, 7 sessions of daily plasma exchange, intravenous tranexamic acid, and 1 dose of Cytoco 500 mg/m2. She briefly had clinical improvement and required decreased ECMO support, but unfortunately, she later developed worsening pulmonary hemorrhage and hypotension, which was attributed to acute respiratory distress syndrome and thrombotic microangiopathy, as opposed to immune mediated capillaritis. After 2 weeks of treatment, she was terminally decannulated.

Discussion: This is a rare case of ANCA-vasculitis likely triggered by COVID-19 infection. The presence of peripheral neuropathy indicates that she probably had extrapulmonary manifestations of vasculitis, although she had no evidence of renal involvement. This case report demonstrates that a high index of suspicion is needed for a new diagnosis of ANCA-vasculitis in patients with a prior history of COVID-19 infection to allow for prompt diagnosis and appropriate management.

PO0121
Deep Learning for Subphenotype Identification in COVID-19-Associated AKI

Background: Acute kidney injury (AKI) is common in COVID-19 and associated with increased adverse outcomes. COVID-associated AKI (COVID-AKI) pathophysiology is heterogeneous, and deep learning may discover subphenotypes.

Methods: We used data from 5 New York City hospitals from adults admitted between March 20–March 21 with COVID and AKI, excluding patients with kidney failure. An autoencoder compressed 58 features containing comorbidities, the first laboratory values and vital signs within 48 hours of admission for unsupervised K-means clustering. Outcomes were mortality, dialysis, mechanical ventilation, and ICU admission.

Results: We identified 1634 patients with COVID-AKI and discovered 3 subphenotypes. Subphenotype one had 576 patients (35%); two had 635 patients (39%), and three had 423 patients (26%) (Table 1). Subphenotype three had the lowest median blood pressures, highest median BMI, and highest rates of all outcomes. (Figure 1)

Conclusions: There are distinct subphenotypes in COVID-AKI indicating the heterogeneity of this condition.

Funding: NIDDK Support

Table 1. Demographics of COVID-Associated AKI Subphenotypes.

<table>
<thead>
<tr>
<th>Subphenotype</th>
<th>N (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1634</td>
<td></td>
</tr>
<tr>
<td>Subphenotype 1</td>
<td>576</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Subphenotype 2</td>
<td>635</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Subphenotype 3</td>
<td>423</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1a: Proportions of ICU admission, dialysis or mechanical ventilation usage, and mortality across subphenotypes. Figure 1b: Top 4 features with the largest log-transformed differences between subphenotypes 1 and 3.

PO0122
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Background: Home dialysis may be able to minimize SARS-CoV2 exposure risks. The pandemic may have introduced unique challenges related to supply disruption and care delivery changes. We sought to assess the global burden of COVID-19 on peritoneal dialysis units (PD) and understand PD unit practice changes during this time.

Methods: The Peritoneal Dialysis/Dialysis Outcomes and Practice Patterns Study (PDOPPS/DOPPS) and International Society of Nephrology (ISN) administered a web-based survey (1) to dialysis units selected based on a random sample stratified by region (November 2020 – March 2021), and (2) to an open invitation via ISN’s membership list and social media (March 2021). Responses were compared across 10 ISN regions.

Results: Returned surveys included 167 PD facilities across 52 countries. Changes in several care domains including clinic communication and frequency, labwork frequency, method of communication, masking policies, changes in handling of PD effluent among several care domains including clinic communication and frequency, labwork frequency, method of communication, masking policies, changes in handling of PD effluent among PD patients to communicate with their physicians has increased during the pandemic, optimal communication frequency, methods and schedule of routine bloodwork needs to be better elucidated.

Conclusions: Variability exists in routine PD care, and the availability and use of PPE, disruption in PD supplies among the different regions reflecting the availability of the resources and infrastructure differences. LMIC tended to be more severely impacted as this gap needs to be addressed in anticipation of future pandemics for treatment continuity. Although remote technology use among PD patients to communicate with their physicians has increased during the pandemic, the optimal communication frequency, methods and schedule of routine bloodwork needs to be better elucidated.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
COVID-19 in the second surge may have contributed to a decline in the incidence of AKI. The difference may be related to less severe disease during the second surge, though of AKI in hospitalized patients with COVID-19 during two different surge periods, compared to the second surge (p=0.0196). significantly more AKI patients in the first surge were on mechanical ventilation as more patients with hypernatremia and with peak CRP > 50 (Ref range: <50) presented decreased from 28.7% in the first surge to 18.6% in the second surge (p<0.0001). This Patients < 18 years, with End Stage Kidney Disease or a kidney transplant were excluded. Medical Center, Mayaguez, Puerto Rico

PO013
Comparison of Rates of AKI Between Two COVID-19 Surges in Hospitalized Patients in the Bronx
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Background: The incidence of AKI in COVID 19 is very variable across the world. In New York City it was as high as 36% in a large series in early 2020. However, the incidence of AKI during the second surge between Oct of 2020 to early 2021 is unknown. In this study, we compared these two COVID-19 periods for the incidence of AKI amongst hospitalized patients.

Methods: This was a multi-center, retrospective cohort study of patients hospitalized with COVID-19 between March 1st and July 16th 2020 (n=1,719), and between October 15th 2020 and February 28th 2021(n=997) in two NYC public hospitals, (total n= 2,716). Patients < 18 years, with End Stage Kidney Disease or a kidney transplant were excluded. Chi-squared test and Fisher’s exact test were used to compare the clinical characteristics of the patients. A p-value less than 0.05 was considered statistically significant.

Results: The baseline clinical characteristics and demographics of the two surges were similar. The incidence of AKI as defined by KDIGO criteria, during admission decreased from 28.7% in the first surge to 18.6% in the second surge (p=0.0001). This trend was seen both at encounter level too as shown below. For laboratory characteristics, more patients with hypernatremia and with peak CRP > 50 (Ref range: <50) presented in the first surge than the second surge (p=0.0001). No differences in the peak potassium and peak D-Dimer, or ICU admission rates were seen between two surges. However, significantly more AKI patients in the first surge were on mechanical ventilation as compared to the second surge (p=0.0196).

Conclusions: To our knowledge this is the first comparison reported between rates of AKI in hospitalized patients with COVID-19 during two different surge periods. The difference may be related to less severe disease during the second surge, though ICU admission rate was the same. Better care established by the time of the second surge may have improved therapies such as early use of anti-viral agents, convalescent antibodies, and anticoagulation may have contributed to better outcomes. Improvement in care of COVID-19 in the second surge may have contributed to a decline in the incidence of AKI. Future studies are needed to see if this trend towards lower AKI incidence continues.

COVID-19-Induced P-ANCA-Associated Nephritic Syndrome in a Woman Without Respiratory Involvement

Introduction: Infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has affected our population worldwide leading to a global pandemic. The most common manifestation was infection to the lungs leading to respiratory failure. As the infection continued to spread, other complications started to emerge. Studies have identified involvement of other organs such as heart and kidneys. It has been observed that patients with severe infection are debuting with renal failure. The most common lesion is acute tubular necrosis (ATN) but other causes such as endothelitis, nephrotic syndrome and glomerulonephritis (GN) have been observed. ANCA associated GN is a rare manifestation of SARS-CoV-2 infection that must be differentiated from ATN. Only two cases of ANCA associated vasculitis have been reported. They were both male and presented with ANCA associated GN responsive to immunosuppressive therapy.

Case Description: Case of a 65 year old female patient with medical history of asthma and dyslipidemia presented to the hospital with complaints of recurrent painless hematuria. Physical examination was unremarkable. Initial laboratory work up was remarkable for acute kidney injury accompanied by the presence of pyuria, hematuria and proteinuria. There was evidence of leukocytosis and anemia. PCR test for COVID19 came back positive. Renal imaging showed thickening of the urothelium at the renal pelvis with parenchymal echogenicity. After multiple efforts there was no significant improvement. Hence, work-up to exclude nephritic syndrome was requested. Reports were remarkable for positive p-ANCA and presence of MPO antibodies. Workup for GBM and antibodies came back negative. Patient was started on intravenous steroids. Renal biopsy showed evidence of ANCA mediated pauci immune GN with crescents. Further on, she was transitioned to oral steroids and Rituxan where improvement of renal function was observed.

Discussion: While ANCA associated GN in SARS-CoV-2 is rare, the incidence of COVID19 cases is on the rise. The incidence of other potential complications are yet to be identified. Thus, it is important to understand and study the disease’s pathophysiology to extrapolate possible complications. This will assist in the early detection of disease and help improve patient’s prognosis. Also, will prevent development of chronic repercussions in patient’s renal function.

PO0125
AKI Secondary to Atypical Hemolytic Uremic Syndrome Caused by COVID-19
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Introduction: Atypical Hemolytic Uremic Syndrome(aHUS) can be triggered by viral infections. So far there has been little data on COVID 19 infection-causing aHUS. We present one such case of acute kidney injury(AKI) secondary to aHUS with COVID-19 infection and its outcome.

Case Description: A 55-year-old woman presented with altered mental status and shortness of breath from 2-3 days. The patient tested positive for the COVID-19 virus. Labs showed creatinine of 4.8g/dl from a baseline of 0.8g/dl, with a hemoglobin of 8.9g/dl and a platelet count of 20,000/uL. Peripheral smear showed evidence of a large number of schistocytes and thrombocytopenia. Haptoglobin and reticulocyte counts were 29mg/dl and 1% respectively. In view of the laboratory findings, there was high suspicion for Thrombotic thrombocytopenic purpura (TTP). Her PLASMIC score was 6. Treatment with plasma exchange therapy (PLEX) and steroids was initiated but there was no significant clinical improvement. An ADAMTS13 level was measured, which was 0%, and resulted in the diagnosis of TTP. Due to lack of evidence of TTP eculizumab was started for suspected aHUS. She responded remarkably well (within days) with remittance returning to baseline, hemoglobin stabilizing, platelet slowly trending towards normal and peripheral smear, labs showed no signs of hemolysis, and an improvement in her RFP. At 5 month follow-up, the patient eventually progressed to end-stage renal disease had to be placed on regular dialysis.

Discussion: aHUS is a rare variety of thrombotic microangiopathy(TMA) which results in a classic triad of Coombs negative hemolytic anemia, renal injury, and thrombocytopenia. aHUS has a mortality rate of 25%. 50% of patients eventually progress to ESRD or have irreversible brain damage. Multiple triggers have been identified including various non-enteric infections, viruses, drugs, malignancies, transplantation, pregnancy, and other underlying medical conditions. At the time of writing this case report, there is only one other case report of COVID-19 virus-induced aHUS resulting in AKI. In AKI renal damage is thought to be caused by microthrombi formation in the kidney vasculature. Endothelial damage is further escalated by anaphylatoxins produced by complement activation. aHUS induced AKI is an alternate mechanism for COVID -19 to cause AKI requiring eculizumab for optimal treatment.

PO0126
Cryoglobulinemia in the Setting of COVID-19 AKI
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Introduction: COVID19 is due to SARS-CoV-2 a single stranded RNA virus with respiratory and epithelial cell targets. As COVID19 has reached pandemic proportions, complicating AKI is common. Pathogenesis is varied and multifactorial but acute tubular injury is most common. Glomerular pathology is possible but not well defined.

Case Description: 66YOM with HTN, Stage III CKD, & COVID19 hypoxemic respiratory failure complicated by AKI & nephritic syndrome. Cr peaked at 5mg/dL. He required CRRT for volume overload & acidosis. Labs showed low C3 & type I cryoglobulinemia. IgG, monoclonal protein on SPEP. Extensive cryoglobulinemic GN on renal bx with lgG immunofluorescence. Negative Congo red stain. Microtubular deposits indicative of cryoglobulins on EM. He received pulsed solumedrol then 5 sessions of PLEX. Renal recovery with good urine output, dialysis discontinued. Cr down to 2.2mg/dL post PLEX.

Discussion: Cryoglobulinemia is due to cold immunoglobulin precipitation. Type I is associated with malignancy or hematologic disease and Types II & III have no associated disease. Our patient had Type I IgG. cryoglobulinemia without evidence of malignancy. BM bx had 10% abnormal plasma cells, perhaps due to plasma cell dyscrasia of cryoglobulinemia. A prior case series reported COVID19 incident MUGS. Patients had monoclonal lgG or lgGk but no mentioned renal injury. They hypothesized gamopathy dysregulated compensating, our patient’s renal manifestations fit a Hemophagocytic Lymphohistiocytosis pattern so we hypothesize they are due to COVID19 associated hyperinflammation and cytokine release. Our case illustrates the benefit of biopsy to identify additional treatment options and the reality that timely biopsy is not always be safely obtained. In COVID19 patients respiratory or hematologic status can make biopsy unsafe which may limit defining associated glomerular pathology.
Methods: 5 patients presenting with nephrotic-range proteinuria 1-3 weeks after COVID-19 vaccine and a KxB were identified (3 Pfizer/BioNTech, 2 Moderna). Past medical history and lab tests including serum creatinine (sCr), urine protein-to-creatinine ratio (UPCR), and serological workup were recorded. KxBs were routinely evaluated by light microscopy (LM), immunofluorescence microscopy (IF), and electron microscopy (EM), followed by confocal examination of relative IgG and nephrin localization in all patients; serological studies for anti-nephrin antibodies using human glomerular extract and recombinant nephrin extracellular domain were performed using plasma available on 2 patients.

Results: In all patients, sCr was 0.5-1.2 mg/dl and UPCR 4.5-7.6 g/g. 1 patient had MCD in remission diagnosed 6 months prior; others had no relevant PMH. All workup was negative, except low positive ANA in 2 patients. On KxBs, diagnosis of MCD was made in 4 and stage 1 membranous nephropathy (MN) in 1 patient(s) (serum albumin 2.0-2.4 g/dl in MCD and 3.4 g/dl in MN patient(s)); all had mild chronic changes. All 4 MCD patients had fine granular punctate podocyte staining for polyclonal IgG colocalizing with nephrin by IF and diffuse FPE by EM; in 1 patient plasma was saved during NS and was serologically positive for anti-nephrin. The MN patient had 3+ fine granular IF staining for polyclonal IgG and PLA2a along GBMs with sparse superficial subepithelial electron-dense deposits on EM, and was serologically positive for anti-nephrin. All MCD patients were successfully treated with oral glucocorticoids, while the MN patient was monitored closely under RAAS blockade.

Conclusions: COVID-19 mRNA vaccines can trigger de-novo or relapsing anti-nephrin- and PLA2a-mediated NS, thus adding both autoimmune-mediated podocytopathies to vaccine-induced complications. Temporal association is essential for diagnosis; prompt accurate diagnosis benefits treatment and response.

Funding: Private Foundation Support

POO129
Real-World Effectiveness and Immunogenicity of BNT162b2 in Dialysis Patients
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Background: BNT162b2 (Pfizer/BioNTech) is a SARS-CoV-2 vaccine that received an emergency use authorization from the US Food and Drug Administration. Clinical trials in the general population demonstrated that BNT162b2 reduced risk of COVID-19 by 95%, however, dialysis patients were not represented in these trials. Here, we estimated the effectiveness and SARS-CoV-2 antibody response among real-world dialysis patients who were vaccinated with BNT162b2.

Methods: Patients included in this analysis were adults dialyzing at a large dialysis organization. For the effectiveness analysis, patients who began a BNT162b2 vaccination series (January-March 2021) were matched (with replacement) to up to 4 previously unvaccinated dialysis controls based on age, diabetes status, sex, race, body mass index, date of first vaccine, US state of residence, and prior known COVID-19 diagnosis. Vaccine effectiveness was estimated by calculating the hazard ratio (HR) for time to polymerase chain reaction confirmed infection between vaccinated and unvaccinated patients over 3 follow-up intervals: days 1-21, 22-42, and 43- after first dose of vaccine. Immunogenicity was measured in a subset of consented patients who completed the 2-dose BNT162b2 vaccination schedule. Blood samples were collected approximately 28 days after the second dose of BNT162b2, and indirect chemiluminescence immunoassays were used to measure immunoglobulin G (IgG) antibodies against SARS-CoV-2. Samples with a reading of ≥1 arbitrary unit (AU) were considered IgG+.

Results: We identified 12,169 patients who received BNT162b2 and were matched to 46,377 unvaccinated controls. The HRs and 95% confidence intervals (CI) were 0.84 (0.65, 1.03), 0.61 (0.40, 0.93), and 0.21 (0.13, 0.35) during 1-21, 22-42, and 43- days postvaccination, respectively. Among the 344 patients with postvaccination antibody measurements, 98.0% (95% CI: 95.2%-99.2%) were IgG+ (median: 63.3 AU of IgG).

Conclusions: Our results indicate that BNT162b2 is effective in preventing SARS-CoV-2 infection in dialysis patients. Moreover, antibodies to SARS-CoV-2 are detected in nearly all patients vaccinated with BNT162b2 in whom antibodies were measured.
inhibition of 11 (3–24) compared with 65 (49–75), respectively. After the second dose, 14/17 (82%) of dialysis patients developed neutralizing antibodies exceeding the threshold for viral neutralization and antibodies against the receptor-binding S1-domain of the spike protein, compared to 46/46 (100%) of healthy controls, respectively. The median (IQR) percent inhibition was 51 (32–86) compared to 98 (97–98) in healthy controls.

Conclusions: Patients receiving long-term dialysis show a reduced antibody response to the first and second doses of the mRNA vaccine BNT162b2. The majority (82%) develop neutralizing antibodies after the second dose, but at lower levels than healthy controls.

Figure 1: SARS-CoV-2 IgG Spike, RBD, and NP Antibody Response Following One Versus Two Dose BNT162b2 Vaccine in Hemodialysis Patients.

PO0131

Humoral Response to the BNT162b2 Vaccine in Hemodialysis Patients

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Background: Hemodialysis (HD) patients have high mortality from COVID-19 and immunity following vaccination remains uncertain. This study evaluated SARS-CoV-2 antibody response in HD patients following BNT162b2 COVID-19 vaccination compared to health care workers (HCW) and convalescent serum.

Methods: This single centre observational cohort study enrolled 142 HD patients and 35 HCW receiving the BNT162b2 vaccine. SARS-CoV-2 IgG antibodies to the spike protein (anti-spike), receptor binding domain (anti-RBD), and nucleocapsid protein (anti-NP) were measured in 66 HD patients receiving one vaccine dose, 76 HD patients receiving two vaccine doses, and 35 HCW receiving two vaccine doses.

Results: In HD patients receiving a single BNT162b2 dose, seroconversion occurred in 53/66 (80%) for anti-spike and 35/66 (55%) for anti-RBD by 28 days post dose, but only 15/66 (23%) and 4/66 (6%), respectively attained a robust response defined as reaching the median level of anti-spike and anti-RBD in convalescent serum. In patients receiving two doses of BNT162b2 vaccine, seroconversion occurred in 69/72 (96%) for anti-spike and 63/72 (88%) for anti-RBD by 2 weeks following the second dose while 52/72 (72%) and 43/72 (60%) reached median convalescent serum levels of anti-spike and anti-RBD. In HCW, 35/55 (100%) exceeded median levels of anti-spike and anti-RBD in convalescent serum 2-4 weeks post second dose.

Conclusions: This study found poor immunogenicity 28 days following a single dose of BNT162b2 vaccine in HD patients, supporting adherence to recommended vaccination schedules, and avoiding delay of the second dose in this population.

Funding: Government Support - Non-U.S.

Figure 1

PO0132

Comparative Effectiveness of Ad26.COV2.S vs. BNT162b2 for the Prevention of SARS-CoV-2 Infection Among Dialysis Patients

Steven M. Brunelli,1 Scott Sibbel,1 Gilbert Marlowe,1 Jeffrey A. Giullian,2 David B. Van Wyk,2 Francesca Tontori,1 Davita Clinical Research, Minneapolis, MN; 2DaVita Inc, Denver, CO.

Background: Elsewhere, we have demonstrated that the BNT162b2 vaccine (Pfizer/BioNTech) is highly effective in reducing risk of COVID-19 among real-world dialysis patients. Because individual vaccines may be differentially available (and acceptable) to patients, it is important to understand the comparative effectiveness of other agents, such as Ad26.COV2.S (Janssen).

Methods: This was a retrospective real-world comparative effectiveness study comparing two vaccination strategies (“use Ad26.COV2.S” versus “use BNT162b”) among adult patients dialyzing at a large dialysis organization. Patients receiving Ad26.COV2.S were matched 1:1 to those initiating a BNT162b2 series based on age, race, US state of residence, calendar week of first vaccine receipt, and prior history of COVID-19. Follow-up time began the day after the first vaccine dose. The outcome of interest was the comparative rate of polymerase chain reaction-confirmed SARS-CoV-2 infections considered over 3 follow-up intervals: days 1-21, 22-42, and 43 post vaccination.

Results: There were 2683 matched pairs of patients who received a first dose of each vaccine. During days 1-21, the incidence rate was 1.26 infections per 1000 patient-weeks (pt-wks) among BNT162b2 recipients and 1.26 among Ad26.COV2.S recipients (incident rate difference [IRD]: 0.00; 95% confidence interval [CI]: -1.10, 1.10). During days 22-42, the incidence rate was 0.93 infections per 1000 pt-wks among BNT162b2 recipients and 0.40 among Ad26.COV2.S recipients (IRD: 0.53; 95% CI: -1.40, 0.93). After day 43, the incidence rate was 0.50 infections per 1000 pt-wks among BNT162b2 recipients and 0.50 among Ad26.COV2.S recipients (IRD: 0.00; 95% CI: -0.8, 0.8). Results were nearly identical when considering only patients without a prior history of COVID-19.

Conclusions: In a large contemporary cohort of dialysis patients, a “use Ad26.COV2.S” strategy versus a “use BNT162b2” strategy would be expected to yield no difference in additional cases of SARS-CoV-2 infections. Given similar effectiveness, vaccine allocation should be based on availability and logistical considerations.
PO0133
Predictors of Response to SARS-CoV-2 Vaccines Among Maintenance Dialysis Patients
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Background: Vaccines against SARS-CoV-2 are highly effective in the general population; however, their efficacy may be diminished in maintenance dialysis patients, a population particularly vulnerable to COVID-19. We assessed vaccine response in a national sample of maintenance dialysis patients.

Methods: Using retrospective clinical data, we assessed seroresponse to vaccine among maintenance dialysis patients cared for at 130 Dialysis Clinic, Inc (DCI) facilities. Via a clinical protocol available to early vaccinating facilities, antibodies against SARS-CoV-2 spike antigen were semi-quantitatively assessed beginning with the monthly blood draw at least two weeks after completion of a SARS-CoV-2 vaccine series. Vaccine response was defined as a titer ≥2 U/L, and logistic regression analysis was used to identify characteristics associated with response. Patients with history of COVID-19 prior to antibody assessment were excluded.

Results: Among 1,352 patients, 996 (74%) had a serologic response. Serologic response differed significantly by vaccine type: 314/386 (81%) among BNT162b2/Pfizer recipients, 615/655 (94%) among mRNA-1273/Moderna recipients, and 67/311 (22%) among Ad26.COV2.S/Janssen recipients. Age greater than 75, lack of hepatitis B immunity, immune-modulating medication, lower serum albumin, and COPD were associated with vaccine non-response (Figure). Conclusion: Seroconversion to mRNA vaccines is robust among chronic dialysis patients, and the use of mRNA vaccines should be promoted aggressively in this vulnerable population. High rates of non-response to the Janssen vaccine warrant further study. Future research should evaluate the potential role for boosters and whether seroresponse is associated with patients' COVID-19 status.

Funding: NIDDK Support

PO0134
Humoral Responses to Single-Dose BNT162b2 mRNA Vaccination in Dialysis Patients Previously Infected with SARS-CoV-2

Background: Seroconversion rates following infection and vaccination are lower in dialysis patients compared to healthy controls. There is an urgent need for the characterization of humoral responses and success of a single-dose SARS-CoV-2 vaccination in previously infected dialysis patients.

Methods: We performed a dual-center study with 43 dialysis patients after BNT162b2 vaccination and 25 dialysis patients after PCR-confirmed COVID-19. Single-dose vaccination was performed in 13 previously infected patients. Anti-S1 IgG, neutralizing antibodies, and antibodies against various SARS-CoV-2 epitopes were measured 6 weeks after the first vaccination or onset of COVID-19 and 3 weeks after single-dose vaccination.

Results: Previously infected patients without vaccination showed a significantly higher neutralizing capacity than patients vaccinated twice (median [IQR] percent inhibition 88.0 (71.5–95.5) vs. 50.7 (26.4–81.0); P=0.018). After one single vaccine dose, infected individuals generated 15- to 34-fold higher levels of anti-S1 IgG than age- and dialysis vintage matched patients after infection or two-time vaccination with a median (IQR) index of 274 (151–791) compared to 18 (8–41) and 8 (1–21) (for both P<0.001). With a median (IQR) percent inhibition of 97.6 (97.2–98.9), the neutralizing capacity of SARS-CoV-2 antibodies was significantly higher in previously infected patients compared to other groups (for both P=0.01). Bead-based analysis showed high antibody reactivity against various SARS-CoV-2 spike protein epitopes after single-dose vaccination in previously infected patients.

Conclusions: Single-dose vaccination in previously infected dialysis patients induced a strong and broad antibody reactivity against various SARS-CoV-2 spike protein epitopes with high neutralizing capacity.
How Well Do Hemodialysis Patients Respond to the BNT162b2 mRNA COVID-19 Vaccine?

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Background: Hemodialysis patients as well as healthcare workers are considered to be in a high-risk category for SARS-CoV-2 infection and a priority for vaccination.

Methods: In a single-center out-patient hemodialysis unit, 46 healthcare workers and 216 patients were vaccinated simultaneously with BNT162b2 (BioNTech-Pfizer) vaccine. They received two doses, 21 days apart. The primary objectives were to evaluate the safety and efficacy of the vaccine.

Results: There were no major adverse events in either group. Lymphadenopathy was reported by some health workers. All (100%) individuals in the healthcare workers group developed a positive antibody response (anti-S IgG) after the second dose compared with 91.7% of patients. Among patients there was a significant negative correlation between anti-S levels and age after both, the first dose (R=-0.176, p<0.01) and the second dose (R=-0.193, p<0.005); there was also a significant negative correlation between anti-S and Charlson Comorbidity Index adjusted for age after both, the first dose (R=-0.150, p=0.028) and the second dose (R=-0.163, p=0.018). Finally, a negative correlation between anti-S and Body Mass Index was found after the first dose (R=-0.140, p=0.04). No correlations were found with dialysis vintage, Kt/V, or diabetes.

Conclusions: Following vaccination, patients had a significantly lower anti-S response than healthcare workers. Age, Charlson Comorbidity Index and Body Mass Index negatively impacted the humoral response. However, with more than 91% response we believe that vaccination can be recommended strongly in the hemodialysis population.

Real-World Effectiveness and Immunogenicity of mRNA-1273 in Dialysis Patients

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Background: mRNA-1273 (Moderna) is a SARS-CoV-2 vaccine that received an emergency use authorization from the US Food and Drug Administration. Clinical trials in the general population demonstrated that mRNA-1273 reduced risk of COVID-19 by 94.5%, however, dialysis patients were not represented in these trials. Here, we estimated the effectiveness and SARS-CoV-2 antibody response among real-world dialysis patients who were vaccinated with mRNA-1273.

Methods: Patients included in this analysis were adults dialyzing at a large dialysis organization. For the effectiveness analysis, patients who began an mRNA-1273 vaccination series (January-March 2021) were matched (with replacement) to up to 3 previously unvaccinated controls based on age, diabetes status, sex, race, body mass index, date of first vaccine, US state of residence, and prior known COVID-19 diagnosis. Vaccine effectiveness was estimated by calculating the hazard ratio (HR) for time to polymerase chain reaction confirmed infection between vaccinated and unvaccinated patients over 3 follow-up intervals: days 1-21, 22-42, and 43 after first dose of vaccine. Immunogenicity was measured in a subset of consented patients who completed the full, 2-dose mRNA-1273 vaccination schedule. Blood samples were collected approximately 28 days after the second dose of mRNA-1273, and indirect chemiluminescence immunoassays were used to measure immunoglobulin G (IgG) antibodies against SARS-CoV-2. Samples with a reading of >1 arbitrary unit (AU) were considered IgG+.

Results: We identified 23,037 patients who received mRNA-1273 and were matched to 64,243 unvaccinated controls. The HRs and 95% confidence intervals (CI) were 0.96 (0.79, 1.16), 0.51 (0.34, 0.75), and 0.27 (0.17, 0.42) during 1-21, 22-43, and 43 days postvaccination, respectively. Among the 329 patients with postvaccination antibody measurements, 96.0% (95% CI: 93.3%-97.9%) were IgG+ (median: 100.5 AU of IgG).

Conclusions: Our results indicate that mRNA-1273 is effective in preventing SARS-CoV-2 infection in dialysis patients. Moreover, antibodies to SARS-CoV-2 were detected in nearly all patients vaccinated with mRNA-1273 in whom antibodies were measured.

Fewer ESKD Dialysis Patients (pts) Reach Antibody (AB) Levels Consistent with Neutralizing Titers When Vaccinated with Ad26.cov2.S Compared with mRNA COVID-19 Vaccines

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Background: The COVID-19 viral vector (VV) vaccine’s single dose and routine storage requirements may be preferred to the mRNA-based vaccine’s 2 doses and low temperature storage requirements. We report an interim analysis of a quality improvement project performed at 2 Arizona dialysis clinics comparing the AB response toVV vaccine with mRNA vaccine in ESKD pts.

Methods: Pts received either the VV vaccine (Ad26.cov2.S) administered in the dialysis clinics or mRNA vaccines (BNT162b2, mRNA-1273) administered in the community. AB response was assessed with remnant blood and a semi-quantitative chemiluminescent assay for IgG directed against the receptor binding domain of the SARS-CoV-2 spike antigen. Values >7 Index produce plague reduction neutralization test (PRNT) titers greater than 1:80 dilution recommended by the FDA standard for measuring neutralizing titer.

Results: AB response was evaluated at an average of 22 days post vaccination (>14 days post Ad26.cov2.S or post 2nd mRNA vaccine). 36.45% pts (80%) who received the VV vaccine failed to develop an AB index >7 after >21 days post vaccine compared to 5/31 pts (16%) who received an mRNA vaccine (84% achieved AB index >7); all 5 pts had no prior COVID-19 history. Of pts receiving the VV vaccine with prior history of COVID-19, 22% of pts had AB index <8 after 14 days post vaccine. 41 pts receiving the VV vaccine had additional AB measurements in the next 14-37 days (avg 26 days after prior measure). In 34 pts with no prior history of COVID-19, 3 pts achieved AB index >7 in the recent sample and had previously been < 1 (n=1) or 1-7 (n=2), bringing the total number with AB > 7 from 2 to 5 (15%). AB levels remained unchanged in pts with a prior history of COVID-19 (n=9). No demographic or laboratory differences were observed.

Conclusions: Our data support the contention that the available VV-based vaccine against the SARS-CoV-2 virus is not effective in producing AB response in most ESKD pts especially when compared to an mRNA counterpart. If AB indices predict immunity and other studies support our findings, alternative vaccination strategies in ESKD pts vaccinated with VV vaccines is needed.

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Humoral Response to Pfizer BNT162b2 in Peritoneal and Hemodialysis Patients: A Comparative Study

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Background: Generalized immunization against COVID19 has become the cornerstone in prevention of Sars-CoV-2. Maintenance dialysis patients (MDP) are at higher risk of both exposure and mortality. Efficacy and security of Pfizer BNT 1622 vaccine well documented for the general population, but not in MDP, particularly in peritoneal dialysis (PD) patients. This study aims to compare humoral response between HD and PD patients.

Methods: Observational prospective study including MDP on HD or PD program from a Portuguese middle-sized Nephrology Center, who received Pfizer-BNT162b2. Specific anti-Spike IgG was measured as arbitrary units per milliliter (AU/mL) on two separate occasions, corresponding to the first and second doses’ humoral response. The two groups were compared both for absolute value and number of non-responders (NR) after both inoculations. Demographic data was also obtained and compared.

Results: Of 73 patients enrolled, 67 were eligible for the final study: 42 HD and 25 PD patients. PD group developed significantly higher antibody titers both after first (Med 5.44 vs 0.99; p<0.01) and second dose (Med 17.043 vs 65.81; p<0.01). HD status was associated with non-responding after the first dose (Phi=0.383; p<0.01), but not after the second one (p=0.08). Age, Charlson Comorbidity Index and dialysis vintage were lower in the PD group (p=0.01; p=0.02; p=0.01, respectively).

Conclusions: This study demonstrated a better humoral response to immunization with Pfizer-BNT162b2 in PD patients when comparing to HD patients, after both inoculations. Both groups showed substantial humoral response after just one dose of the vaccine. Older age and higher comorbidity burden may explain the relative immunogenicity deficit.
PO0140

Time-Dependent Evolution of IgG Antibody Levels After First and Second Dose of mRNA-based SARS-CoV-2 Vaccination in Hemodialysis Patients: A Multicenter Study
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Background: Vaccine preparations are essential for the containment of the COVID-19 pandemic, which has affected significantly the hemodialysis population. Early reports suggest a reduced immunologic response to COVID-19 vaccines in dialysis patients, in spite of a high degree of seroconversion. We aimed to identify risk factors for a reduced efficacy of an mRNA vaccine in a cohort of hemodialysis patients.

Methods: In a multicenter study, including 294 Portuguese hemodialysis patients from multiple centers who had received 2 doses of BNT162b2 with a three-week interval, IgG-class antibodies against the SARS-CoV-2 spike protein were determined 3 weeks after the first dose (M1) and 6 weeks after the second dose (M2). The threshold for seroconversion was 10 IU/mL. Demographic and clinical data was retrieved from a quality registry. Adverse events were registered using a questionnaire.

Results: At M2, seroconversion was 93.3%, with a median antibody level of 197.5 IU/mL (1.2-3327.0) and a median increase of 180.0 IU/mL (82.9-2244.6) from M1. Age (beta -8.9, 95%CI: -12.88 to -4.91; p < 0.0001), ferritin >600ng/mL (beta 183.93; 95%CI: 7.45 to 393.10; p = 0.001) and physical activity (beta 265.79; 95%CI: 30.7 to 500.88; p = 0.03) were independent predictors of SARS-CoV-2 antibody levels after two vaccine doses. Plasma albumin >3.5g/dL independently predicted the increase of antibody levels between both doses (OR 14.72; 95%CI: 74.75 to 293.10; p = 0.001). Only mild adverse reactions were observed in 10.9% of patients.

Conclusions: The COVID-19 vaccine BNT162b2 is safe and effective in hemodialysis patients. Besides age, iron status and nutrition are possible modifiable modulators of the immunologic response to COVID-19 mRNA vaccines.

Positive IgG spike protein antibody response and antibody levels after BNT162b2 vaccination, just before (M1) and six weeks after (M2) the second administration of the vaccine.

PO0141

Antibody Response to COVID-19 Vaccine in Peritoneal Dialysis (PD) Patients: A Single-Center Study
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Background: Patients vaccinated with mRNA COVID-19 vaccines.

Methods: We included patients on PD who received the COVID-19 vaccine. Response to COVID-19 vaccine humoral response in PD patients. We studied the factors associated with COVID-19 vaccine humoral response in PD patients. Besides age, iron status and nutrition are possible modifiable modulators of the immunologic response to COVID-19 mRNA vaccines.

Results: In initial published reports of dialysis patients, response to COVID-19 vaccination tends to be lower as compared to general population. To date, these studies were primarily focused on hemodialysis (HD) patients. We studied the factors associated with COVID-19 vaccine humoral response in PD patients.

Methods: Our research setting was a single-center academic institution in New York City. We included patients on PD who received the COVID-19 vaccine. Response was assessed at a median of 4 weeks after completing the full vaccination series by measuring semiquantitative COVID-19 spike protein total antibody (Ab) level using a chemiluminescent sandwich immunoassay. Chi-squared tests for categorical variables and Wilcoxon rank-sum tests for continuous variables were used to compare characteristics among patients who did and did not have an Ab response.

Results: Of 111 patients on PD in our center, 64 (58%) received COVID-19 vaccine as of April 2021 and had Ab levels checked. A total of 60/64 (94%) of patients had a positive Ab response and 4/64 (6%) did not mount a response. IgG levels in positive responders were a median of 11.5 (interquartile range, 1.9 – 20). Lower Kt/V was associated with a positive Ab response (p = 0.045) and type of vaccine was associated with an Ab response (p = 0.028). Age, BMI, diabetes, hypertension, lymphocyte count, or residual Kt/V were not statistically significantly associated with Ab response to the vaccine (Table 1).

Conclusions: In conclusion, the vast majority of patients on PD developed positive Ab response to the COVID-19 vaccine. While a small sample size limited statistical power, our results show promising COVID-19 vaccine effectiveness among patients on PD.

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<th>Table 1. Characteristics of PD patients with positive and negative Ab response to COVID-19 vaccine</th>
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<td>Characteristic</td>
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<td>Age (years)</td>
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Immunogenic Response of Hemodialysis Patients to COVID-19 Vaccine: A Multicenter Study

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Background: The use of the mRNA-based vaccine BNT162b2 against COVID-19 has shown great success preventing SARS-CoV-2 infection in the general population. Limited data exist regarding its effectiveness in patients requiring dialysis. Dialysis patients have reduced immune response following different types of vaccines including Hepatitis B vaccine. We aimed to assess humoral response and the factors associated with it in a large and diverse maintenance hemodialysis (MHD) patient population.

Methods: SARS-CoV-2 Anti-spike, anti-nucleocapsid and neutralizing antibody (Ab) levels of 424 MHD patients from 13 nationally spread dialysis units in Israel were compared with 155 control subjects (dialysis patients’ family members and dialysis units health care workers). Patients’ history, dialysis treatment details and Hepatitis B Ab (HBsAb) levels were obtained from dialysis units medical records.

Results: Our study included 400 MHD patients and 141 controls (58% males, 42% females), excluding 24 MHD and 14 control samples from anti-N positive cases, signifying previous SARS-CoV-2 infection. Anti-S antibodies developed in 89.3% of MHD patients and 99.3% of controls, (p<0.01) after a median time of 82 and 89 days from second vaccine dose for MHD and controls, respectively. Median anti-S titer was significantly lower in MHD patients compared with controls (median 194, IQR 118-242 vs. 69, IQR 33-119; p<0.001) and correlated well with the level of neutralizing Ab titers in the study group as compared to control group (median 16, IQR 8-64 vs. 256, IQR 64-516; p<0.001, respectively). Notably, age was higher in MHD patients than controls (median 72, IQR 63-80 vs. 49, IQR 38-58; p<0.01) which likely contributed to the association with anti-S titers (p<0.01, r=0.44) as well as neutralizing Ab titers (p<0.01, r=0.42).

Sex, dialysis vintage and etiology of ESRD were not significantly associated with anti-S positivity or titer levels. Interestingly, there was a significant correlation, between anti-S and HBsAb positivity (p<0.01) though campatibility was low (r=0.18).

Conclusions: MHD patients have lower seroconversion rate, lower anti-S and neutralizing Ab levels after BNT162b2 vaccination. HBsAb levels may potentially be used as a marker for estimating the level of humoral response following COVID-19 vaccine. To our knowledge this is the largest cohort of MHD patients studied thus far.

PO0145

Extremely Low Humoral Immune Responses to BNT162b2 Vaccine in Nursing Home Residents Undergoing Hemodialysis

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Background: As coronavirus disease 2019 (COVID-19) can cause lethal outcomes in hemodialysis (HD) patients, they should be protected effectively by vaccination. HD patients are known to have a weak immune response to vaccines, and the seropositive rate three weeks after first vaccination (BNT162b2 Pfizer) is around 15%. However, its efficacy among elderly HD patients remains unknown. We aimed to evaluate spike antibody levels of nursing home residents on long-term maintenance HD after the BNT162b2 vaccine, comparing those of health care workers.

Methods: Between April and May 2021, HD patients from a nursing home (nursing home group) and health care workers (the control group) who received BNT162b2 vaccine were included. Those with a prior history of COVID-19 were excluded. IgG anti-spike against COVID-19 were measured by Elecsys Roche (cut off index <1.0) 3 weeks after the first injection.

Results: The study included 27 nursing home residents on HD and 191 care workers, and 2 care workers were excluded due to a prior history of COVID-19. The nursing home group were 84±9 years old and 41% male, and the median of HD vintage was 51 months (IQR 28-119), and the control group were 45±14 years old and 29% male. Only 6 patients in the nursing group were confirmed as seropositive (22%), whereas the rate of responder in the control group was 99% (p<0.01). Notably, the IgG levels of 20 patients in the nursing home group were under the detectable level (<0.4). In contrast, the median of the IgG levels in the control group was 42 (IQR 18-87). Moreover, the prevalence of adverse reactions, such as developing fever, in the nursing home group was low compared to the control group (p<0.001).

Conclusions: The seropositive rate after BNT162b2 in elderly HD patients was quite low owing to poor immune responses. To prevent a COVID-19 outbreak in nursing homes, IgG levels against COVID-19 in elderly residents on HD should be paid attention to.

PO0146

No Antibody Response to Viral Vector SARS-CoV-2 Vaccine but Subsequent Conversion After COVID-19 Infection in an ESKD Patient

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Introduction: ESKD patients generally have low response rate to vaccines. Early data suggests that viral vector SARS-CoV-19 vaccine is less effective than its mRNA counterparts. This case illustrates AB non-response to a viral vector based SARS-CoV-19 vaccine (Janssen) with subsequent AB response to mild clinical COVID-19 in an ESKD patient.

Case Description: 84 year old male on HD for 12 years. He had a prior response to the Hepatitis B vaccine with a recent titer >10 U/L. SARS-CoV-19 AB (IgG AB to the spike protein) was being checked monthly as part of an observational cohort. SARS-CoV-19 AB was (-) 1 month prior to receiving a viral vector-based vaccine. The AB was rechecked 1 month after the vaccine and remained (-). He was soon after admitted for GI bleed and tested positive for COVID-19 by PCR nasal swab on routine hospital screening. On discharge, he was asymptomatic but was hypoxic requiring oxygen. 17 days post hospital discharge, SARS-CoV-19 by nasal PCR remained positive and AB titer was detectable at 1.3 U/L. Both were checked again 1 week later, viral PCR remained (-) with further increase in AB to 2.3 U/L. A titer of >2.0 U/L has been reported as protective. He was no longer hypoxic by that time.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

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Discussion: SARS-CoV-19 AB was measured longitudinally in this elderly HD patient group. AB titers to the spike protein were negative 4 weeks after receiving a viral vector-based SARS-CoV-19 vaccine. He was relatively immunocompetent based on prior AB response to Hepatitis B vaccination. He became SARS-CoV-19 AB (+) 2.5 weeks after mild COVID-19 infection. Most studies on SARS-CoV-19 vaccination in ESKD have focused on mRNA vaccines, which show a reasonably high AB conversion rate after the second injection. We do not know if lack of detectable spike protein AB after vaccination necessarily precludes resistance to infection, nor do we know if this patient’s eventual seroconversion was due only to his COVID-19 infection or simply a slow response to the vaccine. It is also unknown if the general public that efficacy of the viral vector-based SARS-CoV-19 vaccine may be lower than that of mRNA vaccines. With ESKD patients more susceptible to infection and less able to mount AB’s to vaccines, this case supports the use of mRNA SARS-CoV-19 vaccines preferentially in the ESKD population if AB seroconversion is the targeted intermediary outcome.

ESKD Immunoglobulin Response at 3 Months Post COVID-19 Vaccination

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Background: End stage kidney disease (ESKD) patients (pts) remain at high risk for COVID 19 infection. Inadequate post infection antibody response is reported in 10-11% of pts. Current data is limited on ESKD post vaccination (vac). We report 3-month (mo) post vac response of ESKD pts receiving 2 doses of either Moderna or Pfizer vaccines.

Methods: Twenty-six of 42 stable ESKD pts completed 2 doses of either Moderna or Pfizer’s vaccine at Salem VAMC or at their nursing home facility during mo 01/02-2021. 17/42 were not vaccinated (7 declined, 2 with COVID 19 infection, 6 acutely hospitalized) during that time. Antibody immune response testing using ADIVA Centaur COV2G automated 2-step sandwich immunoassay using indirect chemiluminescent technology and designed to detect the SARS-CoV-2 surface spike protein receptor binding domain (S1RBD) was completed in 05/2021. Measures obtained included reactivity to total SARS CoV-ab (IgM+ IgG) and IgG separately.

Results: Please see table 1 for results

Conclusions: ESKD vaccine response to COVID 19 after 3 months was 96% for total immunoglobulin response (IgM and IgG) and 87.5% for total IgG antibody response compared to no reactivity in those nonvaccinated patients. Age and presence of diabetes did not significantly affect immune response. Approximately 12.5% of patients had nonreactivity to IgG antibody after 3 months. Patients not developing an IgG response by 3 mo were found to have underlying immunosuppressive disease. ESKD with COVID 19 infection maintained IgG reactive response 3 months after active disease. Nonreactivity was seen in those neither infected nor vaccinated, suggesting that these patients have likely not been exposed to COVID 19 viral infection.

Funding: Veterans Affairs Support

PO0149
Durability of SARS-CoV-2 Spike Antibody Levels in Dialysis Patients After COVID-19 Infection

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Background: Durability of SARS-CoV-2 receptor-binding domain spike antibody (RBD s-Ab) levels among patients receiving dialysis after COVID-19 [WDE1] is unknown [EL2] beyond 6 months. We describe the persistence (index value ±1 and ±2 U/L) of semi-quantitative RBD s-Ab levels in dialysis patients over 14 month period.

Methods: All maintenance dialysis patients ≥18 years old within Dialysis Clinic, Inc. 260 clinics in 28 states with COVID-19 infection history and RBD s-Ab levels determined between Jan 1 and May 23, 2021 were included. On the day of RBD s-Ab level determination, patient demographics (age, sex, race, modality, ESKD vintage) and AB seroconversion post vaccination were ascertained, with primary outcome being humoral response to SARS-CoV-2. Statistics included Fischer’s exact test and Wilcoxon rank sum test.

Results: Forty-eight patients with a mean age of 67 (35% female) completed vaccine series with BNT1612b2 (n=19), mRNA-1273 (n=25) and JNJ-78436735 (n=4). Vaccine associated side effects occurred in 27% of patients after 1st dose, with 39% after the 2nd dose. Spike protein antibody was tested at a median of 31 days after vaccination. 30 (61%) patients had demonstrable antibody. All patients (n=44) other than 4 post-transplant patients, were treated with Rituximab- only 17 44% (39%) developed an antibody response. In the setting of rituximab treatment, absence of seroconversion post vaccination was associated with vaccine type, duration elapsing since last rituximab dose (figure 1), low IgM level and absence of B-cell reconstitution (all statistically significant). Two patients without serologic response had severe COVID-19 infection.

Conclusions: This data demonstrates that majority of patients treated with rituximab lack demonstrable serologic response, with risk of severe COVID-19 infections despite vaccination. Confirmation of B-cell reconstitution before vaccination may have a bearing on serological conversion. It is imperative that authorities consider these factors while designing vaccination schedules and provide recommendations for booster doses in this vulnerable population.

PO0148
The SARS-CoV-2 Vaccine Response in ANCA-Associated Vasculitis

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Background: The development of efficacious vaccines against COVID-19 is an overarching achievement of modern medicine. This efficacy, however, may not be achieved in patients on immunosuppression. We looked to ascertain humoral response and tolerability of these vaccines in patients with ANCA associated vasculitis(AAV) treated with B-cell depleting agents

Methods: AAV patients who completed 2 doses of BNT162b2 or mRNA-1273 or a dose of JNJ-78436735, subsequently screened for spike protein antibody against SARS-CoV-2 were included in the study. Clinical details, demographics and immunosuppression regimes were ascertained, with primary outcome being humoral response to SARS-CoV-2. Statistics included Fischer’s exact test and Wilcoxon rank sum test.

Results: Among 102 patients, 64 completed vaccination. Confirmation of B-cell reconstitution before vaccination may have a bearing on serological conversion. It is imperative that authorities consider these factors while designing vaccination schedules and provide recommendations for booster doses in this vulnerable population.

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Underline represents presenting author.
PO0150
COVID-19 Vaccine and Multiple Viral Infection: Cross-Reaction?
Jose Rivera Sepulveda, Elizabeth Papon-Vazquez. Mayaguez Medical Center, Mayaguez, Puerto Rico.

Introduction: The COVID-19 pandemic has brought a lot of challenges in the medical and educational field. Every day, new facts and knowledge are published about the pathophysiology, treatment, and prognosis of COVID-19 patients. In addition, community response to vaccination and vaccine side effects has been one of the major talking points in social media. The general public wants to fully understand if the vaccine really provides immunity and possible side effects of its use.

Case Description: Under this premise, a 36 y/o female patient with a past medical history of type 2 diabetes mellitus, hypertension and obesity came to emergency department 2 days after she received the second dose of Moderna COVID-19 vaccine and developed non-quantified fever, general malaise, vomiting and watery diarrhea. Associated symptoms were scattered non-blanching maculopapular rash from head to shoulders to mid back and abdomen, postules inside ear and decrease urine output. Patient was unable to urinate for at least 48hrs. Laboratory bloodwork was remarkable for hyponatremia, hypochloremia, high anion gap metabolic acidosis and creatinine clearance of 18ml/min. Hepatic enzymes were more than five times elevated, and total bilirubin was elevated as well. Urinalysis reported proteinuria, positive leukocytes esterase, few calcium oxalate crystals and many urate amorphous sediment. Patient was convinced that symptoms were related to COVID-19 vaccination. Etiology of symptoms remained unclear at admission, for that reason she was admitted and received isotonic IV fluids. Further laboratory bloodwork reported elevated LDH, creatinine kinase and esterase, few calcium oxalate crystals and many urate amorphous sediment. Patient was really provides immunity and possible side effects of its use.

Conclusion: Patients with ESRD, particularly TX, mounted delayed and diminished antibody response to vaccination, and lesser response was associated with more infections. Thus, measures to protect non-responsive patients are urgently required.

PO0152
Antibody Response Post SARS-CoV-2 Vaccination in Kidney Transplant Recipients
Maria Butiu, Nicolae Leca, Ramasamy Bakhvatsalams. University of Washington, Seattle, WA.

Background: This project aims to analyze the proportion of patients who did not develop antibodies following COVID-19 vaccination and to ensure that the immune stimulation secondary to the vaccine is not associated with clinical rejection and DSA development.

Methods: Samples collected from COVID-19 vaccinated kidney transplant recipients from 3/1/21-4/26/21 were tested for DSA and COVID-19 antibodies using a multi-antigen detection Luminex platform (BioRad). The following were tested: receptor binding domain IgG, spike 1 IgG, spike 2 IgG, nucleocapsid IgG.

Results: 94 patients were included in this study. 57% had no antibodies post second dose of COVID-19 vaccination. This number decreased to 52% when looking at samples collected 2-3 weeks after the final vaccine dose. Of all positive patients, 19% showed evidence of previous COVID-19 infection based on nucleocapsid positivity, which if excluded from the cohort analysis, lead to a higher rate of patients not responding to the vaccine. We did not observe a correlation between antibody positivity and demographics or clinical characteristics. Only 2 patients developed new DSA post-vaccination (avg MFI 1600). No episodes of clinical rejection were noted. 10 patients provided multiple samples, of which 5 had positive antibodies with an average decrease of 17 U/mL for S1 IgG per week.

Conclusion: When excluding patients previously infected with COVID-19, the rate of positive antibody formation post vaccine is 35%. More research needs to be done to understand the correlation of antibody response and protection against COVID-19 infection.

PO0151
Five-Month Impact of Tozinameran (BNT162b2) Vaccine on Kidney Transplant and Dialysis Patients: Serology and Clinical Outcomes
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Background: Dialysis-treated (DT) and kidney transplant (TX) patients face higher morbidity and mortality risks than the general population during COVID-19 pandemic. Determining humoral response and associated COVID-19 morbidity after vaccination will guide risk assessment and changes in vaccination policy in this vulnerable population.

Methods: Prospective cohort study up to 5 months follow-up after Tozinameran or SARS-Cov-2 infection. Primary outcomes: qualitative and quantitative anti-S1/ S2 antibody (ABs) and disease rates during follow up. Anti-SARS-S IgG ABs were quantified using LIAISON SARS-CoV-2 S1/S2 IgG (DiaSorin) immunosassay in serum of TX, DT and treating team at our hospital. Demographics and clinical data were collected from participants files.

Results: 174 DT patients (40% women, age 65±15 years) 253 TX patients (33%, 53±14 years) and 71 control participants (65%, 44±14 years) were recruited. 3 months or more after vaccination we detected anti S1/S2 ABs in 81% of DT (95%CI, 72-90%), 43% of TX (95%CI, 29-57%) and 100% of controls. After COVID-19 respective rates were 94% (95%CI, 83-100%), 75% (95%CI, 60-90%) and 100%. Quantitative titers were in line with qualitative ones. Predictors of negative serology were older age, diabetes, cancer history, lower lymphocyte count and lower vitamin D. Peritoneal dialysis predicted higher titers compared to hemodialysis. In TX, hypertension and higher levels of immnosuppression predicted lower titers. Vaccination was associated with fewer subsequent COVID-19 infections (HR=0.23, 95%CI 0.05-0.99, p=0.05). Higher antibody titers associated with fewer events, HR 0.41/unit increase in log., titer (p<0.05).

Conclusion: Patients with ESRD, particularly TX, mounted delayed and diminished antibody response to vaccination, and lesser response was associated with more infections. Thus, measures to protect non-responsive patients are urgently required.
Results: A total of 486 patients (407 hemodialysis and 79 peritoneal dialysis) met inclusion criteria. Among these, 112 patients (23%) were treated with remdesivir, with median treatment time of 4 days (IQR: 2-5). Mean age was 63.8 years with 63.8% male and 63.0% Hispanic patients. There were 80.2% of patients who received treatment with steroids during hospitalization. Relative risk (RR) for all-cause 30-day mortality was 0.74 (95% CI: 0.52-1.05) in remdesivir treated patients compared to untreated patients. Acute liver injury occurred in 1.8% and 2.4% of remdesivir treated and untreated patients, respectively. ICU admissions occurred in 14.3% of remdesivir treated and 16% of untreated patients.

Conclusions: Among dialysis patients hospitalized with COVID-19, treatment with remdesivir was not associated with worse outcomes in terms of liver injury or ICU admission, and demonstrated a trend (26% lower risk) toward decrease in 30-day mortality, though no statistical significance was found due to insufficient power.

PO0154
Outcomes Associated with Tocilizumab Use in Patients with COVID-19 Infection Complicated by Severe AKI Requiring Continuous Renal Replacement Therapy

Background: The percentage of critically ill amongst COVID-19 infected patients stands at 5%. The incidence of acute kidney injury in those patients varies according to risk factors. A little is known about the use of Tocilizumab in patients with severe acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT).

Methods: This is a retrospective study of 22 COVID-19 patients. Patients were between 18 and 80 years old, had proven COVID-19 infection, were admitted to the ICU between April 1 and July 15, 2020, received CRRT and Tocilizumab parenterally. Other therapies included antivirals, hydroxychloroquine and convalescent plasma. We included biochemical outcomes related to cytokine storm as well as clinical outcomes; Those included ventilator dependence, renal outcomes, length of hospital stay and mortality.

Results: 21 out of 22 patients were males. Median age was 56 years. 14 patients had hypertension and 13 had diabetes mellitus. All patients had cytokine storm on admission (elevated IL-6 and CRP levels). At the completion of the follow up (average 44.4 days), 20 out of 22 patients experienced improvement in IL-6 and CRP levels. 11 patients died. 13 experienced improvement in oxygen requirements including 9 who were successfully extubated. 13 were still on CRRT (including 10 patients who died) while 9 patients became dialysis independent (5 had complete recovery of kidney function and 4 developed chronic kidney disease). There was no reported side effect from using tocilizumab.

Conclusions: Tocilizumab can be considered in critically ill COVID-19 patients with severe AKI and cytokine storm. No dose adjustment is needed in patients on CRRT. Further studies are required to confirm our results.
On 16 Apr 2021, the EUA was revoked over concerns of resistance among SARS-CoV-2 variants. Between 01 Jan and 16 April 2021, physicians at DaVita dialysis clinics were able to order bamlanivimab (700 mg) treatment during dialysis for nonhospitalized hemodialysis patients who tested positive for SARS-CoV-2 infection and met the eligibility criteria. Here, we report safety data among dialysis patients who received bamlanivimab as a monotherapy for COVID-19.

Methods: Bamlanivimab was administered intravenously as a single dose over the course of 60 minutes during a regularly scheduled hemodialysis session. All patients were monitored for at least 1 hour after bamlanivimab administration. All facilities were required to have emergency medications on-site, and staff were trained to identify and treat potential reactions. A serious adverse event was considered if a patient developed anaphylaxis or any condition requiring use of an epinephrine injection (1:10,000 IM) or albuterol, was sent to the emergency department, or was hospitalized after bamlanivimab administration. An adverse event was considered if a patient developed fever, chills, hives, rash, hypotension, headache, nausea, fatigue, dizziness, angioedema, muscle pain, or throat irritation.

Results: 264 patients with newly diagnosed SARS-COV-2 infections received a single dose of bamlanivimab at DaVita. Among all patients who received the drug, 46% were female and the mean age was 60 years. On average, patients were followed for 64 days postinjection. There were 0 adverse events or serious adverse events documented in the 1-hour postadministration observation window.

Conclusions: Bamlanivimab was found to be safe in dialysis patients.

PO0157
Intravenous Immunoglobulin: Answer to COVID-19?
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Introduction: Traditionally intravenous immunoglobulin (IVIG) has been used for immunodeficiency disorders. It has been also used in certain autoimmune and infectious diseases. IVIG has several immunomodulatory and anti-inflammatory effects. Here, we are reporting a case where IVIG was used for BK viremia in a patient with COVID-19 pneumonia who showed dramatic recovery of COVID-19 symptoms and laboratory parameters.

Case Description: Our patient is a 55-year-old African American male who received simultaneous pancreas and kidney transplant in April 2019 with induction immunosuppression with thymoglobulin and was on chronic immunosuppression with Tacrolimus and Mycophenolic acid. His Post-transplant course was complicated by BK viremia and presumed BK nephropathy after 2 months. His immunosuppression was gradually tapered off but his viremia was persistent despite being off Mycophenolate and low target goal of Tacrolimus. Patient partially responded to high dose IVIG so we decided to continue monthly high dose IVIG with daily Leflunomide. Later in April 2021, patient was admitted with COVID-19 symptoms with normal oxygen saturation at room air. His clinical condition worsened over the following 4-5 days in the form of hypoxic respiratory failure requiring high flow oxygen supplements and Acute Kidney injury (AKI) with nephrotic range proteinuria and gradual rising inflammatory markers. Patient was about to be transferred to the Intensive Care Unit as his clinical condition was worsening and refractory to the traditional treatment with steroid and antibiotics. On day 10 he received his monthly dose due of IVIG therapy (0.5 g/m² of body weight for 4 consecutive days). His COVID symptoms started to improve from day 2 of the treatment. His inflammatory markers were dramatically down trended over the next 3-4 days post IVIG. He was discharged home with oxygen therapy (3L/min) by the day 5 post treatment with IVIG with recovering AKI.

Discussion: Few international studies have reported that initiation of high dose IVIG as adjuvant treatment for COVID-19 disease in selected patients may result in early clinical and laboratory recovery. The studies are limited due to the small sample size and patient selection criteria. Although our patient exhibited dramatic recovery, randomized clinical trial needs to be done to explore more about effect on COVID-19 pneumonia and COVID-19 associated AKI.

PO0158
CRRT with the oXiris Filter Attenuates IL-6 in a Patient with Severe COVID-19
Jennifer C. Tang, Thanh Cao. Keck Hospital of USC, Los Angeles, CA.

Introduction: SARS-CoV-2 infection can result in ARDS and multiorgan dysfunction. The pathophysiology underlying Covid-19 includes a hypercoagulable state and a cytokine release storm with upregulation of IL-6, IL-10, and TNF-alpha, which are associated with ICU admission, ARDS, AKI, and increased mortality. While there are no proven treatments for this cytokine storm, tocilizumab, has shown promise in studies against severe Covid-19, suggesting that cytokine removal via blood purification products like oXiris may help achieve immune homeostasis.

Case Description: A 70-year-old male status post DDRT in 2016 presented with fevers, malaise, and dyspnea. He tested positive for SARS-CoV-2 and was admitted requiring high-flow nasal cannula with a rate of 50L/min and FiO2 of 90%. Urinalysis revealed pyuria, hematuria, and proteinuria. Labs revealed a creatinine of 2.4 and a BUN of 61 as well as a CRP of 130, ESR of 65, D-dimer of 1048, LDH of 325, ferritin of 3891, and IL-6 of 3.6 consistent with severe Covid-19. An ultrasonogram of his allograft kidney was normal. The patient then went into PEA arrest and was intubated with decreasing urine output, therefore was initiated on CRRT with an oXiris filter for 48 hours followed by a M150 filter. His P/F ratio increased and his IL-6 and SOFA score decreased while on the oXiris filter, however both CRP and LDH increased. After switching filters, the patient’s P/F ratio quickly declined with a rapid increase of IL-6. Ultimately, the family decided to withdraw care.

Discussion: The oXiris filter could potentially manage the cytokine storm seen in Covid-19 as it is the only filter shown to remove cytokine and endotoxins, improve renal function, and have antithrombogenic properties as it is grafted with heparin. It is an AN69-based oXiris membrane treated on the inside with a high concentration of polyethyleneimine (PEI) binding cytokines and endotoxins. Given the impact of Covid-19, more studies must be done to assess if oXiris may serve as an effective treatment.
Blood Purification in a Critically Ill COVID-19 Patient with Cytokine Storm: A Case Report

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Introduction: Cytokine storm syndrome (CSS) is a common and severe cause of mortality among critically ill COVID-19 patients. BPTs, especially continuous renal replacement therapy (CRRT), may work by removing cytokines and blocking the cascade of inflammation and thus preventing the progression of CSS. However, the efficacy of Blood purification therapies (BPTs) in patients with complications of CSS but without AKI (acute kidney injury) is still controversial.

Case Description: We report the case of a 66-year-old female who had severe COVID-19 without AKI. She was admitted to our hospital with difficulty breathing, increased respiratory failure and heart failure, and had been treated with venous-venous extracorporeal membrane oxygenation (VV-ECMO). Initially, the level of interleukin-6 (IL-6) increased rapidly and reached 304.8 pg/ml. Although there was no kidney function impairment, and was off all vasopressors within 6 hours. She was treated with CRRT to reduce the levels of cytokines in circulation, while the decrease in IL-6 in serum and dialysate was not significant. Oxis-CRT was then introduced and there was a significant decline in serum levels of IL-6 after 3 Oxis-CRT sessions. However, when we stopped Oxis-CRT after the third treatment, the serum levels of IL-6 were elevated again 12 hours after the suspension of Oxis-CRT Subsequently. Therefore, the patient received 6 additional Oxis-CRTR sessions until the serum IL-6 levels of 2.67 pg/ml. After 144 days of hospitalization, including 2 CRRT sessions, 9 Oxis-CRTR sessions and 2 therapeutic plasma exchange (TPE) sessions, she completely recovered (shown in Fig. 1).

Discussion: In our patient, BPTs, especially Oxis-CRTR, showed unique superiority and application value in the clearance of excess plasma cytokines, promoting a smooth recovery, which suggests that even if AKI does not occur, it is beneficial to use BPTs to prevent the progression of CSS in COVID-19 patients.

IL-6 levels gradually decreased to normal levels after 9 sessions of Oxis-CRTR and two sessions of TPE.

COVID-19 vs. Bloodstream Purification: A Targeted Therapy

Sean Barnett. Brooke Army Medical Center, Fort Sam Houston, TX.

Background: The use of bloodstream purification has been well studied in bacteremia but the emergence of COVID found a new target. Using blood purification in the fight against COVID we have found a potential treatment for viremia and pneumonia, cytokine storm and decompensation, and superinfections in COVID. When used at the appropriate time, blood purification has the potential to prevent further organ injury.

Methods: The following case series is an individual clinical observation of patients with COVID-19 managed without CRRT. In this case we describe the benefit of using Purify PMX in COVID patients with cytokine storm.

Results: 28M w/o significant PMHx, transferred to BAMC for ECMO due to severe COVID. He initially improved, but decompensated with MRSA bacteremia, and required ECMO. On day 15 of his hospital stay, extracorporeal sorbent hemoperfusion via Seraph® filter was delivered through PrismaFlex® in tandem with the ECMO circuit. Her serum IL-6 levels dropped from 154 pg/ml to 29 pg/ml, and C-reactive protein from 317 mg/l to 294 mg/l within 2 hours of treatment completion. She had intermittent fevers up to 40°C, especially in the 48 hours prior to treatment which resolved right away with hemoperfusion and she remained afebrile for the next 72 hours. There was, however, no significant change in her hemodynamics and overall clinical status and the patient remains on ECMO and mechanical ventilation at the time of this report (Day 34).

Discussion:

Conclusions: This case series illustrates that hemoperfusion therapy delivered late in the course of severe COVID-19 disease is still effective in decreasing circulating inflammatory markers, but may not be effective in significantly and positively affecting clinical outcomes. Although circulating inflammatory markers could be used to guide eligibility for hemoperfusion therapy, timing of hemoperfusion should be considered in clinical trials to effectively test the potential of this intervention to ameliorate clinical outcomes in susceptible populations.

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Direct Hemoperfusion Using a Polymeric B-ImmoBilized Polystyrene Column for COVID-19

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Background: The involvement of increased cytokine levels in severe COVID-19 has been noted, and anti-inflammatory therapy including corticosteroids or anti-human interleukin (IL)-6 receptor monoclonal antibody is expected to be beneficial for COVID-19 patients. Direct hemoperfusion using a polymeric B-immobilized polystyrene column (PMX) is a treatment that selectively adsorbs endotoxins; it is also expected to adsorb a variety of endogenous substances.

Methods: The patients (N=22) included were those whose respiratory samples tested positive for SARS-CoV-2 upon real-time reverse transcription-polymerase chain reaction (RT-PCR) and underwent PMX during hospitalization at National Center for Global Health and Medicine, Tokyo, Japan between January 30, 2020 and April 30, 2021. PMX was administered when an imaging of pneumonia consistent with COVID-19 was obtained on chest CT and the P/F ratio was less than 300. Demographic data, information on clinical symptoms, and laboratory data were collected.

Results: On day 15 of first PMX treatment, disease severity decreased in 63.6 % of the patients. PR ratio increased and there was a downward trend in urine (β-microglobulin on days 4 and 8. Cytokine level measurement pre- and post-PMX revealed a downward trend in interleukin-6 levels and decreased levels of the factors involved in vascular endothelial injury, including vascular endothelial growth factor. There were 43 PMX, of which nine treatments were performed as an increased dose and one treatment was administered as a single dose.

Discussion:

Conclusions: PMX is expected to become a therapy to address medical needs and prevent the exacerbation from moderate to severe condition in COVID-19.
suggests a multi-level inflammatory syndrome in some of the most critically ill patients with overlapping features of other hyperinflammatory or autoimmune diseases. Thus, plasma exchange (PE) has become a subject of controversy as potential therapy in these patients. Here, we report the results of the so far largest cohort of critically ill COVID-19 patients treated with PE.

Methods: All critically ill COVID-19 patients treated with PE at Heidelberg University Hospital were analyzed between April and December 2020. Disease course and outcomes were compared with a standard care control group matched for age, sex, and disease severity. Changes in laboratory and clinical parameters were studied longitudinally. Kaplan-Meier and Cox regression analyses were performed.

Results: In total, 28 critically ill COVID-19 patients were treated with an average of 3 PE procedures per patient. No relevant complications occurred during PE therapy. Inflammatory markers and biochemical indicators of end-organ damage and endothelial activation were significantly reduced during PE. These laboratory changes were accompanied by normalization of body temperature, improved pulmonary function, and reduced vasopressor demand. Most importantly, the laboratory and clinical improvements were maintained after the last PE. In contrast, most parameters in the control group did not improve significantly over seven days, although baseline clinical and laboratory parameters were comparable in both groups. Kaplan-Meier analysis showed improved 30-day survival in the PE group compared to the control group (67.9% vs. 42.9%, p=0.044). In a multivariable analysis, the hazard ratio for death was 0.27 (95% CI 0.11-0.66, p=0.005) with PE versus no therapy.

Conclusions: Our data further suggest that PE represents a potential therapeutic strategy for a subset of severe COVID-19 cases. The observed PE-related effects appear to go beyond a purely artificial improvement in blood parameters and may indicate a reversal of the complex COVID-19 immunopathology. Randomized controlled trials are urgently needed.

PO0164
COVID-Related Renal Thrombotic Microangiopathy: Role of Plasma Exchange

Introduction: The most common COVID-19 associated glomerular diseases are COVID associated nephropathy (CINAN) and Thrombotic Microangiopathy (TMA). Other less common glomerular diseases associated with COVID reported are antineutrophil cytoplasmic antibody (ANCA) vasculitis, anti-glomerular basement membrane (Anti GBM) antibody disease, podocytopathies, and IgA nephropathy. We report a case of TMA due to COVID-19 infection.

Case Description: A 67-year-old woman with asthma was admitted for COVID-related respiratory failure and was noted to have acute kidney injury with anemia and thrombocytopenia. She was hypertensive and urine analysis was notable for hematuria and proteinuria. ANA, ANCA, Anti GBM, Coombs, ADAMTS13, disseminated intravascular coagulation panel, serum immune fixation and free light chains, cryoglobulins, and infectious work up were unrevealing. Complement C3 and C4 were low, lactate dehydrogenase and bilirubin were high, haptoglobin was undetectable, and schistocytes were seen on peripheral smear which raised concern for thrombotic microangiopathy. Renal function deteriorated rapidly with ensuing anuria prompting initiation of dialysis. Kidney biopsy confirmed acute thrombotic microangiopathy. She was started on plasma exchange (PLEX) for COVID related thrombotic microangiopathy and she started producing urine with rapid improvement in creatinine (Cr) after two treatments. Cr was down to 3.11mg/dL from a peak of 7.45 mg/dL after PLEX and normalized at discharge. The patient is currently being monitored with renal panel and complete blood picture every three months, as an outpatient.

Discussion: COVID is known to cause TMA that is presumed to be secondary to endotheal dysfunction and complement activation. There are no standard guidelines for treatment. Terminal complement blockade was not used in our patient. Our case demonstrates the efficacy of PLEX in the treatment of COVID related TMA. Early recognition and treatment is crucial and may reduce morbidity and mortality.

PO0165
Sustained Low-Efficiency Dialysis vs Continuous Renal Replacement Therapy in Critically Ill COVID-19 Patients
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Background: Acute kidney injury among patients with COVID-19 infection is a poor prognostic indicator. There is limited evidence to guide the nephrology community if there are any risk or advantages of using sustained low-efficiency dialysis (SLED) or continuous renal replacement therapy (CRRT). We aim to evaluate the clinical outcomes of COVID-19 patients receiving renal replacement therapy in the intensive care unit (ICU).

Methods: This is a retrospective chart review of adult patients with COVID-19 admitted to ICU in the state of Qatar who had 1) acute kidney injury and 2) received renal replacement therapy between February to August of 2020. We evaluated clinical characteristic, severity of illness, morbidity, and renal outcomes at 30 days.

Results: Among 127 patients with acute kidney injury requiring dialysis in ICU, 16 patients were on CRRT, 68 patients were on SLED, and 43 patients were on both. We did not observe significant difference among age, gender, ethnicity or baseline creatinine. Most common indication for indication of dialysis was volume overload followed by acidosis in all groups with serum creatinine of 264µmol/L vs 499µmol/L and 351µmol/L in CRRT, SLED, and CRRT+SLED, respectively. Inflammatory markers, pressure requirement and APACHE II score were similar between all groups. 30-day Survival was 23%, 50% and 9%. Among 34 patients on SLED who survived, 6 were dialysis dependent post COVID-19 infection.

Conclusions: Acute kidney failure in critically ill COVID-19 patients is associated with high mortality. A lower mortality, but high morbidity is observed in patients receiving SLED in critical care setting. Further investigation of SLED in COVID-19 should be considered.

PO0166
Detection of SARS-CoV-2 in Dialysis Effluent on a Peritoneal Dialysis Program in Mexico City: Four Cases

Introduction: Since the rapid spread of the COVID 19 pandemic, it is crucial to identify possible sources of transmission of the SARS-CoV-2 virus in order to perform prevention strategies. There has been interest to identify the presence of SARS-CoV-2 in different compartments including peritoneal compartment. SARS-CoV-2 was detected by reverse transcriptase-polymerase chain reaction (RT-PCR) in dialysis effluent on a few single cases while other authors have reported negative results. Peritoneal membrane pores have a diameter of 20-40 nm while the SARS-CoV-2 virion diameter is between 60 to 140 nm, theoretically the virion could reach the peritoneal cavity by hematogenous diffusion or through the dialysis catheter after contact contamination.

Case Description: We report dialysis effluent findings of four patients, two women and two men, with an age range of 35 to 64 years and different comorbidities including: diabetes mellitus, hypertension and obesity. They were diagnosed with COVID-19 using RT-PCR assay on nasopharyngeal samples or by tomography findings. RT-PCR samples of peritoneal effluent were obtained with a length of stay on peritoneal cavity of 6 hours, without centrifugation of the sample. Three patients were positive for presence of SARS-CoV-2 on nasopharyngeal sample and dialysis effluent, while the fourth patient was negative in both samples despite having tomography findings suggestive of COVID-19 infection. It should be noted that in the 3 patients that had a positive RT-PCR on both nasopharyngeal and peritoneal effluent, samples were obtained within the first 7 days following the onset of symptoms associated with COVID-19 and on the fourth patient the peritoneal effluent sample was obtained 12 days after initial symptoms. All patients presented with acelular peritoneal fluid. No abdominal symptoms were reported.

Discussion: Presence of SARS-CoV-2 on peritoneal fluid continues to be a subject of debate. The consensus by the American Society of Nephrology was to continue dialysis procedures safely. There has been interest to identify the presence of SARS-CoV-2 in different compartments including peritoneal compartment. SARS-CoV-2 was detected by reverse transcriptase-polymerase chain reaction (RT-PCR) in dialysis effluent on a few single cases while other authors have reported negative results. Peritoneal membrane pores have a diameter of 20-40 nm while the SARS-CoV-2 virion diameter is between 60 to 140 nm, theoretically the virion could reach the peritoneal cavity by hematogenous diffusion or through the dialysis catheter after contact contamination. Although based on a small group, these findings should prompt to consider these fluids as potentially infective.

PO0167
A Comparison of Clotting Rate During Hemodialysis in COVID-19 Patients Receiving Anticoagulant vs. No Anticoagulant in an Inpatient Setting
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Background: Anticoagulant use during hemodialysis is a standard practice in both outpatients and inpatients setting. In an inpatient setting with heightened acuteness of illness, the potential for bleeding attributable to anticoagulant is concerning. Hospitals have started applying an anticoagulant free HD protocol with success. COVID-19 patients showed a degree of systemic hypercoagulability with unique features, including a consumptive disseminated intravascular coagulation coexisting with hyperfibrinolysis and increased bleeding risk. Maintaining circuit patency and avoiding bleeding risk has become a challenge. Data regarding anticoagulant in COVID-19 patients who received hemodialysis is limited. This study’s primary objective is to compare hemodialysis clotting rate in COVID-19 patients who received anticoagulant versus those without anticoagulant.

Methods: Retrospective chart review for all COVID-19 patients who received hemodialysis at Banner Medical Center Tucson Campus Between November 2020 and January 2021. Primary outcome was clotting rate during hemodialysis. CRRT was excluded.
Results: 330 total patients observed, 56% sessions in the ICU unit and 44% in the medicine unit. 57% were AKI and 43% were ESRD. Anticoagulant use was 38.5% (heparin IVP during hemodialysis was 12%), continuous systemic heparin was 16% and others (warfarin, DOAC, Argatroban, etc) was 11%. Clotting rate was 12%. Other characteristics can be seen on the Table 1. There was no difference in the clotting rate between group with anticoagulant versus without anticoagulant (8% vs.15%, p value 0.06). Multivariable logistic regression for clotting outcome showed that compared to no-anticoagulation, systemic heparin continuous infusion decreased clotting by 83% (OR 0.17, 95% CI 0.04-0.77, p-value=0.02) and others anticoagulant decreased clotting by 91% (OR=0.09, 95% CI 0.01-0.85); compared to AV fistula, temporary dialysis catheter increased clotting by 2.9x (OR 2.9, 95% CI 1.10-7.44, p-value=0.03); and every 10 increase in platelet count increased clotting by 4% (OR 1.04, 95% CI 1.01-1.07, p value =0.01).

Conclusions: No anticoagulation and temporary catheters carry high risk for clotting in patients with COVID undergoing IHD. Continuous heparin should be considered.

PO0168

Divergence Between Serum Creatinine and Cystatin C in Estimating Glomerular Filtration Rate of Critically Ill COVID-19 Patients

Yunan Liu, Peng Xia. Peking Union Medical College Hospital, Dongcheng-qu, China.

Background: The clinical use of serum creatine (sCr) and Cystatin C (CysC) in kidney function evaluation of critically ill patients has been in continuous discussion. The values of estimated glomerular filtration rate calculated by sCr(eGFRcr) and CysC (eGFRcysc) of critically ill COVID-19 patients were investigated in this study.

Methods: This is a retrospective, single-center study of critically ill patients with COVID-19 admitted in Intensive Care Unit (ICU) at Wuhan, China. Control cases were moderate COVID-19 patients who were matched in age and sex at a ratio of 1:1. The eGFRcr and eGFRcysc were compared. The association between eGFR and death were analyzed in critically ill cases. The potential factors leading to the divergence between eGFRcr and eGFRcysc were explored.

Results: A total of 76 critically ill COVID-19 patients were concluded. The mean age was 64.5±9.3 years and the male : female ratio was 49:27. At ICU admission, their eGFRcr (85.45 [IQR 60.58-93.23] ml/min/1.73m²) were much higher than eGFRcysc (60.6 [IQR 34.75-79.06] ml/min/1.73m²). About 50% of them showed eGFRcysc < 60 ml/min/1.73 m2 whereas 25% showed eGFRcr < 60 ml/min/1.73 m2 (c²=10.133, P=0.001). This divergence was not observed in control group. The potential factors influencing the divergence included serum interleukin-6(IL-6)level, tumor necrosis factor(TNF-α) level as well as APACHEII. Reduced eGFRcr (<60 mL/min/1.73 m2) was associated with death(HR=1.939,95%CI 1.078-3.489, P=0.027).

Conclusions: The eGFRcr was higher than eGFRcysc in critically ill cases. The divergence might be affected by the inflammatory condition. Reduced eGFRcr predicted in-hospital death. In these patients, we advocate for caution when using eGFRcysc.

Funding: Private Foundation Support

PO0169

Serum Sodium and Patient Symptoms in COVID-19 Hospitalizations

Timothy E. Yeo, Andy Kim, Henry Rutherford, Sae Ratnaparkhi, Ann E. Woolley, Finnian R. McCausland. Brigham and Women's Hospital, Boston, MA.

Background: Disorders of serum sodium (SNa) are common in hospitalized patients with COVID-19 and associated with longer length of stay and inpatient mortality. However, the association of SNa with patient-reported outcomes is not clear.

Methods: This is a retrospective, single-center study of consecutive, adult patients admitted with confirmed SARS-CoV-2 infection (n=809). We examined the association of SNa (continuous and tertiles) at admission with: 1) patient symptoms obtained from detailed chart review; and 2) in-hospital mortality using unadjusted and adjusted logistic regression models. Covariates included demographic data and comorbidities. Only index admissions were considered.

Results: Mean age was 60 years, 48% were male, and 35% had diabetes. The most frequent symptoms were cough (64%), fever (60%) and shortness of breath (46%). In adjusted models, higher SNa (per mmol/L) was associated with lower odds of GI symptoms (OR 0.96; 95%CI 0.93-0.99), higher odds of confusion (OR 1.08; 95%CI 1.40-1.13) and higher odds of in-hospital mortality (OR 1.06; 95%CI 1.02-1.11). Compared with the lowest tertile, the highest tertile of SNa was associated with a lower odds of GI symptoms and anosmia/ageusia, and higher odds of confusion and in-hospital mortality (Table 1).

Conclusions: In this prospective cohort study of hospitalized patients with COVID-19, hypernatremia is associated with higher odds of confusion and in-hospital mortality. Evaluation of the lower risk of SARS-CoV-2 anti-spike Igg levels in our kidney transplantation cohort may help identify higher-risk patients with COVID-19 and prompt ascertainment of patient symptoms, both of which may improve patient-centered approaches to care.

Table 1

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Viable Frequency</th>
<th>SNa Tertile 1</th>
<th>SNa Tertile 2</th>
<th>SNa Tertile 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>210 (4.04)</td>
<td>p=0.11</td>
<td>p=0.81</td>
<td>p=0.69</td>
</tr>
<tr>
<td>Fever</td>
<td>443 (5.0)</td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>466 (5.6)</td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Sore Throat</td>
<td>107 (10.3)</td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>89 (10.1)</td>
<td>p=0.11</td>
<td>p=0.37</td>
<td>p=0.37</td>
</tr>
<tr>
<td>Malaise</td>
<td>40 (5.1)</td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Tiredness</td>
<td>105 (16.1)</td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Gastrointestinal Symptoms</td>
<td>301 (27.2)</td>
<td>p=0.43</td>
<td>p=0.51</td>
<td>p=0.51</td>
</tr>
<tr>
<td>Confusion</td>
<td>124 (15.2)</td>
<td>p=0.00</td>
<td>p=0.00</td>
<td>p=0.00</td>
</tr>
<tr>
<td>Headache</td>
<td>103 (12.9)</td>
<td>p=0.23</td>
<td>p=0.37</td>
<td>p=0.37</td>
</tr>
<tr>
<td>Anosmia</td>
<td>90 (11.5)</td>
<td>p=0.37</td>
<td>p=0.37</td>
<td>p=0.37</td>
</tr>
<tr>
<td>In-Hospital Mortality</td>
<td>144 (17.6)</td>
<td>p=0.03</td>
<td>p=0.03</td>
<td>p=0.03</td>
</tr>
</tbody>
</table>

In adjusted models, higher SNa (per mmol/L) was associated with lower odds of GI symptoms and anosmia/ageusia, and higher odds of confusion and in-hospital mortality (Table 1).

PO0170

Lower CD3 and CD4 Counts in Kidney Transplant Recipients Who Did Not Respond to COVID-19 Vaccination


Background: Kidney transplant recipient’s response rate to COVID-19 vaccination is reportedly less than 54% after the 2nd dose, significantly lower than general population and dialysis patients, reported as between 85-90% and 95-100%, respectively.

Methods: We studied SARS-CoV-2 anti-spike Igg levels in our kidney transplant recipients after their COVID-19 vaccination using the OrthoV IgG platform.

Results: 69 kidney transplant recipients received a SARS-CoV-2 vaccine (47 Pfizer, 20 Moderna and 2 Johnson and Johnson) at a median 36 months after transplantation (range, 3 months to 22 years). 61% were male, 39% Black, 29% Hispanic with a median age of 60 (range-22-82). 72% were deceased-donor kidney transplant recipients. 23 patients had previous history of COVID-19 diagnosed by SARS-CoV-2 PCR and/or anti-nucleocapsid antibody and 21 of those patients (91%) developed anti-spike IgG after 1st or 2nd dose. Among the patients with a median length of 13.2 (1.1-16.2). 44% of patients with a previous history of COVID-19, 17 (37%) developed anti-spike IgG at a median of 28 days (range 10-72) after the second vaccine dose with a median level of 5.7 (1.22-15.4). Patients who didn’t develop anti-spike IgG tended to be older, of African-American descent, on MMF > 1 g/day, have lower CD3 and CD4 counts.

Conclusions: In summary, most kidney transplant recipients without history of COVID-19 did not produce anti-spike IgG after being fully vaccinated and it is associated with augmented immunosuppression, lower T cell counts, African-American race and older age.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
### Prognostic Significance of Urinary Biomarkers in Patients Hospitalized with COVID-19

**PO0171**

**Prognosis of Kidney Outcomes in COVID-19**

**Kidney Outcomes in COVID-19**

CT; 3Icahn School of Medicine at Mount Sinai, New York, NY

Chirag Menez,1 Dennis G. Moleedina,1 Heather Thiessen Philbrook,1 Francis P. Wilson,2 Wassim Obeid,1 Michael Simonoy,2 Yu Yamamoto,2 Celia P. Corona villalobos,1 Crystal Chang,1 Brian T. Garibiid,1 William Clarke,1 Shell Farhidjan,2 Charles Dela Cruz,2 Steven G. Coca,3 Chirag R. Parikh,1 TRIKIC Consortium: Translational Research Investigating Kidney Outcomes in COVID-19 1Johns Hopkins University School of Medicine, Baltimore, MD; 2Yale University School of Medicine, New Haven, CT; 3Icahn School of Medicine at Mount Sinai, New York, NY.

**Background:** Acute kidney injury (AKI) is common in patients with COVID-19 and associated with poor outcomes. Urinary biomarkers have been associated with adverse kidney outcomes in other settings and may provide additional prognostic information in patients with COVID-19.

**Methods:** We evaluated 19 urinary biomarkers of injury, inflammation, and repair in patients hospitalized with COVID-19 at 2 academic medical centers between April and June 2020. We associated biomarkers with a primary composite outcome of KDIGO stage 3 AKI, requirement for dialysis, or death within 60 days of admission. We also compared various kidney biomarker levels in the setting of COVID-19 versus other common AKI settings.

**Results:** Out of 157 patients, 24 (15.3%) experienced the primary outcome. Two-fold higher levels of neutrophil gelatinase-associated lipocalin (NGAL) (HR: 1.53; 95% CI: 1.33-1.76), monocyte chemoattractant protein (MCP-1) (HR: 1.86; 95% CI: 1.48-2.33), and kidney injury molecule-1 (KIM-1) (HR: 2.32; 95% CI: 1.69-3.18) were associated with the primary outcome. Higher epidermal growth factor (EGF) levels were associated with a lower risk of the primary outcome (HR: 0.52; 95% CI: 0.40-0.69). Individual biomarkers provided moderate discrimination and biomarker combinations improved discrimination for the primary outcome.

**Conclusions:** Urinary biomarkers are associated with severe kidney complications in patients with COVID-19 and provide valuable information to monitor kidney disease recovery and progression.

**Funding:** NIDDK Support

<table>
<thead>
<tr>
<th>Anti-Spike IgG NEGATIVE (N = 29)</th>
<th>Anti-Spike IgG POSITIVE (N = 17)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD) years</td>
<td>62 (9)</td>
<td>0.04</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>52%</td>
<td></td>
</tr>
<tr>
<td>African American Race (%)</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Time in hospital (days, months)</td>
<td>53 (41)</td>
<td></td>
</tr>
<tr>
<td>Mean BMI (SD), kg/m²</td>
<td>29.6 (1)</td>
<td></td>
</tr>
<tr>
<td>Mm &gt; 1 g/day (%)</td>
<td>31.9 (1)</td>
<td></td>
</tr>
<tr>
<td>Mean CD count (SD, cell/μl)</td>
<td>677 (704)</td>
<td></td>
</tr>
<tr>
<td>Mean CD4 count (SD, cell/μl)</td>
<td>375 (124)</td>
<td></td>
</tr>
<tr>
<td>Mean CD8 count (SD, cell/μl)</td>
<td>61 (49)</td>
<td></td>
</tr>
<tr>
<td>Mean eGFR (SD, ml/min)</td>
<td>53 (42)</td>
<td></td>
</tr>
</tbody>
</table>

![Figure 1. Risk of stage 3 AKI, new dialysis initiation, or death within 60 days of hospital admission by urinary biomarker level, indexed to urine creatinine.](image)

**PO0172**

**Urine Test Predicts Kidney Injury and Death in COVID-19**

Kathleen Xu, Ning Shang, Abraham D. Levin, Alexa Corker, Satoru Kudose, Andrew Yaeh, Jacob Stevens, Sumit Mohan, Rosemary V. Sampogna, Vivette D. D’Agati, Krzysztof Kryluk, Jonathan M. Barasch. Columbia University Irving Medical Center, New York, NY.

**Background:** Kidney injury is a common feature of COVID-19 infection, but serum creatinine (Scr) is not a sensitive or specific marker of kidney injury. We hypothesized that measurement of molecular markers of tubular injury can diagnose COVID-19 associated kidney injury and predict a poor prognosis.

**Methods:** This is a prospective cohort study of 444 consecutive COVID-19 patients in a New York City Emergency Department recruited in March and April, 2020. Urine and blood were collected simultaneously at hospital admission (median time of day 0, IQR 0-2 days) and within 1 day of a positive SARS-CoV-2 test in 70% of patients. Urine NGAL and KIM-1 assays were blinded to clinical data. Primary outcomes included the diagnosis of Acute Kidney Injury (AKI) as defined by AKIN criteria, as well as its duration and severity. Secondary outcomes included death, dialysis, shock, respiratory failure, and length of hospital stay. Kidney biopsies from COVID-19 patients were examined for biomarker gene expression.

**Results:** Elevated urinary NGAL (uNGAL) levels were associated with Scr based AKI (267±301 vs. 96±139 ng/mL, P=1.6x10^-10). uNGAL level >150 ng/mL had 80% specificity and 75% sensitivity to diagnose AKIN stage 2 AKI or higher. Higher uNGAL levels were associated with sustained AKI [aOR per SD of uNGAL (95%CI): 2.67 (1.81-4.06), P=1.8x10^-6], need for dialysis (aOR: 3.67 (1.89-7.57), P=2.2x10^-3), shock (aOR: 1.64 (1.26-2.15), P=2.9x10^-4), length of stay (aHR: 1.22 (1.09-1.36), P=4.8x10^-4), and death (aOR=1.62 (1.19-2.24), P=2.5x10^-3), independent of baseline Scr and pre-existing co-morbidities. These associations were also preserved after adjusting for proteinuria measured in the same urine sample. NGAL is typically transcribed by distal nephron segments but in COVID-19 kidney biopsies with widespread histopathologic acute tubular injury (ATI), NGAL mRNA expression included proximal tubules.

**Conclusions:** Elevated uNGAL in patients admitted with acute COVID-19 was associated with the development of AKI, increased severity and duration of AKI, the degree of histopathological acute tubular injury, shock, prolonged hospitalization, need for dialysis, and death.

**Funding:** NIDDK Support

**PO0173**

**Readmissions After AKI in Colorectal Carcinoma Are Associated with Adverse Outcomes: Findings from the National Readmission Database**

Victor E. Prado,1 Miguel Salazar,2 University of Cincinnati, Cincinnati, OH; 1Cleveland Clinic, Cleveland, OH.

**Background:** Acute kidney injury (AKI) is common in critically ill cancer patients with poor outcomes. Colorectal carcinomas (CRC) are frequently associated with AKI, due to complications of disease or treatment. AKI in CRC remains a well-known but under-represented topic in current literature. We aim to analyze and quantify the impact, healthcare burden, readmission rates and predictors of metastatic CRC with AKI.

**Methods:** We conducted a retrospective cohort study of the 2017 National Readmission Database (NRD) of adult patients readmitted within 30 days after an index admission for AKI with a concomitant diagnosis of CRC. ICD 10 codes were used to identify diagnoses and procedures.

**Results:** A total of 2,239 patients with metastatic colorectal cancer were admitted with AKI. The 30-day readmission rate was 27.9%. Main causes for readmission were sepsis, progression of malignancy, hypovolemia and recurrent AKI. Readmitted patients were associated with higher in-hospital mortality (0.1% vs. 1.5%; P<0.01), mechanical ventilation need (4.7% vs. 1.5%; P<0.01) and chronic kidney disease (CKD) diagnosis (44.6% vs. 36.1%; P<0.01). The total health care in-hospital economic..
burden of readmission was $32.3 million in total charges and $7.8 million in total costs. After adjusting for age and comorbidities, independent predictors of readmission were disposition against medical advice, HIV, CKD, and sepsis. Preventive factors for readmission were found to be radiation therapy and parental parenteral nutrition.

Conclusions: AKI in metastatic CRC has a high rate of readmissions, with poor outcomes in morbidity, mortality and costs making it a significant healthcare burden. Among common causes of readmission, potentially targetable causes include hypovolemia and sepsis while among readmission predictors, CKD and sepsis warrant further attention. Abovementioned preventive predictors consolidate the importance of combination therapy and supportive care in CRC.

Predictors of Readmissions

PO0174
Risk for AKI in the Outpatient Setting
Daniel P. Murphy,1 Scott Reule,2 David M. Vock,1 Paul E. Drawz,1 1University of Minnesota Medical School Twin Cities, Minneapolis, MN; 2Minneapolis VA Health Care System, Minneapolis, MN.

Background: Risk-factors for acute kidney injury (AKI) in the hospital have been well studied. Yet, tools for identifying outpatients at high risk for AKI are not available.

Methods: A development cohort for modelling risk of AKI without concurrent or subsequent hospitalization was defined by repeated primary care encounters in an urban healthcare system. An external validation cohort was similarly defined in the Veterans Health Administration. Logistic regression with bootstrap sampling for backward stepwise covariate elimination was used to develop a model for outpatient AKI in an 18-month outcome period. The model was then transformed into two binary tests to identify high-risk patients: one for research and another for clinical care.

Results: Outpatient AKI occurred in 4611 of 152,371 (3.0%) and 115,744 of 4,864,576 (2.4%) patients in the development and validation cohorts, respectively. The model C-statistics were 0.72 (95% CI: 0.71-0.73) and 0.72 (95% CI: 0.72-0.72) in the development and validation cohorts.

Conclusions: The outpatient AKI-risk prediction model performed well in both continuous and binary forms.

Performance in the validation cohort of two binary tests for outpatient AKI in 18 months

(a) Derived in the development cohort (b) P <0.001 for predicting outpatient AKI in the validation cohort

Kaplan-Meier curves for death by groups, based on presence of AKI or AHF

Relative excess risk of interaction (95% CI) = 1.453 (2.386-20.520); P = 0.013. Attributable proportion due to interaction (95% CI) = 0.401 (0.208-0.594); P <0.001

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

HRs of death within 1 month in subgroups

PO0175
Additive Harmful Effects of AKI and Acute Heart Failure on Mortality in Hospitalized Patients
Hyung Eun Son,1,2 Eunjii Baek,1 Ji Young Ryu,1,2 Jong Cheol Jeong,1,2 Dong-Wan Chae,1,2 Seung Seok Han,1,2 Sejoong Kim,1,2 Seoul National University Bundang Hospital, Seongnam, Republic of Korea; 3Seoul National University College of Medicine, Seoul, Republic of Korea; 4Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea.

Background: Organ crosstalk between kidney and heart has been suggested. This study aimed to investigate the additive effect of both conditions on mortality.

Methods: We retrospectively recruited 102,721 hospitalized patients for 5 years. Acute kidney injury was diagnosed with serum creatinine-based criteria, and acute heart failure with International Classification of Diseases code, within two weeks after admission. Primary outcome was all-cause mortality.

Results: Among the 5,316 (5.2%) patients who died, 20.5% died within 1 month. Hazard ratio for 1-month mortality was 23.25 in patients with both conditions, 13.47 for acute kidney injury only, and 2.76 for acute heart failure only. The relative excess risk of interaction was 8.01, and it was more prominent in patients aged <75 years, and those without chronic heart failure.

Conclusions: Acute kidney injury and acute heart failure had a detrimental additive effect on short-term mortality in hospitalized patients.

Results of analyses on interaction, where AKI and AHF are the two exposures of interest to mortality within 1 month

Synergy index (95% CI) = 1.710 (1.224-2.388); P = 0.002.

Attributable proportion due to interaction (95% CI) = 0.401 (0.208-0.594); P <0.001

Relative excess risk of interaction (95% CI) = 11.453 (2.386-20.520); P = 0.013.

Relative excess risk of interaction (95% CI) = 11.453 (2.386-20.520); P = 0.013.

Attributable proportion due to interaction (95% CI) = 0.401 (0.208-0.594); P <0.001

Synergy index (95% CI) = 1.710 (1.224-2.388); P = 0.002.

AKI, acute kidney injury; AHF, acute heart failure; HR, hazard ratio; CI, confidence interval.
PO0176
Clinical Trajectories of AKI and Clinical Outcomes in Acute Decompensated Heart Failure
Octavio R. Garcia-Flores, Armando Vázquez-Rangel. Instituto Nacional de Cardiología Ignacio Chavez, Mexico, Mexico.

Background: Cardiorenal syndrome (CRS) is a pathophysiologic disorder of the heart and kidneys, with both acute and chronic dysfunction. CRS type 1 is characterized by an acute cardiac disease leading to AKI.

Methods: This is a retrospective cohort study from Jan 2017 to Dec 2018 in 3rd level center in Mexico City. The objective was to describe the incidence and outcome of AKI in patients with CRS type 1. We divide AKI’s trajectory into: ascending and descending AKI, also we used a creatinine (Cr) cut-off point of 1.5mg/dl and identified 6 trajectories. We used a Logistic regression analysis (LRA) for in-hospital mortality and length of stay.

Results: 404 patients were included. Mean age 58.9 ± 16.5 years, 60% were men, 27% had DM, 45% had hypertension. The incidence of AKI was 60.9% and mortality in this group was 46.7%. AKI’s six trajectories are shown in Figure 1. In LRA for the whole cohort, PASP >40mmHg (OR 4.28 CI 2.01-9.16 p=0.001), NT-proBNP >10000 (OR 3.26 CI 1.61-6.57 p= 0.001), ascending AKI (OR 4.08 CI 2.11-7.88 p=0.04) were associated with mortality. In LRA for ascending AKI, BUN/Cr ratio >25 (OR 1.59 CI 1.00-2.54 p=<.001) and neutrophil/lymphocyte ratio (NLR) >6.5 (OR 2.64 CI 1.65-4.23 p=<0.001) were associated with in-hospital mortality.

Conclusions: The incidence and mortality of AKI in patients with decompensated heart failure is high. Patients with ascending AKI had a significant increase in mortality and descending AKI had a better prognosis. Different Cr trajectories indicate different outcomes, the group of patients who at the time of admission had Cr >1.5mg/dl and presented a rise during hospitalization had a worse outcome. NLR>6.5 and BUN/Cr ratio >25 are predictors of mortality.

PO0177
National Epidemiology of Community-Acquired AKI
Clariessa J. Diamantidis,1,2 Lindsay Zepel,1 Matthew L. Maciejewski,1,3 Erin E. Burks,1,4 M. Alan Brookhart,2,3 Brian D. Griffin,1 Virginia Wang,1,2,3 Duke University Department of Medicine, Durham, NC; Duke University Department of Population Health Sciences, Durham, NC; Durham VA Health Services Research and Development, Durham, NC.

Background: Community-acquired acute kidney injury (CA-AKI) is AKI that develops outside of the hospital and is the most common form of AKI globally. National estimates of CA-AKI in the US are absent due to lack of integrated health data and limited availability of outpatient lab data. In this study, we leverage data from the Veterans Health Administration (VA) to estimate CA-AKI incidence and risk factors.

Methods: We constructed a retrospective cohort using national VA administrative and lab data to assess the cumulative CA-AKI incidence among active VA primary care users in 2013-2017. Veterans who did not have recorded outpatient serum creatinine (SCr) and those with a history of severe kidney disease (a Stage 5 or kidney transplant) were excluded. CA-AKI was defined as a 1.5 fold relative increase in outpatient SCr or inpatient SCr (≥ 24 hours from admission), from a reference value defined as the preceding outpatient SCr ≤ 12 months prior. A Cox model was used to estimate the association between CA-AKI risk and baseline variables capturing socio-demographics and comorbidities, accounting for repeated measurements among Veterans.

Results: Of approximately 2.5 million eligible Veterans in each analysis year, the cumulative incidence of CA-AKI was approximately 2% each year and declined slightly over time (2.0, 2.0, 2.0, 1.9, and 1.6% in 2013-2017, respectively). Of these, 79% were Stage 1 AKI, 15% were Stage 2, and 6% were Stage 3 across all years. Only 26% of CA-AKI was observed in the inpatient setting. Veterans with CA-AKI (vs. no CA-AKI) more likely to be older, male, Black race, with greater comorbidity. After adjustment, increasing age, female sex, Black race, Hispanic ethnicity, diabetes, heart failure, hypertension, alcohol use, HIV/AIDS, metastatic cancer, and sickle cell anemia were all associated with increased CA-AKI risk (HR: 1.15).

Conclusions: CA-AKI affects approximately 1 of every 50 US Veterans and is most common in the outpatient setting, with less than a third observed in the inpatient hospital setting. Reliance on inpatient evaluation of CA-AKI likely results in significant under-diagnosis and missed opportunity to prevent and manage the substantial long-term consequences of AKI.

Funding: NIDDK Support

PO0178
National Practice Patterns in the Care of Pediatric AKI Survivors
Anna E. Williams,1 Erin E. Burks,1 David T. Selewski,1 Rasheed A. Gbadebesin,1 Clarissa J. Diamantidis,1 Duke University Hospital, Durham, NC; 2Medical University of South Carolina, Charleston, SC.

Background: Acute kidney injury (AKI) affects 5-10% of all children admitted to the hospital and is associated with adverse outcomes such as increased risk of recurrent AKI, incident and progressive chronic kidney disease (CKD) and death. However, few guidelines exist to optimize post-AKI care. In this study, we surveyed pediatric nephrologists to determine their practice patterns in the care of AKI survivors.

Methods: We administered an email survey to members of the Pediatric Nephrology Research Consortium (PNRC) throughout the US & Canada. Participants were asked questions regarding their practice characteristics, frequency of care of post-hospital AKI survivors and perceptions regarding provider roles in post-AKI outpatient care. Participants were also asked questions regarding the content of their AKI care, patient counseling and disease monitoring.

Results: Of the 52 respondents, most practiced in an academic setting (96%) for >20 years (83%) and reported caring for >10 AKI survivors each year (69%). The majority of respondents (64%) felt pediatric nephrology should always be involved in AKI follow-up care; 33% felt only for a Stage 2 AKI. Most (73%) felt nephrology care was no longer needed when clinical concerns resolved; 60% when eGFR returns to normal; 46% when urine protein/creatinine (UPC) ratio is normal. Most respondents listed professional conferences (79%) and peer-reviewed articles (87%) as information sources. For mild AKI, 60% of participants repeated a creatinine test after 1 month following discharge; 23% repeated checking within 1 week of discharge. In severe AKI, tests were repeated within 1 week (67%). Most reported measuring blood pressure, serum creatinine & UPC at follow-up (>90%). Respondents endorsed counseling patients on risk of recurrent AKI (69%), incident hypertension (92%), incident CKD (81%) and NSAID avoidance (85%). Overall, 90% of respondents felt comfortable managing AKI follow-up in pediatric patients.

Conclusions: Pediatric nephrologists were generally confident in their ability to counsel and manage pediatric AKI survivors. Most felt AKI care required pediatric nephrology input and reported providing education about AKI consequences. Whether primary care providers endorse similar confidence and co-management perceptions requires further study.

Funding: Other NIH Support - This work was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health under award number R38HL143612

PO0179
AKI Stage Is a Poor Predictor of Long-Term Cardiovascular Outcomes
Benjamin R. Griffin,1,2 Jason Wachsmuth,1 Masaaki Yamada,1,2 M. Barbara Sambharia,1,2 Richard P. Girotra,1,2 Eli Peremans,1,2 Heather Reisinger,1 Mary V. Sarrazin,1,2 Diana J. Jalal,1,2 Iowa City VA Medical Center, Iowa City, IA; 3The University of Iowa Hospitals and Clinics, Iowa City, IA.

Background: Trials to improve long-term outcomes in post-AKI patients have enrolled patients primarily based on AKI stage; however, whether AKI stage is a reasonable predictor of cardiac morbidity and mortality is unknown. We developed predictive models for MACE readmissions in post-AKI patients and determined the utility of AKI stage within these predictive models.

Methods: VHA patient data for inpatient admissions was obtained between 2013 and 2018. AKI was defined as a creatinine increase of ≥0.3 mg/dL from baseline. The primary outcome was subsequent hospitalization for congestive heart failure (CHF), myocardial infarction (MI) or stroke (MACE), with follow-up of at least 2 years. Over 50 variables were considered for inclusion in the final model. Bootstrap modeling was used to determine the outcomes of 100 stepwise regressions using random sampling with replacement. Variables included in more than 60 were included in a final model using Cox regression and censored for mortality. If not selected, AKI stage was forced into the model. Due to the association between cardiac disease and the primary outcome, and in order to evaluate risk factors for de novo cardiac disease, separate models were constructed for patients with and without pre-existing cardiac disease.

Results: A total of 241,781 Veterans with AKI were included. AKI stage did not meet selection criteria for either model. In patients without pre-existing cardiac disease, the final model included age, sodium, bilirubin, chronic lung disease (CLD), complicated diabetes mellitus (CxDM), atrial fibrillation (A-Fib), and proteinuria. AKI stage 3 (HR 1.12; CI 1.08-1.16) was compared to AKI stage 1 was a weak predictor of subsequent MACE events. Similarly, in patients with prior cardiac disease, the final model included age, blood urea nitrogen, white blood count, CHF, MI, CLD, CxDm, A-Fib, cardiomyopathy, cardiac device, sleep apnea, complicated hypertension, valvular disease, major electrolyte abnormalities, and proteinuria. AKI stage 3 was again a weak predictor (HR 1.065, 1.03-1.10).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: While AKI stage is commonly used to enroll patients into AKI survivorship clinics, it was not found to be a strong independent predictor of MACE events among post-AKI Veterans. Our findings may inform risk stratification for post-AKI follow up.

PO0180
Urinary Oxygen Partial Pressure to Monitor AKI Risk
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Background: In a prior study, we showed that patients who developed acute kidney injury (AKI) had lower mean urinary oxygen partial pressure (PuO2) following cardiopulmonary bypass (CPB). However, PuO2 is unreliable when urine flow is low and little is known about the distribution of urine flow intraoperatively. The objective of this research was to determine the distribution of the length of sections of unreliable PuO2 data due to low flow.

Methods: Following IRB approval and informed consent, a device that measures PuO2 and urine flow was placed in cardiothoracic surgery patients. PuO2 and urine flow (sampled at 1 Hz) were deemed reliable when urine flow was above a threshold. Patients who did not meet a percent valid data threshold were excluded. Mean PuO2 following CPB and the maximum and median length of sections of invalid data were calculated. Data were generated for a percent valid data threshold of 30 % and urine flow rate thresholds of 0.1 to 1.0 ml/kg/hr at 0.1 increments. Patients who met the KIDIGO criteria for AKI were compared to non-AKI patients. In addition, patients with Stage 2 or 3 AKI based on the KIDIGO serum creatinine criteria were assigned to the Severe AKI group and were compared to patients with stage 1 or no AKI. The area under the curve (AUC) of a receiver-operator (ROC) plot of mean PuO2 estimating AKI development was calculated for each comparison.

Results: AUC was 0.69 for AKI when the flow threshold was 0.4 ml/kg/hr. The average for all patients of the median and maximum length of invalid data was 37 seconds and 397 seconds, respectively. For Severe AKI, the AUC was 0.81 for a flow threshold of 0.7 ml/kg/hr. As the maximum length of invalid data sections increases the AUC decreases.

Conclusions: Sections of unreliable PuO2 data are sufficiently short and do not significantly impact the performance of PuO2, as a marker of AKI when a urine flow threshold is used to filter the data. The data demonstrate the feasibility of measuring PuO2 to monitor AKI risk during cardiothoracic surgery. Further research is needed to determine if intraoperative PuO2 can reduce the incidence of AKI.

AUC of mean PuO2 and distribution of length of invalid data sections

PO0181
Serum Trace Metal Changes Could Potentially Indicate Kidney Damage in Rats with Cisplatin-Induced Kidney Injury
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Background: Cisplatin (CDP), a widely used anticancer drug, is known to exhibit nephrotoxic adverse effects. Nephrotoxicity is a dose-limiting toxicity. Therefore, the early detection of cisplatin-induced nephrotoxicity is crucial. Certain trace metals reportedly change with kidney injury, although their relationship with CDP-induced kidney injury remains unclear. Therefore, in this study, we investigated the trace metal changes after cisplatin treatment in rats.

Methods: Eight-week-old male Wistar-ST rats were divided into a control and a CDP group (n = 6 for both), treated intraperitoneally with saline or CDP 3 mg/kg, respectively. On day 0 and 5, we took serum samples and measured the SCr and BUN levels. The kidneys were obtained on day 5 and subjected to histological studies using HE staining. The serum samples were used for the comprehensive measurement of nine different trace metal types (Mn, Fe, Co, Ni, Cu, Zn, As, Se, and Mo) by ICP-MS. The statistical analysis was performed using Student’s t-test.

PO0182
Identifying Factors Associated with Clinically Adjudicated Drug-Induced AKI in Children
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Background: Drug-induced acute kidney injury (DI-AKI) affects up to 33% of hospitalized children. Clinical adjudication of DI-AKI is challenging since AKI is multifactorial. We report clinical variables that influence ascertainment of DI-AKI cases and inter-rater reliability (IRR) of existing causality assessment tools (CAT) for adverse drug reactions (ADRs).

Methods: We analyzed data from the DIRECT study, an international, multi-center, observational cohort study of clinically adjudicated pediatric cases of AKI stage 2 associated with nephrotoxic medication (NTMx) exposure. Each case was adjudicated by two pediatric nephrologists using CAT. A third adjudicator acted as the tiebreaker. IRR was calculated using Krippendorff’s alpha. We developed variables to capture exposure to NTMx and serum creatinine trends. We constructed a multivariable logistic regression model with clinically adjudicated DI-AKI as the outcome and clinical variables as predictors.

Results: 115 (86.5%) out of 133 children were adjudicated as DI-AKI. The mean age was 12.2 ± 4.5 years, and the most frequent NTMx: vancomycin (43.6%), piperacillin/tazobactam (32.3%), and non-steroidal anti-inflammatory drugs (18.8%). AKI risk factors were comparable between clinically adjudicated DI-AKI and Not DI-AKI groups. Past medical history of malignancy, increased vascular capacity (i.e., sepsis or hypotension), and severe AKI treated with dialysis made DI-AKI adjudication less likely. Longer duration from the start of drug exposure to AKI onset made DI-AKI adjudication more likely. The IRR of the Liverpool (k = 0.35) and the Naranjo (k = 0.31) CAT were poor.

Conclusions: DI-AKI adjudication is a complex and multifactorial process. Current CAT appear to be unreliable. Development of CAT specific to DI-AKI is needed to perform robust outcomes research.

Funding: Other NIH Support - International Serious Adverse Events Consortium, National Library of Medicine (Grant #T15LM001271).

PO0183
Clinically Distinct Subtypes of AKI on Hospital Admission Identified by Machine Learning Consensus Clustering
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Background: Patients with acute kidney injury were clustered at hospital admission into clinically distinct subtypes using an unsupervised machine learning approach. Mortality risk was assessed among these distinct clusters.

Methods: Consensus clustering analysis was performed on demographics, principal diagnoses, comorbidities, and laboratory data on 8,289 hospitalized adult patients with acute kidney injury at admission. The standardized difference of each variable was calculated to identify each cluster’s key features. We assessed the association of each cluster with hospital and one-year mortality.

Results: Consensus clustering analysis identified four distinct clusters. There were 1,201 (28%) patients in cluster 1, 1,396 (33%) patients in cluster 2, 1,191 (28%) patients in cluster 3, and 501 (12%) patients in cluster 4. Figure 1 illustrates cluster differences. Figure 2 highlights associated increased mortality in clusters 2, 3, and 4.

Conclusions: Clinically distinct AKI subtypes are associated with differing mortality risks.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: A total of 190 patients (81 survivors and 109 non-survivors) were included. MPV was significantly higher at each timepoint (24, 48, and 72 hours) in non-survivors compared to CRRT initiation, and increased by a greater amount over time in non-survivors than survivors. MPV at 72 hours was independently associated with in-hospital mortality after adjustments for covariates (OR 1.76, CI 1.15-2.69, p=0.01).

Conclusions: MPV increased after CRRT initiation, especially in non-survivors, and MPV at 72 hours was independently associated with in-hospital mortality. These findings suggest that platelet activation temporally related to CRRT initiation may play a role in platelet loss and mortality in this population. Future studies will evaluate more direct measures of platelet activation in patients on CRRT and the impact of platelet activation blocking agents in this population.

**PO0185**

**Recovery After AKI: Goals of an AKI!Now Workgroup**

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**Background:** The American Society of Nephrology recently established the AKI!Now initiative. AKI!Now aims to promote excellence in the prevention and treatment of AKI by transforming the delivery of AKI care to improve clinical and patient-centered outcomes. Herein, we describe the focused efforts of AKI!Now on “recovery after AKI.”

**Methods:** Three core objectives were identified in the domain of AKI recovery:

1. To determine areas of priority for mechanistic research focused on recovery after AKI. It is expected that these would include a variety of experimental models suitable for various AKI etiologies and disease severities.
2. To benchmark and prioritize strategies to care for patients after AKI including integrated insights from primary care providers, nephrologists, other subspecialty health care professionals.
3. To facilitate implementation and testing of interventions designed to limit short- and long-term complications of AKI and promote recovery. Dialysis dependent and independent AKI survivors should both be considered for these interventions and clinical trials.

**Results:** The AKI!Now initiative will highlight and clarify challenges and opportunities to improve care after AKI. This work will also inform who is followed after AKI and by whom (i.e., primary care and/or nephrology), options for care delivery (i.e., in-person versus telehealth), and potential practices to improve outcomes (i.e., role of ACEi/ARB and SGLT2 inhibitors after AKI, physical/cognitive rehabilitation). The stakeholder relationships formed, including those with patients, healthcare professionals, industry, and academia, will facilitate a collaborative research and practice agenda necessary to understand and outline best practices after AKI.

**Conclusions:** Survivors of AKI are a high-risk and growing population, and AKI is associated with worse long-term outcomes than an acute myocardial infarction. However, how to care for patients after AKI remains ill-defined with substantial practice variation. This represents an opportunity for the “recovery after AKI” workgroup of AKI!Now to provide leadership by raising awareness and promoting strategies focused on equitable and effective post-AKI care throughout the American Society of Nephrology and wider nephrology community.

**PO0186**

**Exploration of the Mitochondria Genes Alteration in AKI**

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**Background:** Acute kidney injury (AKI) is one of the most common complications in clinic, especially in critical ill patients. Recently, the fundamental function of mitochondria in acute kidney injury and repair have gradually been noticed while the mechanism still unclear. Therefore, we aimed to identify the change pattern of mitochondria alteration associated gene in AKI through Gene Expression Omnibus (GEO) database analysis and AKI animal model verification.

**Methods:** A total of 1893 genes involved in mitochondria function and metabolism were screened from Gene Ontology (GO) database and defined as GO terms in mitochondria metabolism. Meanwhile, 2 studies invested transcriptome differences in renal ischemia reperfusion injury (GSE98622 and GSE99703) were extracted from GEO database. By crossing GO terms and 2 datasets from GEO database, 69 and 62 mitochondria metabolism genes were identified in GSE98622 and GSE99703 separately. Among which, 23 genes were overlapped in 2 datasets and verified by real-time PCR in 2 kinds of AKI model (ischemic renal reperfusion injury model and cisplatin induced AKI model).

**Results:** Through GO and KEGG enrichment analysis, these differentially expressed genes (DEGs) were allocated to peroxisome, butanate metabolism, arginine and proline metabolism, neurotrophin signaling pathway and metabolic pathways. Protein-protein interaction analysis demonstrated that Haa2, Acsn3, Amaac, Aaadat may play vital roles of mitochondrial regulation in AKI. The results of real-time PCR showed that 3 genes were significantly increased in both two kinds of AKI model (Arg2, C14l, Lgals3) and 12 genes were decreased (Aaadat, Acsn3, Ags, Aak, Amaac, Bdh1, Gatm, Haa2, Iso2h, Mipv17l, Nat8f1, Nudh19), while others were not altered in animal model or had no consistency changes between 2 kinds of AKI model.

**Conclusions:** We have identified 23 DEGs were associated with mitochondria metabolism in I/R AKI by using bioinformatic technology. Among these genes, GO and KEGG analysis suggests that the DEGs are mainly enriched in lipid metabolism, amino
acid metabolism pathway and tightly associated with peroxisome. Furthermore, 15 DEGs were revalidated in kidney of two kinds of AKI mouse model (I/R AKI and Cisplatin-AKI).

**Funding:** Government Support - Non-U.S.

**PO0187**

**Artificial Intelligence in AKI: Goals of an AKI!Now Workgroup**

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**Background:** In 2019, the American Society of Nephrology established AKI!Now, a collaborative initiative to promote excellence in the prevention, diagnosis, and treatment of Acute Kidney Injury (AKI). Here, we describe the ongoing efforts of the AKI!Now workgroup focused on Artificial Intelligence (AI) to improve the quality, accessibility, affordability, and equity of AKI care.

**Methods:** The workgroup has outlined objectives in 3 key domains: 1. Patients: Input in designing and implementing fair and equitable AI tools and identifying clinical scenarios based on personal and caregiver experience that could be improved. 2. Clinicians: Input in the design, value, and implementation of fair and equitable AI tools and identifying clinical uncertainties that may benefit from new AI tools 3. Researchers: Evaluation of current AI tools, with a focus on removing implicit bias, development of novel, feasible, and effective AI tools to address gaps identified by patients and clinicians; and development and implementation of AI methods along with novel sensors for more sensitive assessment of kidney function and injury to advance the science of AKI.

**Results:** This project, with involvement from a multi-disciplinary group of stakeholders, will yield efficient and effective use of AI for quality improvement in AKI care. Specific deliverables include 1) Risk-stratification and prediction tools; 2) Intelligent alert tools; 3) Decision support for bundled care compliance; 4) Decision support for implementing pragmatic clinical trials, among others. Importantly, this work will help in a more equitable and sustainable AI tool development and deployment which are not currently available.

**Conclusions:** The AKI!Now workgroup on AI is committed to improving value care in AKI and encourages engagement and collaboration with patient, provider, researcher, and industry stakeholders. We seek to improve the care provided to the growing and susceptible AKI population, along the entire lifespan.

**PO0188**

**Incidence of AKI in Individuals Treated with Lithium**

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**Background:** Lithium has been linked to acute kidney injury (AKI) at toxic blood levels but the risk of AKI has otherwise not been well studied. Interestingly, lithium has been shown to protect against tubular injury in experimental AKI models. The aim of the study was to examine the risk of AKI in individuals treated with lithium.

**Methods:** This was a retrospective cohort study of all individuals treated with lithium in Iceland in 2003–2018. A control group comprised patients with affective disorders (ICD 10 codes F30-F39) attending the outpatient clinic of the Mental Health Services at Landspitali–the National University Hospital in 2014–2016, who had never used lithium. Clinical and laboratory data, including ICD-9 and ICD-10 codes and serum creatinine (Scr) values, were obtained from nationwide electronic medical records. Individuals with <2 Scr values available were excluded. AKI was defined using the SCR component of the KDIGO criteria. Multivariable logistic regression was used for the analysis.

**Results:** The lithium-treated group consisted of 2682 individuals, of whom 2310 (86.1%) were included in the study. Of those, 297 (12.9%) developed AKI. Of 1426 individuals in the control group, 1218 (85.5%) were included and 97 (8.0%) developed AKI. Lithium use was not an independent risk factor for AKI (OR 0.93, 95% CI, 0.72–1.20, Table). When lithium users were analyzed separately, lithium intoxication (OR 2.34, 95% CI, 1.33–4.09), duration of lithium therapy (OR 1.01, 95% CI 1.00–1.01) and mean lithium concentration (OR 1.22, CI, 1.14–1.30) were all significant risk factors for development of AKI.

**Conclusions:** Our findings suggest that lithium use does not affect the incidence of AKI after controlling for important covariates. However, lithium intoxication, time on lithium therapy and blood lithium concentration are associated with increased risk of AKI.

**Funding:** Government Support - Non-U.S.
Urine Biomarkers of AKI in Extremely Low Gestational Age Neonates: A Case-Control Study

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Background: Urine biomarkers hold promise to diagnose and differentiate AKI. In premature neonates, biomarker evaluation must address normative gestational age (GA) differences.

Methods: We performed a case-control study from neonates enrolled in the PREterm Erthropoietin Neuroprotection Trial (PENUT) to evaluate differences in urine obtained in the first postnatal week between cases and controls. Twenty (N=20) neonates with severe AKI (Stage 2 or 3) were matched with 2 controls (N = 40) who did not have AKI, had the same GA week (rounded down to the nearest week), gender, and BW (±50 g), without replacement. Biomarkers were analyzed on multi-analyte electro-chemiluminescent or single colorimetric ELISA kits. Biomarker were run in duplicates; the average concentration was converted to log_{10}. Days were grouped into day 0-3, 4-6, 7-9, with day of birth was defined as day 0. For each biomarker, the average pairwise difference between cases and controls was calculated. To account for multiple measurements, a linear mixed model framework was employed incorporating a random intercept for match, random effects across day, and a day case status interaction term. The predicted mean differences (case minus control) at days 1 (0-3), 5 (4-6), and 9 (7-9) for each of 21 urine biomarkers. Urine albumin (day 1), EGF (day 1), creatinine (day 5 and 9), Ghrelin, IGFBP7, IL15, MCP1, TIMP2, VEGF (day 9), Cystatin C (Day 9), KIM-1 (day 9), IL-15 (day 9), and VEGFa (day 5) were significant differences between cases and controls.

Results: Several urine biomarker concentrations differed in extremely low gestational age neonates with severe AKI vs. control. Further evaluation of these biomarkers is necessary before clinical utility can be addressed.

Funding: Other NIH Support - Recombinant Erthropoietin for Protection of Infant Renal Disease (REPAReD) Study is an NIH NIDDK funded U01 DK103608 ancillary study designed to look at kidney outcome in patients enrolled in the Preterm Erthropoietin Neuroprotection Trial (PENUT) which is an NIH NINDS funded U01 NS077953, U01 NS77955 trial. The clinicaltrials.gov identifier is NCT01378273.

Predictors and Outcomes of Post-Left Ventricular Assist Device AKI

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Background: Left ventricular assist device (LVAD) is used to treat advanced heart failure as a bridge to orthotopic heart transplant (OHT) or as destination therapy in patients who are not OHT candidates. With limited donor availability and significant improvement in LVAD outcomes, the number of patients with LVAD implantation as destination therapy has increased. With increased LVAD use, the number of adverse events and complications are expected to increase. Acute kidney injury (AKI) is a frequent complication after LVAD implantation and is associated with high mortality. We studied the predictors of Post-LVAD AKI and the association between AKI and mortality, as well as between AKI and receiving an OHT.

Methods: We conducted a retrospective multi-center study using TriNetX Research Network database, a federated electronic medical records, to identify 486 patients from 24 healthcare organizations from the United States, with no underlying chronic kidney disease (CKD) who had an LVAD implanted between 1/1/2010 and 12/31/2019. Of these, 116 (24%) had developed AKI within the first month of the procedure. The baseline characteristics of this group were compared with the 370 patients who had not developed AKI during the first month after LVAD placement.

Results: There was no statistically significant difference between the two groups in regard to age at time of LVAD placement, sex, or ethnicity. Black race was associated with a higher odds of developing AKI (Odds Ratio [OR]: 1.70; 95% Confidence Interval [CI]: 1.11, 2.59). The two co-morbidities most significantly associated with AKI during the first month after LVAD placement were: persistent atrial fibrillation (OR: 3.33; CI: 1.35, 8.22), and a body mass index (BMI) ≥50 (OR: 3.86; CI: 2.21, 6.75). During the first year after LVAD placement, 73 patients died and 37 patients received OHT. There was no statistical difference in one-year mortality or likelihood of undergoing an OHT within a year between the AKI and non-AKI groups.

Conclusions: In patients with no underlying CKD, black race, persistent atrial fibrillation, and BMI above 50 increase the likelihood of post-LVAD AKI. Development of AKI post-LVAD implantation in these patients is not associated with changes in one-year mortality or likelihood of receiving an OHT.

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External Validation of Simple Postoperative AKI Risk (SPARK) Classification in Noncardiac Surgery: The NARA-AKI Cohort Study

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Background: The aim of the present study was to externally validate Simple Post-operative AKI Risk (SPARK) index which was developed to predict post-operative acute kidney injury (PO-AKI) in non-cardiac surgery.

Methods: In a retrospective cohort study, adults with non-cardiac surgery under general anesthesia were included. Those with obstetric or urological surgery, estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m², pre-operative dialysis, expected surgical duration <1 hour, and missing data for analyses were excluded. The exposures of interest were risk factors for AKI included in SPARK index, and outcomes were PO-AKI and critical AKI. The discrimination and calibration of SPARK index were examined with receiver operating characteristic curves and calibration plots, respectively.

Results: Among 5135 subjects, 303 and 137 developed PO-AKI and critical AKI, respectively. Subjects in our cohort were older, and baseline eGFR was lower compared to SPARK cohort. In addition, the proportion of subjects with comorbidities was higher. The discrimination and calibration of SPARK index were examined with receiver operating characteristic curves and calibration plots, respectively. Subjects in our cohort were older, and baseline eGFR was lower compared to SPARK cohort. In addition, the proportion of subjects with comorbidities was higher. The discrimination and calibration of SPARK index were examined with receiver operating characteristic curves and calibration plots, respectively.

Conclusions: The accuracy of SPARK index in identifying subjects at high risk for developing AKI pre-operatively. However, the use of EHR resulted in a moderate ability to identify those at increased risk of post-AKI MAKE. Further research is needed in identifying those who may benefit from post-AKI care.

Funding: Veterans Affairs Support, Private Foundation Support

A Risk Score for Major Adverse Kidney Events One Year After AKI

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Background: Epidemiologic evidence suggests that those with AKI are at increased risk of post-AKI kidney disease, higher hospital resource utilization, and death. However, literature to support identification of those most at risk of these outcomes is limited. Here we pilot predicting risk of post-AKI MAKE.

Methods: In a cohort of 4.2 million United States Veterans, risks of MAKE within a year of discharge associated with an AKI were detailed using survival regression with inverse probability of treatment weighting. Risk factors for MAKE including demographics, clinical characteristics including diagnoses, medication use, and laboratory tests, as well as hospitalization parameters among those with an AKI were examined, and then a risk score was developed and evaluated following the Framingham Heart risk score algorithm.

Results: In the year after discharge form a hospitalization, compared to those without an AKI, those with an AKI were at an increased risk of a subsequent AKI (HR=1.47; 95% CI=1.45-1.49), incident eGFR less than 60 mL/min/1.73 m² (1.23,1.22-1.24), eGFR decline >50% (1.69; 1.67-1.71), receipt of kidney replacement therapy (2.41; 2.28-2.51), and MAKE (1.24; 1.23-1.25). Results were consistent in Fine and Gray competing risk models. Among those with an AKI, predictors of MAKE included age, albuminuria, bicarbonate, blood pressure before and during hospitalization, cardiovascular disease, cancer, chronic lung disease, dementia, diuretic use, baseline eGFR, hematoctrit level, NSAID use, obesity, platelet count, pneumonia, serum creatinine trajectory during hospitalization, surgeries, and urinary tract infection. A risk score constructed using these predictors achieved an area under the curve (AUC) of 0.72, where corresponding probabilities of having a MAKE within a year of discharge ranged from 7.3% to 59.9% at the lowest and highest risk score values experienced in the cohort. Comparatively, use of KDIGO stage alone marginally predicted future risk of MAKE (0.52). Calibration plots suggested that models were well calibrated.

Conclusions: Use of EHR resulted in a moderate ability to identify those at increased risk of post-AKI MAKE. Further research is needed in identifying those who may benefit from post-AKI care.

Funding: Veterans Affairs Support, Private Foundation Support

The Association of Metabolic Acidosis with AKI in Patients with CKD: A Retrospective Cohort Study in Two Cohorts

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Background: Metabolic acidosis in patients with chronic kidney disease (CKD) results from a loss of kidney function. It has been associated with more rapid CKD progression, all-cause mortality, and other adverse outcomes. Whether metabolic acidosis is associated with a higher risk of acute kidney injury (AKI) remains unknown.

Methods: We conducted a retrospective cohort study in 2 North American cohorts (US EMR cohort and Manitoba Claims cohort) using electronic health records and administrative data of patients with CKD Stages G3-G5. The primary exposure was metabolic acidosis (serum bicarbonate between 12 and <22 mEq/L), and the primary
outcome of interest was the development of AKI (defined using KDIGO and 10 codes at hospital admission and the laboratory-based definition based on KDIGO guidelines). We applied Cox proportional hazards regression models adjusting for common demographic and clinical characteristics.

Results: In both cohorts, metabolic acidosis was associated with AKI: HR 1.565 (95% CI 1.212 - 1.997) in the EMR cohort and HR 1.652 (95% CI 1.578 - 1.729) in the Manitoba Claims cohort. The association was consistent when serum bicarbonate was treated as a continuous variable, and in multiple subgroup and sensitivity analyses including those adjusting for albuminuria.

Conclusions: Metabolic acidosis is associated with a higher risk of AKI in patients with CKD. AKI should be considered as a safety outcome in studies of treatments for patients with metabolic acidosis.

PO0197 Chikungunya Fever: A Trigger for Different Renal Disorders

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Background: Prevalence of chikungunya fever (CHIK)–related kidney injury (KI) is variable, but data are scarce and limited to the acute phase of the disease. Necropsies performed in fatal acute cases of CHIK show viral RNA can be found in renal tissue, but clinical and histopathological aspects poorly characterized. This study aimed to describe renal histopathological features and to detect viral antigens in renal tissue in patients affected by CHIK in different phases of infection.

Methods: This was an exploratory study, conducted between 2016 and 2020. Patients followed in nephrology reference centers due to KI with onset after different phases of CHIK infection were evaluated. These patients had hematuria, proteinuria and/or renal dysfunction. A common history of CHIK infection and were referred for renal biopsy. Viral antigens were investigated by electron microscopy, immunohistochemistry and PCR in renal tissue.

Results: Sixteen patients (aged 10-95yrs) had KI 0.5 to 24months after CHIK, with predominance of glomerular lesions. Initial creatinine ranged from 0.2 to 22.3mg/dl (median 3.9mg/dl; IQR 1.0-5.5). Proteinuria and hematuria were initially detected in 94% and 81% of patients, respectively. Histopathological findings comprised diagnoses of focal segmental glomerulosclerosis (FSGS) (3), class IV lupus nephritis (3), crescentic glomerulonephritis (2), atypical hemolytic uremic syndrome (aHUS) (2), pauci-immune vasculitis (1), PLA2R-positive membranous nephropathy (2), collapsing glomerulonephrosis (CG) (2). One patient was diagnosed with collagen IV-related nephropathy in renal biopsy performed due to macroscopic hematuria after CHIKV infection. No viral antigens were detected in renal tissue. The 2 patients with aHUS included in the study carry heterozygous mutations associated with increased risk of developing the disease. APOL1 high-risk genotypes were identified in 2 patients with CG (G1/G2 and G2/G2) and 1 patient with FSGS (G1/G2). Nine (56%) patients progressed to chronic kidney disease after a median follow-up of 12 months.

Conclusion: Our findings reveal the potential of CHIK virus to directly cause and/or trigger KI. These effects can be translated into a variety of renal lesions potentially with significant severity.

PO0198 Risk Factors and Outcome Variables of Cardiorenal Syndrome Type 1 from the Nephrological Perspective

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Background: In cardiorenal syndrome (CRS) type 1, acute cardiac failure or acute decompensation of chronic heart failure causes acute kidney injury (AKI). Every individual AKI episode increases the risk for chronic kidney disease (CKD) in the long-term. In this study we aimed to evaluate epidemiological characteristics and outcome variables of CRS type 1 individuals from the nephrological perspective.

Methods: The study was performed in a retrospective, observational manner. All AKI patients treated at the Brandenburg Hospital of the Medical School of Brandenburg between January 2017 and August 2019 were screened. Baseline criteria of CRS type 1 endpoints were in-hospital death, need for dialysis, and renal recovery.

Results: During the screening, a total number of 1,189 subjects were diagnosed with acute kidney injury according to KDIGO. One-hundred ninety-eight (19% - 16.6%) out of these patients were assigned to the diagnosis CRS type 1. The overall in-hospital mortality was 19.2%. Non-survivors were not older than survivors. Nine point six (9.6) % of the patients required dialysis due to AKI, respective individuals were significantly older (84.6 +/-1.1 vs. 77.6 +/-0.7 years; p=0.002). Complete recovery of kidney function was observed in 86% (43.4%), incomplete recovery occurred in 55 patients (27.8%), fifty-seven patients (28.8%) did not recover at all. Age-related differences were not identified. Sixty-four (32.2%) demission letters did not contain any cardiac diagnosis at all, nephrology follow-up recommendations were given in only 8%.

Conclusion: The incidence of CRS type 1 is high (>16% of all in-hospital AKI subjects) and the mortality is higher than the average mortality of AKI in general. At the same time complete recovery of kidney function occurs less frequent. The kidney-related follow-up management of CRS type 1 needs to be significantly optimized in order to improve the long-term outcome of affected patients.

PO0199 An Automated, Open-Source Program to Standardize AKI Definition from Time-Stamped Creatinine Data

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Background: Though KDIGO guidelines specify a definition for AKI based on changes in serum creatinine, operationalizing this definition with real-world data requires multiple assumptions that leads to variation across studies. A standardized AKI flagging tool can increase inter-study validity.

Methods: We developed AKIFlagger, an open-source computational tool built in Python, and as a web application which implements a standardized AKI definition based on KDIGO guidelines while allowing for variational definitions of baseline creatinine. We applied the AKIFlagger to a dataset of patients hospitalized with COVID-19 while permitting various operational implementations of the guidelines.

Results: We demonstrate that subtle changes in definition can have a large impact on estimates of AKI prevalence and outcomes. Compared to a rolling window approach, using a baseline definition that leverages outpatient creatinine values and or imputes those values based on an eGFR back-calculation increases the size of captured patient populations by 20.7% and 57.1%, respectively. We characterize the predictive value of the different methods of identifying AKI by determining the sensitivity and specificity for stage progression and progression to death or dialysis. The approaches span sensitivities from 0.18 to 0.20 and specificities from 0.90 to 0.95 for stage progression, and sensitivities from 0.71 to 0.85 and specificities from 0.62 to 0.76 for progression to death.

Conclusions: Subtle differences in the definition of AKI can lead to drastic differences in which patient populations are captured by the definition. A standard mechanism to implement the KDIGO criteria is necessary for the field to accurately advance both clinical and basic science research. This standardized tool can be used by researchers to ensure definitions are uniform across studies.

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PO0200 Community-Acquired AKI: A Prospective Case-Control Study

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Background: Acute kidney injury (AKI) represents an abrupt decline in kidney function occurring over hours or days. While hospital-acquired AKI has been extensively studied, data on community-acquired AKI are scare. The aim of this study was to examine the incidence and causes of AKI among patients presenting to the emergency department (ED).

Methods: This was a prospective case-control study in which serum creatinine (Scr) of all individuals admitted to the ED of Landspítl –The National University Hospital were examined for the presence of AKI. We present data from January 1 until March 3, 2020 and May 19 until September 21, 2020. The study was paused between these periods due to the COVID-19 epidemic. All patients who met the KDIGO criteria for AKI were invited to participate. Randomly selected control cases (1:2) were paired according to age, sex and time of ED admission. Participants answered questions about their medical history and use of medications, including over-the-counter (OTC) drugs. Medical records were reviewed with regard to medical history. Logistic regression was used to identify factors associating with AKI.

Results: A total of 372 persons with AKI were identified, 315 (85%) of whom participated in the study. The mean (±SD) age of AKI cases and controls was 66.6±11.1 years and 66.3±16.2 years, respectively; 46% of cases and controls were female. AKI cases were significantly more likely than controls to have used non-steroidal anti-inflammatory drugs (NSAIDs) (31.1% vs 22.2%, p=0.003) in the week preceding the ED visit. Particularly, the use of OTC NSAIDs (24.7% vs 16.2%, p=0.001). In a multivariable logistic regression analysis, AKI was associated with vomiting (OR 2.40 95%CI 1.74-3.35), diarrhea

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Circulating Endotoxin Levels Correlate with Kidney and Mortality Outcomes in Critically Ill Patients

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Background: Among the critically ill, sepsis is a common cause of acute kidney injury (AKI). Endotoxin is a component of gram negative bacterial cell walls, and is a potent trigger of AKI in sepsis, but may also be present in non-bacteremic patients. Our aim was to determine correlations between endotoxin levels and AKI and mortality outcomes in incident critically ill patients.

Methods: Patients were recruited from those admitted to intensive care units (ICUs) who were over 18, and who did not have end-stage renal failure requiring dialysis, or were on chronic immunosuppressive medications. Blood endotoxin activity (EA) was measured using the FDA-approved chemiluminescent EA Assay. Blood EA was measured on days 1, 4, and 8 of admission to ICU, and results either categorized as low (0.0-0.39), intermediate (0.4-0.59) or high (>0.60), or used as a continuous variable in Spearman correlation analysis. Kidney parameters and dispositions were obtained from electronic medical records. AKI was defined as per KDIGO guidelines.

Results: A total of 35 patients were recruited between November 2020 and April 2021, with 4 testing positive for gram negative bacteria. Initial EA levels were 6 (17%), 10 (29%) and 19 (54%) patients with low, intermediate, and high levels, respectively. During the study, 14 patients’ EA levels changed such that their categorization either went up (4) or down (9), whilst one patient alternated between intermediate and high levels. When stratified by presence of AKI, no patients with low EA (0/6) developed AKI, whilst 9/13 (71%) of patients with AKI had high EA versus 8/20 (40%) of non-AKI patients who had high EA. All of the patients with low EA were discharged, whereas 3/10 (30%) and 4/18 (22%), respectively, of those with intermediate and high EA expired. When analyzed as a continuous variable, there was a significant positive correlation between initial EA and initial sCr (r = 0.56, p < 0.001). Furthermore, there was a significant correlation between the rates of changes in EA and sCr over time (r = 0.47, p < 0.05).

Conclusions: Endotoxin levels on admission to ICU correlated with kidney function, presence of AKI, and mortality. Changes in EA over time also correlated with changes in kidney function, suggesting that EA may be a potential marker in critically ill patients.

Fundings: Commercial Support - Dialysis Clinic Inc.
Methods: Demographics, comorbidities, treatment and 4 weeks outcome data for nephrology referrals for AKI in 7 public hospitals from 1 Jan-30 Apr 2021 prospectively collected and analyzed

Results: Total number of AKI referrals was 1298, that is 3.3% of hospital admissions. Community acquired cases were 12.5%. Males were 57%, mean age 64 (±22.6), and 10% had affected 71% DM, 75% affected 71%, HTN 74% and cardiac disease 36% of patients. Mean baseline eGFR before AKI was 62. Baseline eGFR < 60 seen in 52%, and those compared to patients with eGFR > 60, had mean baseline eGFR of 35 (vs 90), were older (68 vs 60 with 61% above age 65 vs 41%), 81% had DM (vs 60%), 85% had HTN (vs 75%), had CKD (vs 40%), had ischemic ATIN in 87%, COVID-19 related in 8%, contrast-associated in 6%, drug-induced AIN in 5% of cases. Many had more than one possible cause. Sepsis was most common precipitating factor seen in 67% then volume depletion in 50%. Many had more than one factor. 60% had CKD (vs 75% in low eGFR group), IV diuretics in 60% (vs 40% in lower eGFR group), IV vasopressors in 40% (vs lower in low eGFR group) and steroids in 33%, KRT needed in 33%, more in patients who used diuretics or vasopressors. Volume overload and electrolytes / acid-base disorders were most common indication (75% and 79% respectively). CRRT was modality of choice in 85%, however, in 52% of CRRT, correction of pH was not used not due to lack of dialysis adequacy in some sites. At 30 days, mean eGFR was 42%, with complete recovery in 34%, and 38% failed to recover at all. Death occurred in 31%, 55% had baseline eGFR > 60, and 50% of deaths occurred while on KRT. Non-survivors were older and had higher use of vasopressors. AKI associated mortality in 25% of total hospital mortality and in 31% of ICU / CCM mortality.

Conclusions: AKI is common. Most cases hospital-acquired. Use of resources (medications, critical care, KRT) and rates of mortality are high. Kuwaiti citizens represent 3/3 of the population and 2/3 of AKI cases and almost 70% of deaths.

PO0206
AKI in the Month of Ramadan
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Background: Fasting in Ramadan from dawn to sunset is one of Islamic’s 5 pillars. Islamic lunar calendar is 11 days shorter than Gregorian solar calendar, so the start of Ramadan changes every year and hours spent on fasting vary from 12 hours in Australia, 10-11 hours in Europe, 11-12 hours in the U.S. and 12-13 hours in Islamic lunar calendar is 11 days shorter than Gregorian solar calendar, so the start of Ramadan changes every year and hours spent on fasting vary from 12 hours in Australia, 10-11 hours in Europe, 11-12 hours in the U.S. and 12-13 hours in some sites. At 30 days, mean eGFR was 42%, with complete recovery in 34%, and 38% failed to recover at all. Death occurred in 31%, 55% had baseline eGFR > 60, and 50% of deaths occurred while on KRT. Non-survivors were older and had higher use of vasopressors. AKI associated mortality in 25% of total hospital mortality and in 31% of ICU / CCM mortality. However, an increase in the number of AKI cases during the month of Ramadan was observed in our institution (15 cases during the month of Ramadan vs 10 cases outside the month of Ramadan). This study attempts to assess the epidemiology, risk factors, and prevention of AKI in patients who partake in fasting. The long hours of fasting may be a risk factor for AKI in patients with decompensated cirrhosis. It is plausible that thrombocytopenia is also a predictor of SA-AKI. It is not necessary to warn patients taking metformin of the clinical situations potentially inducing AKI (especially dehydration).

PO0208
An Analysis of Risk Factors for AKI in Patients with Decompensated Cirrhosis: A 4-Year Retrospective Study, 2012-2015
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Background: Acute kidney injury (AKI) is a common complication in advanced liver disease and decompensation of AKI in patients with cirrhosis is associated with increased risk of need for dialysis or mortality. We conducted a retrospective analysis, which was a 4-year study involving 945 AKI cases in patients with cirrhosis. AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria. The clinical and demographic data of AKI group was compared with other patients by univariate and multivariate regression analyses.

Results: The incidence of AKI in decompensated cirrhosis was 17.7%. Compared with patients without AKI, patients with AKI had higher white blood cell (WBC) count, longer prothrombin time (PT), higher total bilirubin (TBil), higher serum creatinine (Scr) and higher blood urea nitrogen (BUN), but having lower alanine aminotransferase (ALT), lower albumin, lower cholineser, lower estimated glomerular filtration rate (eGFR), lower total cholesterol (TC), lower triglyceride (TG) and lower serum sodium concentration. But no significant differences in platelet (PLT) count and International Normalized Ratio (INR). In the multivariate logistic regression analysis, hypertension (odds ratio [OR]=3.647, 95% confidence interval [CI]=1.546-8.606, P=0.002), upper gastrointestinal bleeding (OR=4.957, 95%CI=2.177-11.286, P<0.001), Scr(OR=1.019, 95%CI=1.003-1.035, P=0.019), WBC(OR=1.147, 95%CI=1.032-1.275, P=0.011), PT(OR=1.097, 95%CI=1.004-1.198, P=0.04) and eGFR (OR=0.958, 95%CI=1.034-0.983, P=0.001) were independent risk factors for occurrence of AKI in patients with decompensated cirrhosis.

Conclusions: We observed that hypertension, upper gastrointestinal bleeding, Scr, value of WBC count, length of PT and eGFR were independently associated with the development of AKI in patients with decompensated cirrhosis. It is, therefore, necessary to apply early intervention in patients with the risks of AKI.

PO0209
Admission Platelet Count Is an Independent Predictor of AKI
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Background: Thrombocytopenia is a recognized marker of disease severity that is associated with higher mortality in patients with sepsis-associated acute kidney injury (SA-AKI). It is plausible that thrombocytopenia is also a predictor of SA-AKI development due to the characteristic microvascular dysfunction seen in this disease state, but human studies are lacking. In this analysis, we evaluated admission platelet counts and SA-AKI rates in a large VA database of patients with methicillin-resistant staph aureus (MRSA) bacteriaemia.

Methods: We evaluated patients admitted to 124 VA Hospitals who developed MRSA bloodstream infections during a hospitalization from 2007-2014. Patients were excluded if platelet counts or creatinine values were not available on 2 or more occasions. Predictor variables were platelet counts <150 and <100 at admission. Primary outcome was the development of in-hospital AKI, defined as a platelet increase of 0.3 mg/dL over 48 hours, or an increase of 1.5x baseline within 7 days. Cox proportional hazard modeling was used to determine the association between platelet levels and AKI. Covariates were chosen using forward stepwise regression. Potential covariates evaluated for inclusion were age, race, admission laboratory values, comorbidities, antibiotic agents, infection location, healthcare utilization prior to admission, and surgical intervention, among others.

Results: A total of 6,765 patients were included, of which 2,656 (39.3%) developed AKI during admission. At admission, 1,633 (24.1%) and 757 (11.2%) had platelet counts <150 and <100, respectively. AKI rates in these patients were 44.1% and 46.2%, respectively. Hazard ratios for AKI were 1.17 (95% CI 1.07-1.28) in patients with platelet counts <150 vs 1.25 (95% CI 1.10-1.39) in patients <100.
Conclusions: Platelet counts of <150 and <100 at admission were found to be independent predictors of subsequent SA-AKI development in a large database of patients with MRSA bacteremia. These findings may inform future studies in the prevention and prediction of AKI development.

PO0210

AKI!Now: Defining Excellence in the Prevention of and Care for Patients with AKI

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Background: AKI is commonly diagnosed and classified from changes to serum creatinine according to the 2012 KDIGO criteria. When baseline creatinine is missing, the guideline recommends to back calculate it from an assumed MDRD-GFR of 75ml/min/1.73m2. We describe a simple method to estimate missing baseline creatinine.

Methods: From NHANES 2015-2018 data we calculated distribution of serum creatinine values for the adult US population as a whole, and for gender, age and weight subgroups. We then assessed mean values in an external validation cohort (NHANES 2011-14) for performance to predict baseline creatinine in comparison to back calculated MDRD values.

Results: Relative differences between back calculated MDRD and measured creatinine values in the validation cohort show a median bias of +8% and an interquartile precision range of 0% to +26% (Fig 1). Accuracy is rather low, with P15 and P30 values at 42% and 71%. In contrast, our gender/age-based estimation eliminates bias to 0% and improves precision, interquartile range of -6% to +13% (Fig 1). P15 increases to 58%, P30 to 86%. The relative differences show a clear age dependency for MDRD, that is not present in our gender/age-based estimation (Fig 2).

Conclusions: We describe a simple method to estimate missing baseline creatinine values for assessing acute kidney injury. Compared with the current standard approach our method shows no bias, more precision and improved accuracy in predicting baseline creatinine on a population level.

PO0211

Diagnosing and Staging AKI in the Absence of a Baseline Serum Creatinine Value

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Background: AKI is commonly diagnosed and classified from changes to serum creatinine according to the 2012 KDIGO criteria. When baseline creatinine is missing, the guideline recommends to back calculate it from an assumed MDRD-GFR of 75ml/min/1.73m2. We describe an alternative method.

Methods: We describe an alternative method.

Results: Our method shows no bias, more precision and improved accuracy in predicting baseline creatinine on a population level.

Conclusions: Our method shows no bias, more precision and improved accuracy in predicting baseline creatinine on a population level.
PO0213
Phenotyping Inpatient AKI by Serum Creatinine Trajectory
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Background: Clinical guidelines for risk stratification of acute kidney injury (AKI) do not fully consider characteristics of changes in serum creatinine that may be informative for future risk of adverse outcomes. Identification of patient groups that display distinct patterns in trajectory of SC during an AKI may enhance risk stratification.

Methods: Latent trajectory model identified trajectory patterns of SC in a cohort of United States Veterans hospitalized with AKI. Trajectories and outcome profiles were used to establish AKI phenotypes. Risk factors for phenotypes were examined, and phenotype discrimination in short-term outcomes was assessed via-vis KDIGO stages.

Results: In a cohort of 360,560 US Veterans with a hospitalization with an AKI, we identified 6 phenotypes representing distinct patterns in trajectory of SC during hospitalization. Compared to a trajectory with mild changes in SC (59.4% of cohort), moderate (23.1%), and more severe changes (8.7%) with moderate recovery were associated with decreasing odds of non-recovery in SC by discharge (OR=0.52 and 0.23, respectively), and increased odds of mortality (8.0). Phenotype with highly increased SC with incomplete recovery (2.81%), or dynamic change in the first few days of hospitalization (2.15%), were associated with higher odds of AKI in discharge (57.3 and 89.4, respectively) and lower odds of recovery (0.08 and 0.11). A prior history of chronic kidney disease, albuminuria, and prior AKI, as well as major in-hospital events including sepsis, admission to ICU, and mechanical ventilation, were associated with trajectories with worse outcomes. Discrimination in future outcomes during course of hospitalization suggested that as the hospitalization progressed, phenotypes increasingly provided more information on risk of future outcomes (C-statistic: 0.72; recovery: 0.87; KRT: 0.92; 0.62, death) than KDIGO stages (0.62, recovery: 0.75; KRT: 0.59; death).

Conclusions: Our results suggest that leveraging EHR data to profile changes during the occurrence of AKI in kidney function may enhance risk stratification of AKI patients during the course of hospitalization.

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PO0214
Provider Acceptance of Electronic AKI Alerts in a Cardiac Surgery ICU
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Background: Electronic acute kidney injury (AKI) alerts can improve the rates of detection of AKI, though their effect on improving patient outcomes has been variable. Their focused utilization in cardiac surgery patients, a population at high risk for both AKI and its complications, is likely to lead to more consistent improvement in outcomes. We implemented AKI alerts in the cardiac surgery ICU of a tertiary care, high volume cardiac surgery center starting July 2020. As electronic alerts can be disruptive to the workflow and lead to alert fatigue, we surveyed health care providers in our cardiac surgery intensive care unit (ICU) regarding their acceptance of these electronic AKI alerts.

Methods: Our AKI alerts used a previously validated logic to trigger an alert when serum creatinine increase by 0.3mg/dl or more within last 52 hours. They were implemented as passive alerts in the EPIC electronic medical record. Alerts were situated in the EPIC storyboard and provided information in the format “Possible AKI Stage X” with the option to get more information by hovering over the alert. The alerts were set to disappear if no further increase in creatinine by at least 0.3mg/dl was noted in next 52 hours. We emailed a validated survey regarding alert usefulness to providers 6 months after alert implementation to assess their acceptance.

Results: Out of 19 ICU providers (7 intensivists and 12 advanced practice providers) all but one responded to the survey. 7/18 (38.8%) providers reported that they recognized AKI earlier due to the alert. 16/18 (88.9%) shared that they re-dosed or discontinued medications earlier due to the AKI alert. Majority of participants also reported early detection of volume status (72.2%), avoidance of iv contrast use (72.2%) and point of care ultrasound use (77.8%) in response to the alert. 15/18 (83.3%) providers reported satisfaction with the way AKI alerts are displayed and overall satisfaction with the AKI alerts. 16/18 (88.9%) providers reported satisfaction with the duration the alert is displayed for.

Conclusions: Among providers taking care of patients at high risk for AKI, the electronic AKI alert well received. A follow up survey is planned to assess the changes in longitudinal perception of the AKI alert.

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PO0215
Kratom, an Herbal-Induced Cholestatic Liver Failure, Leads to Cholemic Nephropathy Requiring Liver Transplant and Hemodialysis
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Introduction: Kratom, an herbal supplement, has opioid-like and stimulant effects. Its recreational use has increased in the United States (US). Its alkaloid components consist primarily of mitragynine and 7-hydroxymitragynine and are metabolized in the liver. Reports have shown many side effects, notably confusion, seizures, coma, and hyperbilirubinemia. Hepatic injury presents as cholestatic liver injury, which has a consequence on renal function. Patients with hyperbilirubinemia, bile casts damage the nephron directly and is known as bile cast nephropathy, a rare or undiagnosed pathology. We present a case of Kratom usage that play a role in causing cholestatic liver failure, leading to cholemic nephropathy and liver transplant and hemodialysis.

Case Description: A 26-year-old woman with history of Kratom usage presented with complaint of 5-days of abdominal distention and pain, jaundice, and heavy mucosal bleeding. Laboratory testing revealed Na+ 123 mmol/L, BUN 84 mg/dL, Cr 6.9 mg/dL, AST 104, ALT 31, total bilirubin 32 mg/dL and ALP 124 units/L, WBC 27.8, platelets 109, and Hb 7.2 g/dL. There was no serology evidence of viral infection. Tylemol and alcohol level were unremarkable. Urinalysis positive for bile acid cast. Abdominal ultrasound and Computed Tomography findings are consistent with liver cirrhosis. She underwent liver transplantation and required hemodialysis due to acute renal failure from profound hyperbilirubinemia.

Discussion: Bile cast nephropathy represents a wide spectrum of disease, ranging from mild reversible to irreversible needing dialysis. It occurs when total bilirubin levels >20mg/dl, exceeding the binding capacity of albumin to bilirubin. It causes tubular obstruction and injury, oxidative damages, and ATPase activity. Most of the damage occurs in distal tubules but can occur in the proximal tubules. While Kratom has stimulant and opioid-like effects, its use can be harmful to health. There are currently no treatment guidelines for bile cast nephropathy. In irreversible nephropathy in cirrhotic patient, patient may be evaluated for both liver and kidney transplant. Renal replacement therapy has no role in treating bile cast nephropathy in any direct case. It should keep cholemic nephropathy as a differential diagnosis in patient with hyperbilirubinemia and be aware of the increasing consumption of kratom in the US.

PO0216
Dietary Hyperuricemia Causes Nephropathy in a Cancer Patient
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Introduction: Hyperuricemia is associated with several diseases including kidney disease. Everyday drinks (sodas/juices) have very high fructose content, contributing to hyperuricemia through various mechanisms. Here we report a case of a cancer patient with Acute Kidney Injury (AKI) secondary to hyperuricemia in the setting of a sudden high intake in fructose rich drinks.

Case Description: A 49-year-old Asian man with history of myelofibrosis, coronary artery disease and chronic kidney disease stage 2, was admitted for AKI. He was recently admitted for septic shock due to scrotal abscess and discharged to a nursing home for wound care. He endorsed recent high intake of sodas and juices, due to dislike of food at the nursing home. His creatinine at previous admission was 1.1–1.4 mg/dl (similar level to current admission). His urinalysis (UA) routinely did not show uric acid crystals, and uric acid levels were within reference range. One week prior to admission, his creatinine was 1.97 mg/dl and UA showed occasional uric acid crystals. At current admission, creatinine was 3.02 mg/dl with uric acid level of 23.3 mg/dl, and UA showed uric acid crystals. He underwent 3 doses of 3 mg Rasburicase (0 mg total) the first day, after which uric acid level improved to 6.4 mg/dl, and creatinine dropped to 2.14 mg/dl. Three days later his creatinine improved to 1.76 mg/dl, and repeat UA did not show uric acid crystals. A week after discharge, his creatinine was at baseline and uric acid level was normal. By the time visual examination of urine could be done, uric acid level had returned to baseline.

Discussion: It is known that fructose is the only carbohydrate that increases uric acid levels. Fructose-induced hyperuricemia results from an increased degradation of purine ribonucleotides and causes increased purine synthesis. Hyperuricemia is common in patients with hematologic malignancies with or without chemotherapy. Our patient had a hematological malignancy and endorsed drinking large amounts of soda and juice. Given many patients drink fructose rich drinks daily, it is imperative that the dangers of this dietary habit are highlighted, both to physicians and patients. Cancer patients can benefit from nutrition education and dietary modifications prior to and during chemotherapy to reduce hyperuricemia and risk for hyperuricemic nephropathy and help avoid need for hospitalization as well as use of expensive uric acid lowering agents.
PO0217

Turmeric-Associated Oxalate Nephropathy
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Introduction: Turmeric contains Curcumin which has anti-inflammatory properties that may be beneficial in patients with osteoarthritis, hyperlipidemia, pruritus, and Rheumatoid Arthritis. Thus it’s a popular herbal supplement. Here we present a rare case of severe acute kidney injury (AKI) due to calcium oxalate nephropathy in a patient with heavy turmeric consumption.

Case Description: An asymptomatic 69 year male with no significant past medical/surgical history was evaluated for a spike in Creatinine from 1.2 to 3.1mg/dl over a few months. There was no history of drug/NSAID use, contrast exposure, or other nephrotoxins. He did mention taking Turmeric 2g daily for the past 2 years. There was no personal or family history of nephrolithiasis. Urine sediment was bland. Serum C3, C4, ANA, ANCAs, anti-GBM, anti-dsDNA, hepatitis B & C, screen, SPEP&UPEP were negative. Kidney Biopsy revealed widespread calcium oxalate deposition in tubules(Renal Oxalosis-Hyperoxaluria) with diffuse acute tubular injury. Turmeric was discontinued, but the patient soon started on dialysis. 24h urine oxalate was elevated; serum oxalate was also high at 14micromol/L. Genetic testing (AGXT mutation) for primary hyperoxaluria(PH) is pending, but lack of recurrent nephrolithiasis or nephrocalcinosis or systemic oxalate deposition and only marginally high S.oxalate make PH less likely.

Discussion: Although many herbal remedies have shown promising results, these supplements often evade the rigorous standards that conventional therapies are subject to. Turmeric has been studied for its anti-inflammatory & analgesic benefits and recently was publicized as an immunity booster and studied for prophylactic and therapeutic use in COVID. Compelling evidence for its efficacy comes from osteoarthritis trials, but recommendations for safe daily allowances aren’t elucidated. Contrarily, turmeric has been publicized as an immunity booster and studied for prophylactic and therapeutic use. Many herbal supplements often evade the rigorous standards that conventional therapies are subject to.

PO0218

Chronic Tubulointerstitial Nephropathy and Nephrotic Range Proteinuria in a Patient with an Underlying Eating Disorder
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Introduction: Eating disorders in particular anorexia nervosa; binge eating/purging type, have been reported as an established cause of CKD with chronic tubulointerstitial nephritis as a prominent histopathological feature seen on kidney biopsy.

Case Description: A 40-year-old woman with hypertension, generalized anxiety and an eating disorder was referred to our clinic for new onset nephritic range proteinuria and elevated serum creatinine (Scr). Patient endorsed remote NSAID use without any recent use. Physical exam notable for uncontrolled hypertension and bilateral lower extremity edema. Scr was elevated at 2.33 mg/dl, higher than 1.6 mg/dl two months prior to evaluation. Urinalysis showed proteinuria and trace hematuria but was otherwise unremarkable. Spot urine TP/CR was elevated at 9.4 g/mg. Serologic work up including PLAC2R antibody levels, ANA, ANCAs, Hep B surface antigen were negative. Serum immunofixation did not reveal any monoclonal bands. Renal sonogram showed bilateral echogenic kidneys with no renal artery stenosis or hydronephrosis. Of note, patient presented with severe hypokalemia (2.2 mmol/L) and hypomagnesemia (0.8 mg/dl), which were found to be chronic. Electrolyte derangements were attributed to purging disorder in the past, however she adamantly denied active purging or diuretic/ laxative abuse. She also denied taking any herbal medications. A kidney biopsy showed widespread fibrosis and advanced global and segmental glomerulosclerosis (more than 50% of glomeruli) with diffuse chronic tubulointerstitial nephropathy (TIN). The tubules also revealed microscopic dilatation with several simple cysts. CKD and TIN were most likely secondary to underlying eating disorder. Lithium exposure can have a similar pattern on histology, however there was no history of lithium use as confirmed by prior providers. Given the chronicity, she was initiated on dialysis. A Renasight genetic test revealed no genetic abnormalities explaining the renal findings.

Discussion: Diffuse TIN with glomerulosclerosis and widespread fibrosis can be associated with anorexia nervosa. Clinicians should be aware of the potential implications of kidney disease in patients with eating disorders. Early recognition and referral to Nephrologists can help improve outcomes by preventing irreversible kidney damage.
Performance of Validated Indices for Risk of Death for Patients with AKI Requiring Dialysis: A Systematic Review and Meta-Analysis

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Background: Acute kidney injury (AKI) requiring renal replacement therapy (RRT) is associated with high morbidity and mortality. Multiple mortality indices have been developed, however, the most optimal index for predicting survival in AKI requiring RRT is unknown. Objective: To assess performance of validated mortality indices for patients with AKI requiring RRT.

Methods: Design, setting, participants and measurements: Systematic review and meta-analysis following the PRISMA guidelines. Multiple databases (MEDLINE, Embase, Central Register of Controlled Trials, Cochrane, and Scopus) were searched from inception to Jan 31 2019. Selection Criteria: Studies evaluating the performance of validated mortality indices in adult AKI patients requiring RRT were included. Studies not separating AKI patients requiring RRT or used validated indices only as covariates were excluded. Articles were screened and data extracted in duplicate. Risk of bias was assessed using the PROBAST tool. Pre-planned random effects meta-analysis was performed stratified by index, population, renal specific vs. general mortality index, and predictive window.

Results: Of 10,115 articles screened, 37 (2 development, 21 validation and 14 combined) were included totaling 35 different indices tested in 11,142 patients. Average age was 60.8 years with 34.6% women. Predictive windows ranged from ICU to 60-day survival. The most used indices were APACHE II, Liano, SOFA, and SAPS II. Meta-analysis by index showed overall discrimination area under the curve (AUC) of 0.69 (95% CI 0.67–0.71) with high heterogeneity ($I^2$=82.37) with highest AUC for APACHE III (0.73(0.68-0.78) Liano 0.73(0.65-0.78) and MODS 0.71(0.62-0.80).

Conclusions: There is insufficient discrimination and heterogeneity in the performance of prognostic indices for AKI requiring RRT. Additional studies are needed to optimize mortality prediction in this population.

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Risk Factors for AKI in the Intensive Care Unit

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Background: Acute Kidney Injury (AKI) is defined by a sudden decrease in glomerular filtration rate. It currently represents a global public health issue as it is associated with short and long-term morbidity and mortality. In the Intensive Care Unit (ICU) there is an overall incidence of AKI ranging from 20-50% and a mortality rate from 15-60%. Its development leads to increased length of stay and costs. The main objective of this proposed study is to identify risk factors associated with the development of acute kidney injury in a community hospital and a tertiary hospital in Puerto Rico. Also, to investigate if there is a relationship between AKI, length of stay and mortality.

Methods: This retrospective case control study included patients 18 years of age or older admitted to the ICU between January 2015 to December 2016. Patients with chronic kidney disease (CKD) stage 4 or 5, maintenance renal replacement therapy (RRT), or AKI before ICU admission were excluded. The population was divided between patients with AKI and patients without AKI. AKI was diagnosed according to KDIGO criteria. Demographic (age, gender) and clinical data (comorbid conditions, APACHE II score, sepsis or septic shock, vasopressors status, mechanical ventilation, creatinine levels, urine output, nephrotoxic drugs, RRT use, and mortality) was collected from medical records.

Results: Among 121 patients included (median age 54.40, 50% male), 44.6% were diagnosed with AKI and 3.31% underwent RRT. All 7 patients with diagnosed Chronic Obstructive Pulmonary Disease (COPD) had AKI during ICU stay (p-value 0.0024). Diuretics, aminoglycosides, and amphotericin B had a statistically significant relationship with AKI (p-value 0.012, 0.002, and 0.050 respectively). Mechanical ventilation, vasopressor use, sepsis or septic shock and mortality also had a statistically significant relationship with AKI (p-value 0.015, 0.002, 0.018 and <0.0001 respectively).

Conclusions: In our study AKI had a statistically significant association with COPD, diuretics, aminoglycosides, amphotericin B, mechanical ventilation, vasopressors, sepsis or septic shock and mortality. Nephrotoxic agents described as statistically significant are modifiable risk factors to be considered in their administration. This study aids in the characterization of an epidemiologic pattern on ICU patients for future applicability.
Intravenous Administration of Vitamin B Complex Improves Renal Recovery in Patients with AKI
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Background: Preclinical studies have identified NAD+ augmentation as a potential strategy for the prevention and treatment of AKI. NAD+ is the final metabolized form of vitamin B3 (niacin). Since there is no availability of niacin in the country, we tested if I.V. vitamin B complex (vitamin B1, B6 and B12) could improve renal recovery in patients with AKI. By oxidation, vitamin B6 (pyridoxine) through the pathway of pentose phosphate lead to the formation of NADPH an analog of NAD+.

Methods: We conducted randomized, blind, placebo-controlled study in hospitalized patients with AKI (NCT04893733). During the study I.V. vitamin B complex or placebo was given twice a day for 5 consecutive days. For AKI management in each patient, a protocol-based approach was used (STOP AKI protocol from the ISN 0by25 trial https://doi.org/10.1371/journal.pmed.1003408). We evaluated if vitamin B complex could improve renal recovery and if it could reduce de novo CKD incidence or CKD progression.

Results: From September 2020 to May 2021, 191 patients were enrolled in this ongoing RCT with 160 patients completing the follow-up by day 7 and 91 patients completing the follow-up by 3 months. Peak sCr was higher in patients randomized to vitamin B complex (2.8 ± 1.2 vs. 2.2 ± 1.3 mg/dl; p = 0.006). A higher percentage of patients randomized to vitamin B complex arm had severe AKI (stage ≥ 2) 74% vs. 43% randomized to placebo; p = 0.011. The drop in sCr values by day 7 was higher in the vitamin B complex group (1.01 vs. 0.65 mg/dl; p < 0.001). No differences were found in the percentage of patients with complete recovery (54.3% vs. 45.6%; p=0.268), partial recovery (25.9% vs. 25.3%; p=0.930) and non-recovery (19.8% vs. 29.1%; p=0.168). At 3 months, the incidence of de novo CKD and CKD progression was not different in both arms (23.9% vs. 20%; p = 0.652 and 28.2% vs. 26.6%; p = 0.865 respectively). No difference was found in mortality rate at day 90 (vitamin B complex 31.1% vs. placebo 28.2%; p = 0.544).

Conclusions: The administration of vitamin B complex could potentially accelerate renal recovery in patients with AKI by day 7, reducing the percentage of patients who will not recover renal function after an AKI episode. No differences were found in terms of CKD progression or de novo CKD. The preliminary data of our ongoing study warrants future studies to validate these findings.

GDF-15 Predicts In-Hospital Mortality of Critically Ill Patients with AKI Requiring Continuous Renal Replacement Therapy: Results from a Prospective Randomized Controlled Trial
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Background: Growth differentiation factor-15 (GDF-15) is a stress-responsive cytokine that is positively associated with inflammation. This study evaluated the association between GDF-15 and in-hospital mortality among patients with severe acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT).

Methods: Among the multicenter prospective CRRT cohort between 2017 and 2019, 66 patients whose blood sample was available were analyzed. Patients were divided into three groups according to the GDF-15 concentrations. In-hospital mortality was compared using Cox proportional hazards regression model.

Results: The mean age was 67.7 ± 14.3 years and 47 (71.2%) were male. The median GDF-15 level was 7865.5 pg/ml (496.9 pg/ml in the healthy control patients). Baseline characteristics were not different among tertile groups except the severity scores (Acute Physiology and Chronic Health Evaluation II [APACHE II] and Sequential Organ Failure Assessment [SOFA]) and serum lactate level, which were higher in the third tertile. After adjusting for confounding factors, the patients with higher GDF-15 had significantly increased risk of mortality (second tertile: adjusted hazards ratio [aHR], 3.67; 95% confidence interval [CI], 1.05–12.76; P=0.041; third tertile: aHR, 6.81; 95% CI, 1.98–23.44; P=0.002). Furthermore, GDF-15 predicted in-hospital mortality (area under the curve, 0.710; 95% CI, 0.585–0.815) better than APACHE II and SOFA scores (Figure 1).

Conclusions: Serum GDF-15 concentration was elevated in AKI patients requiring CRRT, higher in more severe patients. GDF-15 is a better independent predictor for in-hospital mortality of critically ill AKI patients than the traditional risk scoring system such as APACHE II and SOFA scores.

The Effect on Renal Function and Vascular Decongestion in Type 1 Cardiorenal Syndrome Treated with Two Strategies of Diuretics: A Randomized Trial
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Background: In cardiorenal syndrome 1 (CRS1), is probable that sequential blockage of the renal tubule with combined diuretics (CD) will obtain similar benefits compared with stepped-dose furosemide (SF).

Methods: In a double-blind randomized controlled trial of CRS1 patients were allocated 1:1 to SF or CD. The SF group received a continuous infusion of furosemide 100mg during the first day, with daily incremental doses to 200 mg, 300 mg and 400 mg. The CD group received a combination of diuretics, including 4 consecutive days of oral chlorothalidone 50 mg, spironolactone 50 mg and infusion of furosemide 100 mg. The objectives were to assess renal function recovery and vascular decongestion.

Results: From July 2017 to February 2020, 80 patients were randomized, 40 to SF and 40 to CD group. Groups were similar at baseline and had several very high-risk features. Their mean age 59 ± 14.5 years; 37 were men (46.2%). Primary endpoint occurred in 20% of the SF group and 15.2% of the DC group (p = 0.49). All secondary and exploratory endpoints were similar between groups. Adverse events occurred frequently (85%) with no differences between groups (p = 0.53).

Conclusions: In patients with SCR-1 and a high risk of resistance to diuretics, the use of CD compared to SF offers the same results of renal recovery, diuresis, vascular decongestion and adverse events, and it can be considered an alternative treatment.
Resistance of Sulfur-Containing Amino Acid Intake for Prevention of AKI in Cardiac Surgery: UNICORN, a Randomized, Controlled, Double-Blinded Trial

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Background: Acute kidney injury (AKI) can result in short- and long-term complications and increased mortality. Nonetheless, preventive and therapeutic strategies are lacking. Protein restriction has been shown to protect from organ failure in mice and this protection depended on restriction of sulfur-containing amino acids (SAAs). The UNICORN study aims to evaluate the impact of restricting SAA intake by replacing milk-derived dietary protein by collagen prior to cardiac surgery on AKI.

Methods: In this single-center, randomized, controlled, double-blinded trial 115 patients scheduled for cardiac surgery, were assigned in a 1:1 ratio into a LowS group (SAAs depleted formula diet) or a regular formula diet (control group, CG) for 7 days prior to surgery. The primary endpoint was incidence of AKI within 72 hours after surgery (KDIGO), secondary endpoints included increase of serum creatinine at 24h, 48h and 72h as well as safety parameters. Quantitative variables were analyzed with t-test or nonparametric methods, while categorical variables were evaluated by means of Chi-Square or Fisher’s test.

Results: Baseline characteristics: LowS: n=57, CG: n=58. In the LowS group, there was a greater proportion completing serum creatinine (94% versus 84%) and proteinuria (49% versus 25%) tests within 90-days of hospital discharge. Care in the AKI Follow-up Clinic was associated with changes in care processes and a reduction in major adverse kidney events in comparison to survivors of AKI who received usual care.

Conclusions: In this first-in-humans translational clinical trial, dietary SAA restriction before cardiac surgery did not result in a lower incidence of AKI. However, larger studies are needed to confirm this finding.

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Use of Peritoneal Dialysis for the Treatment of AKI was Associated with Lower Risk for 30-Day All-Cause Mortality During the COVID-19 Surge

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Background: Survivors of AKI are at higher risk of chronic kidney disease and death, but few patients see a nephrologist following hospital discharge. Our objectives were to determine whether an AKI Follow-up Clinic is associated with changes in care processes and a reduction in major adverse kidney events in comparison to survivors of AKI who received usual care.

Methods: We identified patients ≥ 18 years of age who survived a hospitalization with AKI from February 1, 2013 to September 30, 2017 and visited our hospital’s AKI Follow-up Clinic within 6-months of hospital discharge. We used propensity scores to match each patient to 4 patients in the region who received usual care. We randomly assigned the control group index dates to ensure these patients were alive and could have received follow-up care. The primary outcome was time to a major adverse kidney event, defined as death, chronic dialysis, or CKD (newly sustained eGFR < 60mL/min/1.73m2).

Results: We matched 170 AKI Follow-up Clinic patients to 680 patients who received usual care. Approximately 75% in each group had KDIGO stage 2-3 AKI, with similar mean eGFR (SD) at baseline (64.6 [25.1] versus 64.2 [27.2] mL/min/1.73m2) and hospital discharge (49.6 [24.6] versus 49.0 [28.1] mL/min/1.73m2). The AKI Follow-up Clinic group had more nephrology visits per patient-year (1.4 [3.1] versus 0.7 [1.5]), with a greater proportion completing serum creatinine (94% versus 84%) and proteinuria (49% versus 25%) tests within 90-days of hospital discharge. Care in the AKI Follow-up Clinic was not associated with time to a major adverse kidney event (HR=0.90, 95% CI 0.72-1.13), but it was associated with a decreased risk of death (HR=0.55, 95% CI 0.37-0.82).

Conclusions: The AKI Follow-up Clinic was not associated with a decreased risk of major adverse kidney events, possibly due to an increased risk of CKD from more serum creatinine testing. The association with reduced mortality warrants confirmation in randomized controlled trials.

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POO231
Risk Factors for Long-Term Mortality Following AKI
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Background: Acute kidney injury (AKI) occurs in over 20% of hospitalized patients and is associated with increased long-term mortality. The purpose of this study is to identify risk factors for mortality following a hospitalization with AKI in US Veterans.

Methods: AKI was defined as a creatinine increase of ≥0.3 mg/dL at or after admission to a VA hospital between 2013 and 2018. The primary outcome was mortality, with follow-up ranging from 2-7 years. Overall 50 variables were considered for inclusion in the final model, including demographics, comorbidities, and laboratory data. Bootstrap modeling was used to determine the outcomes of one hundred stepwise regressions using random sampling with replacement, and those included in more than 60 of the 100 models were retained in the final model using Cox regression. Given that over a quarter of post-AKI mortality is due to cardiac disease, separate models were constructed for patients with and without pre-existing cardiac disease at baseline.

Results: A total of 241,781 Veterans with AKI were included. There were 47,390 deaths outside of the non-cardiac group, and 54,384 deaths outside of the cardiac group (53%) in the cardiac disease group. The final Cox regression models for each population are given in Table 1. Harrell’s Concordance values were 0.67 and 0.66, respectively. Cardiac comorbidities were major predictors of mortality in the cardiac group. Notably, kidney metrics such as admission creatinine and discharge creatinine were not selected for inclusion, and AKI stage was not a strong predictor in the non-cardiac model where it was included.

Conclusions: We report factors in AKI survivors that predict long-term mortality among US Veterans. Mortality was significantly higher in the cardiovascular disease group, and cardiovascular history was a major risk factor. Variables related to creatinine values or AKI stage were not strong predictors of mortality.

POO233
Reduction of Intraoperative Nephrotoxic Antibiotic Exposure Can Decrease the Severity of Stage of AKI and Improve Renal Recovery in Patients Undergoing Heart Transplantation
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Background: Acute Kidney Injury (AKI) is very common complication post-heart transplant with a reported incidence of approximately 47-76%. Antibiotic combinations, such as piperacillin-tazobactam and vancomycin can cause nephrotoxicity and AKI especially in high doses. The mechanism for this nephrotoxicity is not clear. The purpose of this study was to evaluate the impact of reducing intraoperative nephrotoxic antibiotic exposure on the rate of Acute Kidney Injury and renal recovery in adult patients undergoing heart operation.

Methods: This is a single-center prospective study design of all adult patients undergoing heart transplants at Medical University of South Carolina between 4/12/2015 to 5/1/2020. In 06/2019, as part of a quality improvement effort to reduce our AKI rate, we changed empiric intraoperative antimicrobial coverage from piperacillin-tazobactam to cefepime while continuing vancomycin use. We collected data using the electronic health record. AKI severity and recovery were extracted for patients exposed to piperacillin-tazobactam and vancomycin or cefepime and vancomycin. AKI was identified using KDIGO serum creatinine criteria. Renal recovery was defined as 25% improvement in serum creatinine within 7 days. We assessed rates of nephrotoxic exposure and KDIGO AKI rates in all heart transplant inpatients for at least 4 years pre-intervention and almost 1 year post-intervention.

Results: While the overall rate of AKI remained the same after the intervention, the rates of severe stage 3 AKI decreased by 32%. Recovery of AKI prior to hospital discharge improved 4-fold in the intervention group (24.0% vs 6.0 %, P < 0.05). There was a trend towards less readmissions at 6 months with the intervention group (48.6% vs 65.9%; p = 0.117).

Conclusions: Reduction of nephrotoxic antimicrobial exposure can decrease the severity of heart transplant-related AKI and improve AKI recovery rates.

POO232
The Clinical Characteristics of Inpatients with AKI and the Risk Factors for Progression to CKD
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Background: To explore the incidence of AKI in hospitalized patients and demonstrate the distributions and clinical characteristics of AKI and the risk factors for progression to CKD.

Methods: Medical records of inpatients were acquired from Nanjing Health Information Platform from January 1 to December 31, 2019. A total of 20258 patients with 2 or more serum creatinine records during one single hospitalization were enrolled. Information Platform was used to determine the outcomes of one hundred stepwise regressions using random sampling with replacement, and those included in more than 60 of the 100 models were retained in the final model using Cox regression. Given that over a quarter of post-AKI mortality is due to cardiac disease, separate models were constructed for patients with and without pre-existing cardiac disease at baseline.

Results: A total of 241,781 Veterans with AKI were included. There were 47,390 deaths outside of the non-cardiac group, and 54,384 deaths outside of the cardiac group (53%) in the cardiac disease group. The final Cox regression models for each population are given in Table 1. Harrell’s Concordance values were 0.67 and 0.66, respectively. Cardiac comorbidities were major predictors of mortality in the cardiac group. Notably, kidney metrics such as admission creatinine and discharge creatinine were not selected for inclusion, and AKI stage was not a strong predictor in the non-cardiac model where it was included.

Conclusions: We report factors in AKI survivors that predict long-term mortality among US Veterans. Mortality was significantly higher in the cardiovascular disease group, and cardiovascular history was a major risk factor. Variables related to creatinine values or AKI stage were not strong predictors of mortality.

POO234
Clinical Trajectories of AKI in Hospitalized Patients
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Background: In surgical sepsis patients, AKI trajectory subgroups have unique physiologic signatures of immunologic and endothelial dysfunction, suggesting potential utility for targeted, therapeutic interventions. It is unknown whether the same phenomena occur among all hospitalized patients. Our objectives are to understand the baseline characteristics of patients who will develop distinct AKI trajectories, determine differences in clinical outcomes, resource use, and long-term survival by AKI trajectory groups defined by persistent kidney injury and renal non-recovery on, and assess the relative importance of AKI severity, duration, and recovery on survival.

Methods: We performed a retrospective study of 156,699 patients admitted to a quaternary care academic hospital between January, 2012 and August, 2019. We used Kidney Disease Improving Global Outcomes and Acute Dialysis Quality Initiative criteria to stage AKI and classify patients as having no AKI, rapidly reversed AKI, persistent AKI with recovery, or persistent AKI without renal recovery. Clinical outcomes, resource use, and long-term survival rates were compared among AKI trajectory groups. Cox proportional-hazards regression was used to assess associations between AKI trajectories and time to death while controlling for demographics, Charlson comorbidity score, and provision of mechanical ventilation and ICU admission for two days or greater.

Results: Fifteen percent (54,212/355,678) of the encounters developed AKI. Fifty-eight percent (31,500/54,212) of AKI episodes rapidly reversed within 48 hours; among patients with persistent AKI, two-thirds (14,122/22,712) did not have renal recovery. Multivariable logistic regression was used to analyze the risk factors for the progression of AKI from CKD to a risk predictive model was established accordingly. Results: Among the enrolled patients, 2194 (10.8%) developed AKI in this study. The prevalence of AKI in medical department, surgical department and ICU were 9.1%, 10.5% and 27.9%, respectively. Compared with the non-AKI group, there were more men and elderly in the AKI group. Patients with AKI were more likely to be complicated with diabetes, hypertension, and CKD. The baseline serum creatinine, uric acid, fasting blood glucose and inflammatory biomarker in AKI group were significantly higher than those in non-AKI group. On the contrary, those with AKI had lower blood lipids, albumin and hemoglobin. The presence of AKI predicted a significant increase in hospitalization cost, duration and all-cause mortality. Furthermore, 110 individuals (11.0%) progressed to CKD in the prospective cohort. Age, AKI stage, hypertension, baseline serum creatinine, uric acid, creatinine clearance were independent risk factors for progression to CKD. A risk predictive model of progression from AKI to CKD was established with an area under the ROC curve of 0.822 (95%CI 0.788 – 0.877, P < 0.001).

Conclusions: Age, AKI stage, baseline serum creatinine, hypertension, hyperuricemia and hyperlipidemia were independent risk factors for the progression of CKD in AKI patients. Predictive model established using these variables can help us screen those high-risk populations.

Funding: Government Support - Non-U.S.
PO0235

Incidence and Prognosis of Different Stages of Acute Kidney Disease: A Single-Center Retrospective Cohort Study

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Background: The 16th Acute Disease Quality Initiative (ADQI) recommends that the definitions and staging criteria for acute kidney disease (AKD) be congruent with the stage of AKI. To delineate the prognostic values of the AKD staging system, we constructed a large retrospective cohort and evaluated the disparate outcomes among patients with different stages of AKD.

Methods: This study was a retrospective cohort study including 4,741 adult AKI patients in a single tertiary medical center from 2015 to 2018, with at least 1 serum creatinine measurement between 7 to 90 days after AKI. The 16th ADQI recommendations were used to estimate the proportion of patients at different AKD stages (Figure 1). All patients were followed up for 1 year (study end date, Dec 31st, 2019) to analyze risk factors associated with eGFR decline, initiation of dialysis and in-hospital mortality.

Results: Among the 4,741 AKI patients included in the cohort, AKD stages 1-3 after AKI was common (53% in the CKD group and 51% in the non-CKD group). In the logistic regression model adjusted for demographics and comorbidities and after a 1-year follow-up, AKD stages 1/2/3 (AKD stage 0 as reference group) were associated with higher risks of eGFR decline (AKD stage: Odds ratio, 95% CI, AKD 1: 1.79, 1.47-2.18; AKD 2: 3.23, 2.65-3.94; AKD 3: 5.59, 4.69-6.67). Patients with AKD stages 1/2/3 (AKD stage: Odds ratio, 95% CI, AKD 2: 1.88, 1.39-2.53; AKD 3: 5.59, 4.69-6.67) had a higher discharge Cr, and inpatient nephrology involvement. Most discharge summaries were missing key post-AKI elements, including Cr trajectory and AKI-specific follow-up recommendations, even in patients receiving KRT. These gaps suggest an opportunity exists to improve discharge summary quality and communication post-AKI, especially for patients not assessed by nephrology as inpatients.

Conclusions: Staging criteria for AKD identified AKI patients at higher risk of kidney function decline, dialysis, and mortality. AKI patients with a more severe stage need to receive intensified care.

Funding: Government Support - Non-U.S.

PO0237

Risk of Renal Recovery Post Dialysis-Requiring AKI in Critically Ill Transplant Patients Receiving Calcineurin Inhibitors

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Background: The use of the calcineurin inhibitors has led to major advances in the field of transplantation, with excellent short-term graft outcomes. However, these agents are associated with chronic nephrotoxicity and long-term may lead to ESRD. The purpose of this study was to assess the risk of renal recovery at 3 months in critically ill transplant and non-transplant patients who required continuous renal replacement therapy (CRRT) (AKI-D).

Methods: This is a single center retrospective study aimed to assess differences in renal recovery from AKI-requiring dialysis (AKI-D) in both non-transplant (CNI - patients) and transplant patients taking calcineurin inhibitors (CNI + patients). Our study was undertaken from 02/2017 to 07/2019 at the Medical University of South Carolina, and our analysis included 153 critically ill patients who received CRRT for AKI-D. Non-renal recovery from AKI-D was defined as ESRD as per KDIGO guidelines. We performed a Cox Hazard Risk Model to assess risk of CNI use on renal recovery at 3 months adjusted for transplant status, mortality at 28 or 90 days, age, sex, hypertension, DM, APACHE score and initial number of vasoactive medication used at that time of CRRT initiation.

Results: CNI users had 61% lower risk of developing end stage kidney disease compared to non-CNI users at 90 days (HR 0.49, p = 0.49, CI 0.07 -3.69) although this risk was not statistically significantly. Interestingly, there was a statistically significant lower rate of 28-day and 90-day mortality in the critically ill transplant AKI-D cohort (21% and 37%, p< 0.05) when compared to the critically ill non-transplant AKI-D cohort (57% and 61%, p<0.05, respectively) when compared to the critically ill non-transplant AKI-D cohort (57% and 61%, p<0.05, see figure).

Conclusions: Even in this small retrospective cohort analysis, critically ill AKI-D patients requiring CNI agents did not have a statistically significant higher rate of ESRD despite CNI use and was associated with a lower 28- and 90-day mortality. More research is required to study the relationship between CNI use on renal recovery.

PO0236

The Quality of Discharge Summaries After AKI

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Background: Patients who survive acute kidney injury (AKI) are at increased risk of hospital readmission, chronic kidney disease (CKD), and death. However, most patients are unaware they experienced AKI, emphasizing the importance of high-quality communication between inpatient and outpatient health care providers. Our objectives were to determine how often different elements of AKI were mentioned in discharge summaries and to identify predictors of discharge summary quality after AKI.

Methods: We performed a retrospective chart review of 300 randomly selected discharge summaries from 2015 to 2019. We included 150 hospitalizations before and after introduction of a post-AKI clinic in August 2017, with 50 patients from each Kidney Disease Improving Global Outcomes (KDIGO) AKI stage. We assessed each discharge summary for 10 elements, including AKI course and follow-up recommendations. We used multivariable logistic regression to determine predictors of discharge summary quality.

Results: The median number of AKI elements mentioned was 4/10 (IQR, 2-6). Follow-up with nephrology was documented for 33 (11%) patients. AKI-specific recommendations for labs and medication changes were noted in 66 (22%) and 80 (27%) discharge summaries, respectively. The odds of having a higher quality discharge summary (AKI elements ≥4/10) were greater for every increase in baseline creatinine (Cr) of 25 umol/L (OR, 1.86; 95% CI, 1.42-2.43); intrarenal etiology (OR, 2.33; 95% CI, 1.23-4.41); increased AKI severity (stage 3 or kidney replacement therapy (KRT)) (OR, 6.85 and 4.39; 95% CI, 2.83-16.59 and 1.53-12.58, respectively); inpatient nephrology consultation (OR, 10.53; 95% CI, 4.82-22.98); and discharge Cr ≥a00 above baseline (OR, 4.88; 95% CI, 1.80-13.26). Discharge summary quality did not improve with the introduction of a post-AKI clinic (OR, 0.76; 95% CI, 0.44-1.31).

Conclusions: Overall discharge summary quality in AKI survivors is poor, improving modestly for patients with baseline CKD, intrarenal etiology, severe AKI, higher discharge Cr, and inpatient nephrology involvement. Most discharge summaries are missing key post-AKI elements, including Cr trajectory and AKI-specific follow-up recommendations, even in patients receiving KRT. These gaps suggest an opportunity exists to improve discharge summary quality and communication post-AKI, especially for patients not assessed by nephrology as inpatients.

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PO0238
Outpatient Dialysis Prescription as Predictor and Modifiable Factor for Outcomes of Patients with Dialysis-Requiring AKI
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**Background:** Patients with acute kidney injury requiring hemodialysis (AKI-D) have poor prognosis. Beginning January 1, 2017, End Stage Kidney Disease (ESKD) facilities were allowed to furnish dialysis services to AKI-D patients. Identifying modifiable predictors of AKI outcomes will allow better care of patients with AKI-D.

**Methods:** Patients with AKI-D discharged for outpatient hemodialysis (HID) to one of 11 University of Virginia dialysis units from 1/1/2017 to 12/31/2019 (n=274) were followed for up to 6 months. Multinomial logistic regression was used to estimate association between clinical and dialysis factors and outcomes: recovery (patient off dialysis), ESKD, or death at 3 and 6 months. Dialysis data from the first 28 days were analyzed.

**Results:** Patients were 42% female, 67% Caucasian with mean age 62.8 ± 15.4 years. Comorbidities included diabetes mellitus (42%), hypertension (78%), congestive heart failure (18%), coronary artery disease (27%), prior AKI episode (36%) with pre AKI eGFR 33.8 ± 29.1 ml/min. Median (IQR) number of dialysis sessions was 11 (6–16), lasting 3.6 ± 0.6 hours. Patients declined ESKD had more median drops in blood pressure (BP) (16) than those who recovered (9) or died (10). At 90 days post start of outpatient HID, 45% recovered, 45% were declared ESKD and 9.9% died. Two more patients recovered, 2 patient died with one patient who was initially off HD was declared ESKD by 180 days. Patients with more frequent BP drops had increased odds ratio (OR) of ESKD compared to patients in the lowest quartile. Adjusted odds ratios (95% CIs) for ESKD were 3.8 (1.4 – 9.7, p<0.001) and 2.7 (1.1 – 7.2, p=0.05) for patients in 3rd and 4th quartiles, respectively, adjusting for prior AKI, age, baseline eGFR, hypertension, and UF rate. The magnitude of drop in mean arterial blood pressure was not associated with ESKD or death. Net ultrafiltration (UF) (Liters) and UF rate (ml/kg/hour) were associated with ESKD. OR (95% CIs) 1.6 (1.0 – 2.5, p<0.05) and 1.2 (1.0 – 1.3, P<0.01) respectively.

**Conclusions:** Optimizing dialysis prescription and close monitoring of outpatient dialysis for patients with AKI-D is crucial and may improve outcomes of these patients

PO0239
Exploratory Diagnostic and Prognostic Biomarkers in Adults with Atypical Hemolytic Uremic Syndrome (aHUS): Analysis of the Phase 3 Study of Ravulizumab (NCT02949128)
Tobin J. Cunningham, Katherine Garlo, Ellen E. Millman, Kara Rice, Susan Faas. Alexion Pharmaceuticals Inc, Boston, MA.

**Background:** Validated biomarkers for diagnosis and monitoring of patients with complement-mediated thrombotic microangiopathy (CM-TMA) are not clinically available. Characterization of biomarkers in patients with aHUS, a form of CM-TMA, may inform diagnosis, treatment decisions and monitoring for patients with other types of CM-TMA.

**Methods:** Using data from the phase III study of ravulizumab (terminal C5 complement inhibitor) in adults with aHUS (NCT02949128), baseline (BL; prior to treatment) serum, plasma and urine biomarkers levels in patients were compared with levels in healthy volunteers (HV), and evaluated for associations with kidney function (e.g. estimated glomerular filtration rate [eGFR] and urine protein/creatinine [Cr] ratio [UPCR]) at BL and 26 weeks post-treatment initiation. Regression coefficients and p-values (two-sided t-test) are reported.

**Results:** This analysis included 55 patients: median age 39 (range 19–76) years; 67% female; 53% White, 27% Asian. Specific BL biomarkers were elevated compared with HV, and associations between BL biomarker levels and both BL eGFR and BL UPCR were identified (Table 1). BL plasma complement factor Ba was associated with eGFR changes after 26 weeks of ravulizumab treatment, while urine sC5b-9, sC5b-9/Cr, Ba and Ba/Cr were associated with UPCR changes after 26 weeks of treatment.

**Conclusions:** The complement biomarkers Ba (plasma and urine) and sC5b-9 (urine) were associated with kidney function in patients with aHUS at baseline and over 26 weeks of treatment with anti-C5 therapy. Such biomarkers demonstrate diagnostic potential in CM-TMA and may predict renal response to terminal complement inhibition.

**Funding:** Commercial Support - Alexion Pharmaceuticals

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Table 1: Baseline biomarkers

*compared with observed maximum for HV. **urine sC5b-9 is undetectable in HV, therefore HV values were set at 1/100.

POO11
Urinary Follistatin: A Novel Biomarker for Monitoring the Severity of AKI
Jitendra J. Singh,1 Stuart Singh,2 Michael Lyons, Jennie Z. Ma,1 Daisuke Nagata,1 Hajime Hasegawa,2 Akito Maeshima,1 Richard Lyons,1 Akito Hasegawa,1 Daisuke Nagata,1,2 Richard Lyons,1 Hajime Hasegawa,1 Akito Hasegawa,1 Daisuke Nagata,1,2

**Background:** Activin A, a member of the TGF-beta superfamily, which was absent in normal kidney, was increased in the ischemic rat kidney and negatively regulates the repair process of the kidney after injury. However, the role of follistatin, an endogenous antagonist of activins, in the kidney is unknown. To address this issue, we examined the localization of follistatin in normal and ischemic rat kidney, and measured urinary follistatin in both rats and human with AKI.

**Methods:** Using vascular clamps, renal ischemia was induced for 45 min in 8-week-old male Wistar rats. Localization of follistatin in the kidney and urinary follistatin was examined by immunostaining and ELISA, respectively. Renal tissues of Nephrectomized rat kidney was used as normal human kidney (Approved number A18-150). Patients with AKI (n=98) and healthy adults (n=10) were enrolled in this study (Approved number A18-081 and A18-089). Serum and urinary follistatin was measured by ELISA. Correlations of urinary follistatin with other clinical parameters were analyzed.

**Results:** Follistatin was localized in renal tubules of normal rat kidney. Follistatin-expressing cells were positive for NCC and uromodulin, but were negative for AQP1 or AQP2. In contrast, follistatin expression was increased in the inner medulla of the kidney after renal ischemia. Urinary follistatin, undetectable in normal rats, was significantly increased with a peak at 24 h after renal ischemia. Consistent with normal rat kidney, follistatin was localized in renal tubules of normal human kidney. Urinary follistatin, undetectable in healthy adults, was significantly increased in patients with AKI (0.0 ± 0.0 vs. 43.3 ± 38.0 pg/mL, p<0.05) and was positively correlated with the severity of AKI. Urinary follistatin was significantly increased in patients requiring renal replacement therapy compared to those who did not (911.7 ± 428.3 vs. 94.4 ± 40.0 pg/mL, p=0.05). There was a significant correlation of urinary follistatin with urinary protein, alpha1-microglobulin, NAG, but not with erythropoietin, follistatin.

**Conclusions:** Follistatin, which is localized in the distal tubules of normal kidney, become detectable in the urine of AKI patients. Urinary follistatin may reflect the severity of acute tubular damage.

PO0241
RBT-1 Safety and Cytoprotective Response Biomarkers in Healthy Volunteers and Subjects with CKD
Bhupinder Singh,1 Stuart Goldstein,2 Navdeep Tangri,2 Richard A. Zager,3 1University of California Irvine, Irvine, CA; 2University of Manitoba, Winnipeg, MB, Canada; 3University of Washington, Seattle, WA; 4Cincinnati Children’s Hospital Medical Center, Cincinnati, OH.

**Background:** RBT-1 (stannous protoporphyrin [SnPP] with iron sucrose [FeS]) is a novel drug designed to precondition organs to prevent acute injury via activation of Nrf2, anti-inflammatory, and iron sequestering pathways. Pretreatment with RBT-1 in a novel model of acute kidney injury (AKI) has demonstrated protection from AKI in conjunction with upregulation of cytoprotective proteins. Here, we report results of a Phase 1b study of RBT-1 that assessed safety and cytoprotective response biomarker induction in healthy volunteers and subjects with stage 3 and 4 chronic kidney disease (CKD).

**Methods:** Fifty-four (54) subjects (18 healthy volunteers and 36 subjects with CKD) were enrolled and received a single IV dose of RBT-1 (0, 27, 45, 63, or 90 mg SnPP with 240 mg FeS). Plasma hemoglobin (HbO2), interleukin-10 (IL-10) and ferritin were selected as surrogate measures of organ protective activity. Safety was assessed through Day 29, and cytoprotective response biomarkers were assessed through 168 hours post-dose.

**Funding:** None

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Results: RBT-1 was well tolerated in both healthy volunteers and subjects with CKD. Toxicology and non-clinical adverse event was photosensitivity reaction (a known reaction to SnPP), which occurred in 15 subjects (27.8%) and was more commonly observed in the higher dose groups (63 and 90 mg SnPP/240 mg FeS). Photosensitivity was transient and generally mild in intensity. No serious adverse events were reported. RBT-1 was dose-dependent and, statistically, increased increases in cytoprotective response biomarkers in both healthy volunteers and subjects with CKD. Peak increases from baseline in healthy volunteers and subjects with CKD were: 386% and 402% for HO-1, respectively; 99% and 332% for IL-10, respectively; and 152% and 469% for ferritin, respectively.

Conclusions: RBT-1 is well tolerated with a similar safety profile in healthy volunteers and subjects with CKD Stage 3 or 4 and elicits a biomarker response in humans that is associated with RBT-1-mediated organ protection in animal models of AKI. The positive safety and biomarker efficacy data provided a strong scientific basis to study RBT-1 as an AKI prevention strategy in patients undergoing elective cardiac surgery.

Funding: Commercial Support - Renibus Therapeutics, Inc.

PO0244

Urinary Epidermal Growth Factor and CKD Progression: The ASSESS-AKI Study

Steven Menez,1 Heather Thiessen Philbrook,1 David G. Hu,1 Wassim Obeid,1 Pawan K. Bhattraj,1 Talat Alp Biezler,2 Edward D. Siew,2 Vernon M. Chinchilli,10 Amit X. Garg,3 Alan S. Go,4,5 Kathleen D. Liu,4 James S. Kaufman,6 Paul L. Kimmel,2 Jonathan Himmelfarb,4 Steven G. Coca,4 Chirag R. Parikh,4 ASSESS-AKI Consortium John Hopkins University School of Medicine, Baltimore, MD; Vanderbilt University School of Medicine, Nashville, TN; University of Washington School of Medicine & Dentistry, London, ON, Canada; University of California San Francisco, San Francisco, CA; Kaiser Permanente, Oakland, CA; New York University Grossman School of Medicine, New York, NY; National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD; University of Washington, Seattle, WA; Icahn School of Medicine at Mount Sinai, New York, NY; Penn State College of Medicine, Hershey, PA.

Background: Acute kidney injury (AKI) and chronic kidney disease (CKD) are interconnected syndromes with AKI recognized as a risk factor for CKD incidence or progression. However, biomarkers of repair or resilience, such as epidermal growth factor (EGF), may help inform risk, given the limitations of serum creatinine (sCr) in the setting of AKI.

Methods: We enrolled 1,538 hospitalized patients prospectively in the multicenter Assessment, Serial Evaluation, and Subsequent Sequence of Acute Kidney Injury (ASSESS-AKI) Study. We measured urinary epidermal growth factor (uEGF) from samples at 3 months post-discharge. The primary outcome was a composite of AKI incidence, progression, or development of end-stage kidney disease (ESKD). We also evaluated change in estimated glomerular filtration rate (eGFR) over time by EGF quartile.

Results: 299 (20%) patients developed the primary outcome at a median of 4.3 years follow-up. Patients in the fourth quartile of uEGF had higher eGFR at baseline and at 3-month follow-up compared to those in quartiles 1-3, as well as significantly lower albuminuria. Each 2-fold higher uEGF level was significantly associated with decreased risk of the composite outcome (HR 0.65; 95% CI: 0.59-0.71). This association remained robust after adjustment for demographic factors, baseline kidney function, urinary albumin, and other urinary biomarkers of injury and inflammation (aHR 0.65, 95% CI: 0.54-0.79). Patients in uEGF quartile 1 had the fastest decline in eGFR (-5.6% per year), compared to patients in uEGF quartiles 2-4 (-3.2, -2.8, -2.3% per year, respectively).

Conclusions: Urinary EGF is a marker of repair after kidney injury, and higher levels of albuminuria were associated with reduced risk of CKD and progression to ESKD in hospitalized patients with and without AKI.

Funding: NIDDK Support

PO0243

Serum Renin and Major Adverse Kidney Events in Critically Ill Patients: A Multicenter Prospective Study

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Background: Inflammatory markers of AKI have garnered attention for having potential to be sensitive biomarkers for AKI prognosis. We demonstrated that TH17 cells are increased in ICU patients diagnosed with AKI vs. those without AKI. The main objective of this study was to examine the association of serum IL-17 with mortality and major adverse kidney events (MAKE) in critically ill patients with and without AKI.

Methods: Multicenter prospective study of 299 critically ill patients with AKI stage 2 or 3 and matched healthy controls without AKI. Blood samples were collected within 48 hours after AKI diagnosis (n=153) or within 48 hours of ICU admission in those without AKI (n=146). Serum IL-17a was measured using extremely sensitive ELISA (S-Plex technology, Mesos Scale Discovery). Logistic regression was used to examine the association of IL-17 levels with hospital mortality and MAKE at 90 days post-discharge (composite of death, need of renal replacement therapy or inability to recover at least 70% of baseline eGFR).

Results: Patients in the highest tertile of IL-17 were more severely ill than those in lower tertiles, including more frequent AKI (73% vs. 47% vs. 33.3%, p<0.001), more frequent mechanical ventilation (63% vs. 48% vs. 44.0%, p=0.021), and higher APACHE-II scores (19 vs. 15.5 vs. 14, p=0.001). Moreover, patients in the highest tertile of IL-17 had higher rates of inpatient mortality (26% vs. 8% vs. 9.1%, p<0.001) and MAKE-90. In multivariable models, patients in the highest tertile (vs. lowest tertile) had increased risk of hospital mortality (aOR 2.80, 95%CI 1.09-7.20) and MAKE-90 (aOR 3.51, 95%CI 1.72-7.14). Concordant results were obtained when IL-17 was analyzed as a continuous variable.

Conclusions: Higher levels of IL-17 during acute illness were independently associated with hospital mortality and MAKE-90 in critically ill patients with and without AKI. Further studies are needed to validate the use of IL-17 as a surrogate pathobiologic and prognostic marker in this susceptible population.

Funding: NIDDK Support, Other NIH Support - NHLBI

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**Preoperative Plasma TNFR1, TNFR2, and KIM-1 and Long-Term Adverse Events After Cardiac Surgery: The TRIBE-AKI Study**

George Vasquez-Rios, Dennis G. Molgedina, Eric McArthur, Sherry Mansour, Steven Menz, Heather Thiessen Philbrook, Michael Shilipak, Jay L. Kreymer, Amit G. Parikh, Steven G. Coca, TRIBE-AKI Consortium

**Background:** Detection of abundant “muddy” brown granular casts (MBGC) during microscopic examination of the urinary sediment (MicExU) is pathognomonic of acute tubular injury (ATI). Because hospital laboratories do not optimally report MBGC, nephrologists have to independently perform MicExU. Thus, a diagnostic test to identify MBGC without performance of MicExU/UrSed could be clinically useful. Unlike most AKI biomarker discovery approaches, we hypothesized that MBGC-enriched urinary sediment (MBGC-sedi) contains unique proteins that could serve as biomarkers of ATI.

**Methods:** MicExU/UrSed was performed in specimens from patients with acute kidney injury (AKI) seen for nephrology consultation with a suspected etiology of ATI. Specimens from 3 patients containing numerous MBGC (>10 per low power field in >50% of slide) were collected, subjected to low speed centrifugation (100g), proteolytically digested and analyzed by nano-LC tandem mass spectrometry. Identified proteins were quantified by normalized spectral abundance factor (NSAF). Proteins were identified by Mascot and accepted at <1% false discovery. Presence of proteins in casts was verified by immunofluorescence (IF) and western blotting (WB).

**Results:** A total of 242 proteins were significantly more abundant in MBGC-sedi specimens respect to the supernatant (p<0.05). Among the identified proteins unique to the MBGC-sedi, we selected the dicarbonyl L-xylulose reductase (DCXR) as a candidate ATI biomarker because it was the protein with the lowest p value for MBGC-sedi specificity (p=0.00012, per NSAF) and only identified in MBGC-sedi. To validate the proteomics, in a separate set of MBGC-sedi specimens from patients with AKI due to ATI (n = 10), presence of DCXR was probed by WB and detected in 6 of 7 cases, and DCXR localization within MBGC by IF was verified in 3 of 3 cases.

**Conclusions:** DCXR is abundant in MBGC-sedi and may be a biomarker of ATI as an etiology of AKI. DCXR is an enzyme expressed in the kidney, primarily localized in proximal tubuli, absent in glomeruli. In the cellular level, DCXR is involved in metabolic detoxification and osmotic stress detoxification. We conclude that urinary DCXR is a potential target biomarker molecule for ATI diagnosis.

**Funding:** Other NIH Support - NIH R51DK124846

**Preoperative Biomarkers and Mortality Risk After Cardiac Surgery**

Caroline Liu, Steven Menez, Dennis G. Molgedina, Heather Thiessen Philbrook, Eric McArthur, Wassim Obeid, Sherry Mansour, Amit G. Parikh, Steven G. Coca, TRIBE-AKI Consortium

**Background:** Cardiac surgery patients are at an increased risk for developing adverse outcomes. Preoperative blood and urine biomarkers may help stratify cardiac surgery patients at high risk for mortality.

**Methods:** The TRIBE-AKI study enrolled 1526 patients undergoing cardiac surgery in the USA and Canada from 2007-2010 and was randomly split into a training and test dataset (70:30). A total of 32 plasma and 17 urine biomarkers were measured preoperatively. The primary outcome was 3-year mortality. Random forest (RF) and LASSO logistic regression models were used to identify top biomarkers. Logistic regression models with the highest performing biomarkers and the Society of Thoracic Surgeons (STS) risk calculator were evaluated and the discriminatory ability was assessed in the test dataset.

**Results:** Death by 3 years occurred in 163 of the 1526 (10.7%) patients. LASSO logistic regression models predicted the STS score and 6 plasma biomarkers (Troponin, IL-6, KIM, NT-proBNP, TNFR1, YKL-40). The top 6 biomarkers identified by random forest were plasma KIM-1, TNFR1, eGFR, TNFR2, hsTNT, and urine IL-8. In logistic regression models, the AUC in the test dataset for the STS clinical model was 0.68 (0.61, 0.76) and increased to 0.72 (0.65, 0.79) with the addition of 8 plasma and 2 urine biomarkers (plasma Troponin, IL-6, KIM-1, NT-proBNP, TNFR1, YKL-40, hFABP, TNFR2, and urine IL-8 and albumin; p=0.24).

**Conclusions:** The addition of biomarkers improved discrimination for 3-year mortality prediction minimally beyond clinical characteristics alone. The clinical utility of measurement of biomarkers pre-operatively prior to cardiac surgery is suspect.

**Funding:** NIDDK Support

**Considerations in Controlling for Urine Concentration in Performance of Biomarkers of AKI**


**Background:** Urine biomarkers are often indexed to urine creatinine (Ucr) to control for urine concentration. Whether the biomarker-outcome associations are altered using this or other approaches, such as indexing to urine osmolality (Uosm), in AKI patients has not been examined.

**Methods:** We studied 769 hospitalized patients with AKI enrolled in the multicenter prospective Assessment, Serial Evaluation, and Subsequent Sequelae in Acute Kidney Injury (ASSESS-AKI) Study. Using Cox proportional hazards regression, we assessed urine biomarkers’ associations with a composite outcome of incident chronic kidney disease (CKD) and CKD progression using four approaches to account for urine concentration: indexing to Ucr or Uosm and adjusting for Ucr or Uosm as covariates.
PO0250
CRRT Dose Variation Across Multiple ICUs: A Single-Center Study
Dariusz Liske-Doornandt,1 Keisuke Okamoto,2 Maria C. Browne,1 Ruth C. Campbell,1 Blaithin A. McMahon,3 MUSC Nephrology CRRT QI 1Medical University of South Carolina, Charleston, SC; 2Nara Kenritsu Ika Daigaku Fuzoku Byoin, Kashiwara, Japan.

Background: Continuous Renal Replacement Therapy (CRRT) is increasingly a cornerstone of critical care provision in Intensive Care Units (ICUs) but variation in utilization and differences in culture of practice impact percentage of dose delivered, bearing on outcomes. Efforts to establish timing for initiation, modality, and type of anticoagulation continue, but standardizing local practice may be a more feasible approach to improvement, through establishing standards across units and measuring adherence to those standards.

Methods: Our single center quality improvement study aimed to assess adherence in CRRT utilization, clotting events, percent CRRT dose delivered, and other contributors to differences in CRRT delivery. This initial study is part of a long-term quality improvement project to identify routes to improve CRRT dose delivery and further standardize CRRT modalities best suited to different ICU environments. We tracked “clotting events,” “filter life,” and “percent dose delivered,” to assess unit specific practice patterns and outcomes. Our study was undertaken from 02/2017 to 07/2019, and includes 150 ICU patients who received CRRT across our system’s 5 adult ICUs.

Results: We found CRRT delivery ranging from 92.7% to 96.4% of prescribed dose across our ICUs, with 12,745 hrs of CRRT delivered out of 13,575 hrs CRRT prescribed, and a weighted mean of ~7.8 hrs undelivered CRRT per patient for all patients in the study; ~<0.001 hrs undelivered CRRT/ICU/patient/day. Undelivered CRRT ranged from 3.4 hrs/patient in the Medical ICU to 13.1 hrs/patient in our Cardio Vascular ICU; the use of a smaller French catheter size for the patients on a specialty surgical ICU, and interruptions for surgical procedures, accounted for the greatest deviation from the mean for undelivered CRRT; significant inter-unit variability of delivered CRRT dose per patient was also noted.

Conclusions: Increased clotting events and decreased percent dose delivery were associated with the use of smaller catheters, and significant variation in average undelivered hours of CRRT per patient across units, both of which highlighted the need for shared institutional standards and more frequent measuring of adherence to those standards to improve overall CRRT delivery.

Funding: Clinical Revenue Support
Background: Cefepime can be removed by continuous renal replacement therapy (CRRT) due to its pharmacokinetics. Physiologic alterations in obesity and critical illness commonly impact the pharmacokinetics of antibiotics and may result in suboptimal dosing. The information regarding drug dosing in this population is relatively limited. The objective of our study is to determine the appropriate dosing of cefepime in obese critically ill patients receiving continuous renal replacement therapy (CRRT).

Methods: All necessary pharmacokinetic and pharmacodynamic parameters from obese critically ill patients were obtained to develop one-compartment mathematical models with first-order elimination. Obesity is defined as a body mass index (BMI) greater than 30 kg/m² according to WHO classification. Cefepime concentration-time profiles were calculated to determine the efficacy based on the probability of target attainment (PTA) of both pharmacodynamics targets of 70% T> MIC and 70% T> 4MIC for Gram-negative infections. A group of 10,000 virtual patients was simulated and tested using Monte Carlo simulations for each dose in the models. The optimal dosing regimens or the “successful dose” were defined as the lowest daily dose that achieved target PTA in at least 90% of the virtual patients.

Results: Our results showed the highest FDA-recommended dosing of cefepime to 2000 mg every 8 hours for patients receiving CRRT with an effluent rate of 25 mL/h cannot achieve at least 90% of PTA for Gram-negative infection due to pseudomonas aeruginosa with an MIC of 8 mg/L. In addition, when a higher effluent rate of 35 mL/h and an aggressive pharmacodynamic targets were applied, the % PTA decreased. The survival dose of 12000 mg loading dose on day 1 followed by 2500 mg every 8 hours was far exceeded the maximal FDA-approved doses.

Conclusions: Using cefepime in obese critically ill AKI patients receiving CRRT with traditional dosing of 2000 mg every 8 hours cannot be recommended as an empiric therapy due to suboptimal efficacy. The MIC target and replacement fluid rate directly impact the pharmacodynamic outcome.

PO0254

The Temporal Relationship Between Ultrafiltration and Mortality in Continuous Renal Replacement Therapy

Nathaniel Hocker, Sean Pickthorn, Lewis Mann, Ravi Ravindran, Venkatasubramanian, Meenakshi Samharia, Jonathan Nizar, Benjamin R. Griffin. The University of Iowa Hospitals and Clinics, Iowa City, IA.

Background: In acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT), studies suggest that higher ultrafiltration rate (to a point) is associated with higher mortality, but fluid gain is associated with increased mortality. However, the impact of the timing of net ultrafiltration rate (NUF) on mortality is unknown. Here we evaluated whether the relationship between NUF and mortality is mediated by temporal factors.

Methods: Adults requiring CRRT at the University of Iowa from 2019-2020 were included. Patients were excluded if they survived less than 48 hours on CRRT. Cumulative fluid volume was collected at CRRT initiation and at 24, 48, and 72 hours after initiation. NUF was calculated for each day on therapy by taking the difference in cumulative volume between timepoints and dividing by patient weight. The primary outcome was in-hospital mortality. Covariates were age, gender, BMI, illness severity, CRRT days, volume at CRRT initiation, and comorbidities.

Results: A total of 200 patients met inclusion criteria. Neither NUF from CRRT initiation to 24 hours, nor NUF from 48 to 72 hours, differed significantly between survivors and non-survivors. Strikingly, however, NUF from 24 to 48 hours was strongly statistically associated (Table 1), and remained independently associated after adjustments for covariates.

Conclusions: A temporal relationship was observed between NUF and in-hospital mortality in AKI-CRRT patients. NUF from 24-48 hours was a strong predictor of mortality, but outside of this interval no association was observed. Modern fluid resuscitation strategies emphasize the importance of timing and of appropriate de-resuscitation. A similar paradigm may be advisable in CRRT, but further studies are needed.

Table 1. Net ultrafiltration rate by day in survivors and non-survivors

<table>
<thead>
<tr>
<th>NUF Category</th>
<th>Survival (n=73)</th>
<th>MUF (n=127)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NUF &lt; median</td>
<td>14 (19%)</td>
<td>27 (21%)</td>
<td>0.022</td>
</tr>
<tr>
<td>NUF &gt; median</td>
<td>59 (81%)</td>
<td>97 (79%)</td>
<td></td>
</tr>
</tbody>
</table>

* By convention, positive NUF means greater fluid loss, and negative NUF mean an overall fluid gain; NUF = net ultrafiltration.

PO0255

Kinetic Estimated Glomerular Filtration Rate May Be a Useful Tool to Guide Hemodialysis Discontinuation


Background: There are no objective criteria for the discontinuation of renal replacement therapy (RRT) in patients who have acute kidney injury (AKI). It is unknown if Kinetic Estimated Glomerular Filtration Rate (KeGFR) can be used as assessment of renal recovery in patients who underwent RRT.

Methods: All critical patients in the Hospital das Clínicas during September 2020 to May 2021 who started hemodialysis due to AKI and remained free of RRT for at least 2 consecutive days were included. Patients who stopped RRT due to decision for exclusive palliative care or hemodynamic instability were excluded. Patients were divided in two groups: Success group (free from RRT for 7 consecutive days after their last RRT session) and failure group. Discontinuation day was defined as the second day without RRT. Variables were expressed as median (25th and 75th percentile) and categorical data as percentage. Mann Whitney test was used. Statistical significance was defined as p<0.05.

Results: 72 patients were enrolled. COVID19, ischemia-reperfusion and sepsis were the main causes of AKI (57%; 28.7%; 24.6%, respectively), with no difference in prevalence between groups. Success group (n=47) presented higher KeGFR on the day of discontinuation (keGFR1) and in the day after (keGFR2) when compared to failure group (n=25): KeGFR1: Success: 18.76ml/min vs. failure: 10.21ml/min, p=0.05. KeGFR2: Success: 29.38ml/min vs. failure: 16.03ml/min, p<0.05. Success group had lower non-

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO0256

Survival Comparison Between Continuous Venovenous Hemodiafiltration (CVVHDF) and Continuous Venovenous Hemofiltration (CVVH) for Septic AKI

Mun Jaeg. Yemidam Hospital, Cheonju, Republic of Korea.

Background: The mortality rate of septic acute kidney injury (AKI) remains high despite improvements in renal replacement technology. Adding dialysis to continuous veno-venous hemofiltration (CVVH) can increase survival in these patients, although hemodiafiltration leads to better clearance of inflammatory mediators in sepsis than hemodialysis. We tested whether continuous veno-venous hemodiafiltration (CVVHDF) is more effective than CVVH with the same net effluent according to body weight in intensive care unit (ICU) patients with septic AKI.

Methods: CVVHDF was performed using a Prismaflex (Baxter International, Deerfield, IL, USA) with a blood flow rate (BFR) of 150 ml/min at a dialysate flow rate of 20 ml/kg/hour, in addition to a replacement fluid flow rate of 20 ml/kg/hour. In contrast, the replacement fluid flow rate of CVVH was 40 ml/kg/hour. The patient’s removal rate was individually adjusted by attending staff based on clinical status.

Results: In this prospective randomized pilot study, 100 patients were assigned to CVVH (n=47, M:F=25:22, age 64±15 years) or CVVHDF (n=53, M:F=30:19, age 65±11 years). Baseline characteristics including age, sex, body weight, serum creatinine, blood urea nitrogen (BUN), beta-2 microglobulin, Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores did not vary between the two groups. There were no significant differences in the reduction ratios of serum creatinine, BUN, beta-2 microglobulin, APACHE II and SOFA scores between the two groups. Seven-, 28-, and 60-day survival also did not vary.

Conclusions: In conclusion, CVVH and CVVHDF led to similar clearance of waste products and survival at the same net effluent in this study. Future large-scale randomized prospective studies will be needed to confirm these results in critically ill patients with septic AKI.

Outcomes by treatment groups

<table>
<thead>
<tr>
<th>Total CRRT days</th>
<th>CVVH group</th>
<th>CVVHDF group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total ICU days</td>
<td>15 ± 15</td>
<td>15 ± 15</td>
<td>0.96</td>
</tr>
<tr>
<td>Renal response at hospital discharge (%)</td>
<td>35</td>
<td>28</td>
<td>0.32</td>
</tr>
<tr>
<td>Survival (%)</td>
<td>67%</td>
<td>70%</td>
<td>0.82</td>
</tr>
<tr>
<td>7 days</td>
<td>67%</td>
<td>67%</td>
<td>1.00</td>
</tr>
<tr>
<td>28 days</td>
<td>40%</td>
<td>40%</td>
<td>1.00</td>
</tr>
<tr>
<td>60 days</td>
<td>26%</td>
<td>25%</td>
<td>0.64</td>
</tr>
</tbody>
</table>

CRRT, continuous renal replacement therapy; CVVHDF, continuous veno-venous hemodiafiltration; CVVHF, continuous veno-venous hemofiltration; ICU, intensive care unit.

PO0257

Systematic Review of the Effects of High-Volume High-Flow (HVHF) in Pediatric Sepsis

Rupesh Raina,1,2 Ronith Chakraborty,1 Siddhartha S. Singh,1 Nikhil Nair,1 Cleveland Clinic, Akron, OH; Akron Children’s Hospital, Akron, OH.

Background: Pediatric sepsis is a significant public health issue. This condition is exacerbated by the presence of excess serum creatinine and inflammatory cytokines that lead to deleterious effects upon the body. The current standard of care involves the use of continuous kidney replacement therapy to remove harmful cytokines until the body returns to homeostasis. In order to promote faster clearance and reduced stay in the ICU, high volume high flow has been posited as a potential new modality of choice. However, there is a paucity of studies to fully elucidate its benefits.

Methods: A literature search was done using PubMed/Medline and Embase. Keywords used while conducting the literature search were, “hemofiltration OR haemofiltration OR hemodiafiltration” AND “high-volume”. The literature was reviewed by two independent reviewers, who independently assessed the quality of randomized controlled trials by using the Cochrane risk of bias tool for RCTs. The Newcastle Ottawa Scale (NOS) for assessing the quality of non-randomized controlled trials. Data was combined from studies with similar design.

Results: The primary endpoint of all cause mortality was found to be reduced by 40% across all of the pooled studies. For secondary endpoints, significant reductions of serum creatinine were found after 24 and 48 hours of use compared to the current standard of care. Additionally, duration of ICU stay and treatment course was found to be significantly shorter in HVHF patients than the current standard of care. Finally the rate of adverse effects were analyzed and there was no difference in the proportion of patients developing hypokalemia, hyperkalemia, hypernatremia or hyponatremia. The proportion of patients developing hyperglycemia was higher in patients undergoing HVHF whereas hyperglycemia was significantly less in patients undergoing HVHF. One study reported a total number of adverse events between the two groups which were significantly lesser in patients undergoing HVHF.

Conclusions: HVHF shows promise as a modality to treat pediatric patients with sepsis. In order to confirm the benefits of this modality, future studies need significantly more patients for analysis.

PO0258

AKI and Hospital-Acquired Sepsis in Critically Ill Children: A Retrospective Single-Center Study

Cassandra L. Fornecke,1,2 Robert Feldman,1 Andrew D. Althouse,1 John A. Kellum.1,3 1University of Pittsburgh School of Medicine, Pittsburgh, PA; 2Children’s Hospital of Pittsburgh of UPMC, Pittsburgh, PA; 3University of Pittsburgh Medical Center, Pittsburgh, PA.

Background: Acute kidney injury (AKI) is common among critically ill children and is associated with an increased risk for de novo infection, however little is known about the temporal relationship between AKI and risk for subsequent infection. The objective of this study was to describe the risk of developing hospital-acquired sepsis over time following AKI onset.

Methods: We conducted a single-center retrospective cohort study of critically ill children admitted to the pediatric and cardiac ICUs at a tertiary pediatric care center in the United States. The cohort included children, ages birth to 18 years, without a diagnosis of chronic kidney disease, primary immunodeficiency, or sepsis within the first 48 hours of hospital admission. The relationship between the primary exposure (AKI) and primary outcome (development of hospital-acquired sepsis) was assessed using Cox proportional-hazards models using AKI as a time-varying covariate.

Results: Among the 5695 children included in the study, hospital-acquired sepsis was more common in the 1153 children that developed AKI (n=117, 10.7%) than in the 4542 children that did not develop AKI (n=210, 4.6%). Over a median follow-up of 3.1 days, the development of AKI was associated with an increased risk for development of hospital-acquired sepsis with an adjusted HR of 1.41 (95% CI 1.11-1.80, p=0.005). The median time from AKI onset to sepsis was 2.6 days (IQR 1.5 – 4.7). Among the 117 children who developed hospital-acquired sepsis following AKI (from 48 hours after hospital admission through hospital discharge or 30 days), 80.3% of children developed sepsis within 7 days and 96.6% within 14 days of AKI onset.

Conclusions: AKI is an independent risk factor for de novo infection. Children with AKI are at highest risk for developing hospital-acquired sepsis within 14 days following AKI onset.
**PO0259**

**Disseminated Intravascular Coagulation Is Associated with AKI in Pediatric Severe Sepsis**

Ayse Akan Arikan,1,2 Michael P. Smaglick,1 Vinod Vijayan,1 Curtis E. Kennedy,2 Brady S. Moffett,3 Poyyapakkam Srivaths,1 Trung C. Nguyen,1 Baylor College of Medicine, Houston, TX; 2Texas Children’s Hospital, Houston, TX; 3Texas Children’s Hospital, Houston, TX.

**Background:** Exact mechanism of pediatric septic acute kidney injury (AKI) remains unknown. Coagulation perturbations like disseminated intravascular coagulation (DIC) are frequent in sepsis and associated with organ dysfunction. The link between DIC and septic AKI has not been adequately explored in pediatric patients.

**Methods:** Single center cohort study of pediatric patients with severe sepsis Jan 2017-Apr 2018. Primary outcome was AKI (per Kidney Disease Improving Global Outcomes criteria), primary exposure was DIC (per International Society of Thrombosis and Haemostasis criteria).

**Results:** 287 patients were enrolled, median age 7.3 (IQR 1.6-14.5) years; 58% had AKI, 34% had DIC. Pediatric risk of mortality score was 8 (IQR 4-13), 57% were mechanically ventilated and 67% were on vasopressors. DIC prevalence was 52% in AKI vs 19% in no AKI pts (p<0.001). DIC score was higher in AKI (4,27 (IQR3.85-4.67) vs 2.25 (IQR1.92-2.58) in no AKI (p<0.001)). In adjusted analysis controlling for severity of illness, mechanical ventilation, and vasopressor use, DIC presence (aOR 2.6 (95%CI 1.45-4.67)) and DIC score (aOR 1.33 (95% CI 1.17-1.51)) were both independently associated with AKI.

**Conclusions:** DIC is very common in pediatric septic AKI. Severity and presence of DIC are both independently associated with septic AKI. Mechanistic contribution of coagulation perturbations to septic AKI and identification of potential modifiable factors require further study.

**PO0260**

**Midterm Renal Outcomes and Renal Recovery in Pediatric Continuous Renal Replacement Therapy**

Saner Thadani,1 Dana Y. Fuhrman,1 Claire Hanson,1 Joseph A. Carcillo,3 Poyyapakkam Srivaths,1 Ayse Akan Arikan,1,2 Baylor College of Medicine, Houston, TX; Texas Children’s Hospital, Houston, TX; University of Pittsburgh, Pittsburgh, PA.

**Background:** Most pediatric continuous renal replacement therapy (CRRT) outcome studies focus on crude mortality. Recent data highlighted incomplete recovery and dialysis dependency in pediatric acute kidney injury treated with dialysis. We described midterm outcomes and renal recovery in pediatric CRRT.

**Methods:** Multicenter cohort study between 2/14-2/20. Primary outcome was Major Adverse Kidney Events at 90 days (MAKE90), secondary outcome was renal recovery (noMAKE90 in survivors).

**Results:** 419 patients received CRRT for 9 days (IQR3-21) (age 93 mo (17-180), 51% male). PELOD2 was 9(7-14), 55% were ventilated, 67% were on vasoactives. 276 (66%) patients had MAKE90 (61% dead, 21% dialysis dependent, 18% persistent renal dysfunction). ICU admission reason, peak mean airway pressure, thrombocytopenia, and leukopenia were associated with MAKE90. Urine output at CRRT start was independently associated with renal recovery. Each ml/kg/h was associated with 47% (95%CI 12-235%) increase in odds of renal recovery.

**Conclusions:** Majority of pediatric CRRT patients develop MAKE90. Worse lung disease requiring higher respiratory support is independently associated with MAKE90, while admissions for metabolic/endocrine reasons are more likely to survive with intact renal function. Urine output at CRRT start is an independent predictor of renal recovery among pediatric CRRT survivors.

MAKE90 and Renal Recovery In Survivors

<table>
<thead>
<tr>
<th>MAKE90</th>
<th>Covariate</th>
<th>Uncorrelated OR</th>
<th>Adjusted OR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.0</td>
<td>0.99-1.01</td>
<td>1.00-1.01</td>
<td></td>
</tr>
<tr>
<td>FELOD-2</td>
<td>0.99</td>
<td>0.97-1.02</td>
<td>0.98-1.01</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia (&lt;100k)</td>
<td>2.6</td>
<td>1.31-5.38</td>
<td>2.60-5.21</td>
<td></td>
</tr>
<tr>
<td>Leukopenia (≤4 x 10^9/l)</td>
<td>2.60</td>
<td>1.37-5.32</td>
<td>1.35-5.31</td>
<td></td>
</tr>
<tr>
<td>Mean airway pressure on CRRT</td>
<td>1.16</td>
<td>1.06-1.27</td>
<td>1.15-1.26</td>
<td></td>
</tr>
<tr>
<td>ICU admissions</td>
<td>0.22</td>
<td>0.85-0.48</td>
<td>0.10-0.42</td>
<td></td>
</tr>
<tr>
<td>ICU admission</td>
<td>0.50</td>
<td>1.45-2.57</td>
<td>1.32-1.80</td>
<td></td>
</tr>
</tbody>
</table>

*All controlled for each other

**PO0261**

**AKI and Mortality in Patients Prescribed Immune Checkpoint Inhibitor Therapy**

Megan L. Baker,1 Yu Yamamoto,1 Mark A. Perazella,1 Chirag R. Parikh,2 Francis P. Wilson,1 Dennis G. Moledina,3 Yale University Department of Internal Medicine, New Haven, CT; 3Johns Hopkins Medicine, Baltimore, MD.

**Background:** In patients on immune checkpoint inhibitor (ICI) therapy, acute kidney injury (AKI) is relatively common, and can occur from tubular injury or pre-renal azotemia unrelated to ICI use, or from off-target immune activation resulting in acute interstitial nephritis (AIN). The association of AKI and its specific etiologies with mortality is not known.

**Methods:** In participants initiated on ICI between 2013-2019, we tested the association of serum creatinine-based AKI with mortality up to 1 year after therapy initiation using Cox proportional hazard models controlling for demographics, comorbidities, cancer type, severity, therapy, and baseline laboratory values. In patients with AKI, we tested the association of AKI severity, AKI duration, and, using a validated risk score, AIN risk with mortality.

**Results:** Of 2,207 patients initiated on ICI therapy, 549 (25%) developed AKI. Mortality rate was higher in those who developed AKI (905 vs. 445 per 1000 person-years). AKI was independently associated with higher mortality [adjusted HR, 2.18 (95% CI, 1.38-3.45)] and this hazard was highest in the first month after AKI [9.7 (7.8-12.1)] and progressively diminished to the background rate by four months. Among patients with AKI, mortality was higher in those with severe AKI [2.03 (1.01-4.11)] and longer duration AKI [2.58 (1.01-6.60)], but lower in those with the highest likelihood of AIN [adjusted HR highest vs. lowest tertile, 0.07 (0.02-0.29)].

**Conclusions:** We noted that occurrence of AKI was independently associated with higher mortality in patients treated with ICI. Among patients with AKI, mortality was higher in those with severe AKI and longer duration AKI, but lower in those with features suggestive of AIN.

**Funding:** Other NIH Support - R01DK113191, R01DK128087, P30DK079310, and K23DK117065

**PO0262**

**Sodium-Glucose Cotransporter 2 Inhibitors and the Risk of AKI in Older Adults With Type 2 Diabetes**

Min Zhuo,1,2 Julie M. Paik,1,2 Deborah J. Wexler,4 Joseph V. Bonventre,1,2 Seoyoung C. Kim,3 Elisabetta Patorno,1,2 Beth Israel Deaconess Medical Center, Boston, MA; 3Brigham and Women’s Hospital Department of Medicine, Boston, MA; 4VA New England Geriatric Research Education and Clinical Center, Boston, MA; 5Massachusetts General Hospital, Boston, MA.

**Background:** We compared the association of AKI with the initiation of a sodium-glucose cotransporter-2 inhibitors (SGLT-2i) to the initiation of a dipeptidyl peptidase 4 inhibitor (DPP-4i) or a glucagon-like peptide 1 receptor agonist (GLP-1RA) in adults aged ≥ 66 years with type 2 diabetes (T2D).

**Methods:** In this nationwide cohort study, we used Medicare fee-for-service from 2013 to 2017 to identify older adults with T2D. SGLT-2i initiators were 1:1 propensity score (PS)-matched to DPP-4i or GLP-1RA initiators, in two pairwise comparisons. More than 100 variables were used in the PS model, including demographic characteristics, comorbid conditions, medication use, and health care utilization. The primary outcome was a hospital discharge diagnosis of AKI in the primary or secondary position. Cox proportional hazards regression models were used to generate hazard ratios (HRs) in PS-matched groups.
Results: A total of 68,130 and 71,477 SGLT-2i new users were PS-matched to new users of DPP-4i or GLP-1RA (Table), respectively. The risk of AKI was lower in the SGLT-2i group than the DPP-4i group (HR 0.71, 95% CI 0.65-0.76) or the GLP-1RA group (HR 0.81, 95% CI 0.75-0.87), over a median follow-up of 181 days.

Conclusions: Among older adults with T2D, initiating an SGLT-2i was associated with a reduced risk of AKI compared to initiation of a DPP-4i or GLP-1RA.

Table. Selected baseline characteristics of SGLT-2i versus DPP-4i and SGLT-2i versus GLP-1RA cohorts after PS-matching

Characteristics were measured during the 365 days before treatment initiation, standardized differences < 0.1

PO0263
Urine Sediment Examination: Comparison Between Laboratory-Performed vs. Nephrologist-Performed Microscopy
Adam Fawaz,1 Elias Bassil,1 James F. Simon,1 Susana Arrigain,1 Jesse D. Schold,2 Remy Daou,3 Ali Mehdi,4 Jonathan J. Taliercio,5 Georges Nakhoul,6 Cleveland Clinic, Cleveland, OH; 7Universite Saint-Joseph, Beirut, Lebanon.

Background: Urinalysis is a commonly performed diagnostic test in clinical laboratories and automated urine technology is becoming the standard for providing urinalysis data to clinicians. Time constraints, and automated technology has resulted in clinicians no longer performing their own urine sediment exam. We believe that there is a critical value in performing this important unappreciated skill to improve patient care.

Methods: Using our Electronic Medical Records, we identified 140 adult in-patients with acute kidney failure that had urine microscopy with sediment analysis performed both by the laboratory and by a nephrologist within 72 hours of each other. We performed a chart review to determine the following: number of RBCs (≤ 5 or > 5 HPF), number of WBCs (≤ 5 or > 5 HPF), presence of casts (<1 or ≥1 LPF), type of casts (hyaline, fine granular, coarse granular, muddy brown, WBC casts, RBC casts and mixed cellular casts), and presence of dysmorphic RBCs. We used Kappa statistics to evaluate agreement between urine microscopy by lab versus by nephrologist reviews.

Results: The reported agreement was moderate for RBCs with 79% of samples in agreement (Kappa 0.54 – 95% CI 0.39, 0.69), fair for WBCs with 74% of samples in agreement (Kappa 0.39 – 95% CI 0.23, 0.54), and there was no agreement for casts (Kappa 0.0). Nephrologist detected 8 dysmorphic RBC’s (Kappa 0) while the laboratory did not detect any. Additionally, the laboratory only detected hyaline and fine granular casts, while the nephrologist reported coarse Granular / muddy brown casts, RBC and WBC casts.

Conclusions: Urine sediment exam is an important procedure that provides evaluative information about kidney disease. In our study, we report a disagreement between laboratory vs. nephrologist performed analysis, notably for the recognition of structures that can provide important information in the diagnosis of acute tubular ischemia and glomerulonephritis. This highlights the importance of clinicians continuing to perform sediment exam.

PO0264
Accuracy of Nephrologist Performed Urine Microscopy in Predicting Pathologic Diagnosis in Patients with AKI
Adam Fawaz,1 Elias Bassil,1 James F. Simon,1 Susana Arrigain,1 Jesse D. Schold,2 Remy Daou,3 Ali Mehdi,4 Georges Nakhoul,6 Cleveland Clinic, Cleveland, OH; 7Universite Saint-Joseph, Beirut, Lebanon.

Background: Urinalysis is a commonly performed diagnostic test in clinical laboratories and automated urine technology is becoming the standard for providing urinalysis data to clinicians. Time constraints, and automated technology has resulted in a decline in clinicians performing their own urine sediment exam. We hereby look at the diagnostic accuracy of sediment suggested diagnoses in predicting the respective pathologic diagnoses.

Methods: Using our Electronic Medical Records, we identified 33 adult patients with acute kidney injury with documented nephrologist performed urine microscopy and a kidney biopsy within one week of the sediment analysis. We performed chart review to ascertain the analysis based on urine sediment exam and compared it to the respective pathologic diagnoses

Results: The cohort demographics consisted of 18 (54.5%) male patients, 23 whites (69.7%), and a mean age of 56.6 years. Sediment analyses was bland in 6 patients (8.45%) with 5 (71.4%) sATI, 22 (66.67%) sGN, and no sAIN cases. All 5 cases with sATI on sediment analysis showed ATI on the kidney biopsy. Similarly, all 22 cases with sGN on the sediment had a pathologic diagnosis consistent with GN on the biopsy. Of the 6 patients with bland sediment analyses, 3 showed ATN pathologically while the other 3 had GN on the kidney biopsy.

Conclusions: Urine sediment examination remains an important test than can provide important information about kidney disease. Our data shows 100% agreement between sediment analyses suggestive of ATI or GN and the pathologic diagnoses. This is important in patients in whom a kidney biopsy might be contraindicated precluding the luxury of a pathologic diagnosis. While a suggestive sediment analysis seems to carry a high predictive value, the negative predictive value of a bland sediment was low however.

Overall, we believe urine sediment analysis is an important skill for the nephrologist with important patient care implications.

PO0265
Histopathological Confirmation of Acute Tubular Injury in Patients with “Muddy Brown” Granular Casts in the Urinary Sediment
Vinip Varghese,1 Akankan Vamanan,1 Jean Carlos Q. Velez, Department of Nephrology, Ochsner Clinic Foundation, New Orleans, LA.

Background: Microscopic examination of the urinary sediment (MicrExUrSed) can be a useful tool in the differentiation of acute kidney injury etiology. In particular, “muddy brown” granular casts (MBGC) are thought to be pathognomonic for acute tubular injury (ATI). However, the ability of MBGC to predict biopsy-proven ATI has not been formally examined. Thus, we hypothesized that the identification of MBGC by MicrExUrSed can accurately predict a histopathological diagnosis of ATI.

Methods: In a single-center prospective study, we selected cases of patients seen in nephrology consultation who had a urine specimen subjected to MicrExUrSed as part of the clinical evaluation. Within this cohort, we identified cases in which a kidney biopsy was performed within 2 weeks of the MicrExUrSed. Presence of MBGC in those cases was determined. We assessed the performance of identification of MBGC for the diagnosis of biopsy-proven ATI. Sensitivity, specificity, negative predictive values (NPV), and positive predictive values (PPV) of MBGC to diagnose ATI were determined.

Results: Among 371 patients in whom MicrExUrSed was completed, 49 underwent kidney biopsy and were included. Mean age was 61 years, 38% were women. White race accounted for 59% and black race accounted for 33%. Mean serum creatinine was 1.4 mg/dL. Biopsy diagnosis was ATI in 36 (73%) and non-ATI in 13 (27%). Among the 36 cases of biopsy-proven ATI, concomitant glomerular pathology was present in 19 (53%). The sensitivity of MBGC for biopsy-proven ATI diagnosis was 78% (95% CI 61-90%), while the specificity was 100% (95% CI 75-100%). The PPV of MBGC for ATI diagnosis was 100% (95% CI 100%) and the NPV was 62% (95% CI 47-93%).

Conclusions: Our data demonstrate that MBGC on MicrExUrSed are pathognomonic for ATI confirmed by kidney biopsy – with high PPV and specificity of 100%. While MBGC reflect ATI, concomitant glomerular pathology can be present in patients with MBGC in the urine sediment.

PO0266
Feasibility of Point-of-Care Solid Organ Doppler for Assessing Emergency Department Patients with AKI
Forrest F. Lindsay-McGinn, Christy Moore, Jeffrey A. Kramer, Nova Panebianco, Felice Teran, Nathaniel C. Reisinger. University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.

Background: Acute kidney injury (AKI) in the emergency department (ED) portends worse in-hospital outcomes for patients. Point-of-care ultrasound (POCUS) can assist with volume assessment, which is critical to diagnose the underlying cause of AKI.

We describe clinical and ultrasonographic characteristics of patients with AKI using a
Addition of High-Dose Furosemide to Norepinephrine During Treatment of Acute Kidney Injury (AKI): Clinical, Outcomes, and Trials

PO0267

Utility of a Point-of-Care Ultrasound Volume Assessment for Emergency Department Patients with AKI: A Pilot Study

Forrest F. Lindsay-McGinn, Christy Moore, Jeffrey A. Kramer, Nova Panebianco, Felipe Teran, Nathaniel C. Reisinger. University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.

Background: Acute kidney injury (AKI) identified in the emergency department (ED) portends worse in-hospital outcomes for patients. Point-of-care ultrasound (POCUS) for AKI is recommended to rule out obstructive uropathy but does not routinely include volume assessment, which may be informative regarding the underlying cause of AKI. POCUS evaluation of heart and lungs has proven to be useful in assessing intravascular volume status in patients on dialysis and with heart failure. This study aims to describe the clinical and ultrasonographic characteristics of patients with AKI using a POCUS volume assessment.

Methods: This is a prospective convenience sample of adult patients presenting to an academic, urban ED found to have AKI from September 2020 to May 2021. Ultrasounds were performed using a 5-point lung, 5-point cardiac, kidney and bladder views. The diagnosis of AKI was established by Kidney Disease Improving Global Outcomes (KDIGO) criteria. US images were obtained and interpreted by an US fellowship trained emergency medicine physician. The institutional review board approved this study.

Results: Thirty-seven patients were included. 22 were African American and 20 were male. Median age was 63 and average BMI was 29. 15 experienced stage 1 AKI, 5 had stage 2 AKI, 17 had stage 3 AKI. 7 required dialysis. We assessed the change in urine output (UOP) and the trajectory of serum creatinine (sCr) values before and after the initiation of NE and before and after the addition of FURO.

Conclusion: Our study describes the findings of a POCUS volume assessment of ED patients with AKI. Abnormal cardiac and lung findings were common and may be a useful adjunct to IVC, kidney and bladder assessment alone.

PO0268

Addition of High-Dose Furosemide to Norepinephrine During Treatment of Hepatorenal Syndrome Type 1 Increases Diuresis and Does Not Halt Kidney Function Recovery

Kasra Tayebi,1 Juan Carlos Q. Velez,1 Ochsner Medical Center - New Orleans, New Orleans, LA; 2University of Arkansas for Medical Sciences, Little Rock, AR; 3The University of Queensland Ochsner Clinical School New Orleans, New Orleans, LA.

Background: Decongestion is an important goal in the management of acute heart failure (HF) among patients with heart failure with reduced ejection fraction (HFrEF), but whether the rate of decongestion is associated with cardiovascular (CVD) outcomes remains unknown.

Methods: Using data from the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) trial, we used multivariable Cox regression models to evaluate the association between the rate of in-hospital change in assessments of volume overload, including b-type natriuretic peptide (BNP), N-terminal pro B-type natriuretic peptide (NT-proBNP) and clinical congestion score (0-12), as well as change in hemocentromination including measures of hematocrit, albumin and total protein with risk of the trial’s primary endpoint of a composite outcome of CVD mortality or HF hospitalization.

Results: Among 3500 patients with median 10 month follow-up, 1369 (39%) experienced the composite outcome of CVD mortality or HF hospitalization. There were no differences in baseline kidney function between those in the quartile of most rapid decongestion compared to least rapid (mean eGFR 59±23 vs 57±23 ml/min/1.73m², respectively). Overall, despite in-hospital eGFR decline with decongestion (-0.2±0.2 ml/min/1.73 m² per day), faster decongestion was associated with decreased risk of both CVD mortality and HF hospitalization (Table).
**PO0271**

**Effect of Intensive vs. Standard Blood Pressure Targets on AKI and Subsequent Cardiovascular Outcomes and Mortality**


**Background:** Using linked electronic health record (EHR) data, this study evaluated the effect of intensive vs. standard blood pressure (BP) treatment in SPRINT on acute kidney injury (AKI) and whether incident AKI was associated with cardiovascular disease (CVD) and mortality.

**Methods:** Inpatient AKI was defined by a) serious adverse event (SAE) reports based on diagnosis codes for AKI (KDIGO) and discharge notes and b) a ≥ 50% or ≥ 25% increase in creatinine using EHR labs. Outpatient AKI was defined by a ≥ 50% increase in creatinine using EHR labs, compared to the most recent creatinine measured in trial follow-up. Cox regression was used to evaluate the effect of intensive BP lowering on the incidence of AKI, and to examine the time-varying association between incident AKI and CVD and mortality.

**Results:** 3321 participants (1690 intensive vs 1631 standard) had linked EHR data. The mean age was 69 years, 23% were female, and 29% were black. More inpatient AKI events were identified using EHR labs (162 intensive vs 137 standard) as compared to SAE reporting in the trial (87 intensive vs 56 standard). Outpatient AKI similarly occurred more frequently with the inclusion of EHR labs (216 intensive vs 156 standard). Intensive treatment was associated with an increased risk for inpatient AKI based on SAE reports (HR 1.48, p≤0.02) and for outpatient AKI (HR 1.36, p≤0.004), but not for inpatient AKI based on EHR labs (HR 1.16, p=0.21). Irrespective of the definition, the incidence of AKI was associated with increased risk for all-cause mortality in adjusted analyses, but not with incident CVD. Despite this increased risk, intensive treatment reduced the risk of all-cause mortality (HR 0.70, p=0.003) in this subset of SPRINT participants.

**Conclusions:** Lab based ascertainment of AKI, facilitated by the EHR, may be more sensitive and less biased than traditional SAE reporting, particularly for open-label trials and for capturing more frequent outpatient AKI events. Given that inpatient and outpatient AKI were associated with increased risk for all-cause mortality, identifying ways to prevent AKI may reduce mortality even further with intensive BP lowering.

**PO0272**

**Fostering Scientific Innovation to Impact AKI: A Roadmap from the AKI!Now Basic Science Workgroup**

Samir M. Parikh, Anupam Agarval, Amandeep Bajwa, Sanjeev Kumar, Sherry Mansour, Mark D. Okusa, Jorge Jerda, AKI!Now Basic Science Workgroup Beth Israel Deaconess Medical Center, Boston, MA; The University of Texas Southwestern Medical Center, Dallas, TX; The University of Alabama at Birmingham, Birmingham, AL; The University of Tennessee Health Science Center College of Medicine, Memphis, TN; Cedars-Sinai Medical Center, Los Angeles, CA; Yale University School of Medicine, New Haven, CT; University of Virginia, Charlottesville, VA; St. Peter’s Health Partners, Albany, NY.

**Background:** The American Society of Nephrology convened a new initiative in 2020, AKI!Now, to promote excellence in the prevention and treatment of acute kidney injury (AKI). AKI!Now’s interests are broad, spanning molecular and cell biology research through provider education and patient advocacy. Here we describe current efforts of AKI!Now’s Basic Science Workgroup to foster innovation in the prevention, diagnosis, and treatment of AKI by leveraging fundamental discoveries. Both in hospitals and the community, the incidence of AKI is high and increasing worldwide. For the individual patient, severe AKI is a life-altering event with profound future consequences. At the society level, AKI is recognized as a major public health burden.

**Methods:** We propose the following goals to promote collaborative and inclusive discovery research that could translate more effectively to our patient care.

**PO0273**

**Telenephrology (TN) vs. Face-to-Face (F2F) Visits: A Comparison of Inpatient Nephrology Outcomes and Provider Perspectives**

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**Background:** Clinical outcomes, patient, and provider perspectives on inpatient synchronous telenephrology care remain largely unstudied. In this retrospective study, we compared outcomes in patients who received inpatient synchronous TN plus F2F (cases) versus only F2F (controls) at two Mayo Clinic Health System (MCHS) community hospitals.

**Methods:** Hospitalized adults who had nephrology consults from 3/1/2020 to 2/28/2021 were classified in several diagnoses groups. Logistic regression was used to assess 30-day mortality, readmissions, and hospital transfers. Penalized regression was used in the case of rare events. Negative binomial regression was fit to account for overdispersion in length of hospital stay data. Unadjusted and Adjusted odds ratio with 95% confidence interval (CI) were computed using (1) multinomial logistic regression (Table 1). Both non- nephrology hospital providers and tele-nephrologists reported the most frequent reasons for consults were AKI, ESRD, electrolytes, or acidosis. Tele-nephrologists preferred video consultations (82%) to phone for communication. More than half (64%) of tele-nephrologists spent less time on TN compared to F2F consults. Non-nephrology hospital providers were very satisfied (10 (48%) and satisfied 6 (29%) with TN response time, and most felt TN was as safe as F2F (67%) and provided them enough information to make patient care decisions (76%)...

**PO0274**

**Renal Cytosolic Phospholipase A2 Mediates AKI in Humans**

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**Background:** Increasing evidence suggests that cytosolic phospholipase A2 (cPLA2) and the prostaglandin E2 (PGE2) drive the progression of various forms of kidney disease. Whether renal cPLA2-dependent PGE2 production significantly contributes to the progression of acute kidney injury (AKI) in humans is currently unknown. We compared the lipidomic and metabolomic profile of kidneys from deceased transplant organ donors with or without AKI and used molecular and tissue culture techniques to investigate the role of cPLA2-PGE2 pathway in AKI.
Methods: Kidneys with or without AKI were collected from deceased human transplantation donors (n=10 donors), and kidneys from 7 donors and AKI: 12 kidneys from 8 donors). We used LC-MS and mass-spectrometry imaging (MSI) to investigate the abundance of relevant metabolites, RT-PCR and Western blotting were used to examine the levels of lipid enzymes and PGE2 levels were investigated by ELISA. To determine whether cPLA2-PGE2 pathway mediates AKI, we stimulated RPTEC and human kidney organ culture using interleukin-1β (IL-1β) and cPLA2 inhibitor and investigated changes in kidney injury markers.

Results: To validate this human model of AKI, kidney injury (Kim-1 and NGAL) and inflammatory (IL-6) markers were significantly higher in kidneys collected from donors with AKI compared to kidneys collected from donors without AKI. Lipidomics showed significantly lower levels of phosphatidylcholine (PC) species (PC 29:1, 31:1, 32:4 and 35:5) and MSI showed significantly higher abundance of arachidonic acid and prostaglandins in kidneys from donors with AKI. Kidneys from donors with AKI demonstrated significant upregulation of cPLA2 mRNA and protein, and higher levels of PGE2, compared to kidneys without AKI. cPLA2 inhibitor significantly reduced PGE2 and kidney injury markers in IL-1β-stimulated RPTEC and human kidney organ culture model.

Conclusions: Lipidomics, MSI and molecular data identify changes in the PC-cPLA2-PGE2 pathway in human kidneys obtained from AKI donors. The inhibition of cPLA2 ameliorates kidney injury in vitro suggesting that this enzyme is a key driver of AKI in humans.
effects, including uveitis. To our knowledge, TINU syndrome has not been reported with bisphosphonate use.

**Case Description:** 77-year-old female with a history of hypertension on lisinopril, osteoporosis on alendronic acid for 2 years, baseline creatinine of 0.7 mg/dL, was admitted for worsening renal function. On labs obtained 3 weeks prior to presentation, her creatinine was 1.46 mg/dL. Around that time, she was being treated for an “iritis” episode. Despite holding her lisinopril and alendronate, her creatinine was found to be 3.53 mg/dL 1 day prior to admission. Patient was stable and her exam was unremarkable. Review of system was positive for frothy frothy. She denied NSAIDs or antibiotics use. Labs revealed a non-anion gap acidosis and a creatinine of 3.2 mg/dL. Urinalysis showed sterile pyuria and microscopic hematuria; urine protein-creatinine ratio was 1.97. Renal ultrasound was unremarkable. Her autoimmune, infectious, and monoclonal gammopathy workups were negative. A renal biopsy revealed a lymphocytic predominant severe interstitial nephritis with focally destructive tubulitis and edema. During her admission, she developed recurrence of her ocular involvement and was diagnosed with anterior uveitis by ophthalmology. As a result, a diagnosis of TINU syndrome secondary to alendronic acid use was made. Patient was started on 1 mg/kg of daily prednisone and discharged after 5 days of hospitalization. Her creatinine was 1.82 mg/dL 1 week later, and 0.98 mg/dL 3 weeks later.

**Discussion:** Association of Bisphosphonates use and TINU syndrome has not been reported. Prompt recognition of this rare complication and drug discontinuation are crucial to the management. In our patient, since discontinuation of medication did not improve her renal function, we treated her with steroids, with excellent response.

**PO0279**

**AKI Associated with Hydrophilic Polymer Embolism: A Case Report**

**Poster**

**J. Am Soc Nephrol 32: 2021**

**Abstract:** We present the case of a 73-year-old male with history of peripheral artery disease and no previous diagnosis of kidney disease who was admitted to the hospital due to acute oliguric acute kidney injury (AKI), four weeks after undergoing an endovascular aneurysm repair with aorto-uni-iliac stent, right femoral endarterectomy and right femoral-popliteal bypass. Laboratory work-up such as complement levels, viral and antibody serologic testing were unremarkable. His hospital course was complicated by anuria, hyperkalemia and hyperphosphatemia. Kidney biopsy (figure 1) showed a foreign material consistent with a hydrophilic polymer embolism, as well as histiocytes with similar ingested foreign material, along with atheromatous emboli, and mild to moderate interstitial fibrosis. Treatment was supportive, including renal replacement therapy (RRT), with improvement in kidney function to the point of having adequate urinary output, no electrolyte derangements and no further need for RRT at discharge.

**Discussion:** In this case report, we compare our findings to other reported cases of hydrophilic polymer embolism to increase awareness of this under-recognized cause of organ dysfunction.

**PO0280**

**A Nutty Case of Oxalate Nephropathy**

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**Introduction:** Oxalate nephropathy occurs when considerable amounts of calcium oxalate crystals deposit in the renal parenchyma. Excessive dietary intake of oxalate-rich foods (including some associated with healthy eating) in otherwise healthy individuals can lead to secondary oxalate nephropathy. We report a case of severe AKI related to excessive nut consumption.

**Case Description:** A 41-year-old man with history of Hashimoto’s disease and pancytopenia presented to the hospital with 1 week of nausea and vomiting. Evaluation showed AKI with elevated serum creatinine (19.9 mg/dL), BUN (229 mg/dL), hematuria, and proteinuria (urine protein/creatinine ratio 1.6 gm/gm). Serologic workup showed mildly elevated kappa/lambda ratio (3.52) and low C3 (71mg/dL) but was otherwise unremarkable. Serum uric acid was high at 11.6 mg/dL. Renal ultrasound revealed normal kidney size with increased parenchymal echogenicity and punctate echogenic foci bilaterally. A renal biopsy was performed demonstrating widespread oxalate deposition with associated interstitial inflammation and tubular injury. Further history revealed no recent medications, infections, or ingestions, but did uncover a high intake of nuts (~1 pound) daily over the prior 1 year due to perceived health benefits. He remained hemodialysis dependent on hospital discharge.

**Discussion:** Secondary oxalate nephropathy can result from increased enteric oxalate availability from dietary consumption. Diagnosis can be delayed when a review of diet and supplements is deferred. It is therefore essential to obtain a detailed dietary and pharmacologic history, particularly in all patients with unexplained kidney disease. Treatment is supportive including decreasing the high oxalate culprit foods in the diet.

**H&E stain showing arteriole occluded by hydrophilic polymer emboli.**
PO0282

The Answer Is in the Urine

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Introduction: Ethylene glycol toxicity carries significant morbidity. Prompt recognition and treatment prevents mortality. Given time needed for confirmatory laboratory testing, high suspicion should be raised in cases of anion gap metabolic acidosis. Here we present a case of ethylene glycol toxicity diagnosed with simple urine microscopy.

Case Description: The patient is a 48-year-old male presented in an obtunded state. Laboratory evaluation was notable for a severe metabolic acidosis with a CO2 <5 mmol/L on basic metabolic panel. Anion gap was unable to be calculated but was at least 27. Serum labs were: Sodium 139 mmol/L, potassium 4.9 mmol/L, chloride 108 mmol/L. Glucose level 144 mg/dL. Creatinine 1.14 mg/dL and BUN 16 mg/dL, Lactic acid 7.63 mmol/L. ARB showed a pH of 7.14, pCO2 of 11 mmHg, pO2 of 114 mmHg, pHC03 of 3.6 mmHg, and calculated base excess of -25.0. Measured serum osmolality was 7.63 mmol/L. ABG showed a pH of 7.14, pCO2 of 11 mmHg, pO2 of 114 mmHg on basic metabolic panel. Anion gap was unable to be calculated but was at least 27.

Discussion: Toxins ingested needs to be considered in any obtunded patient. Workup should include careful assessment of acid-base status and osmolar gap. Prompt Treatment may need to be initiated prior to confirmatory lab results. Simple methods including urine microscopy and fluoresce the urine with Wood's lamp can assist in prompt diagnosis. In our case, crystalluria was present. A teaching point is that the crystals need not be the classic "envelope shape" as a six-sided needle-like structure often occurs as noted in our patient. While labs may confirm the diagnosis, the answer can be found in the urine.

PO0283

AKI: Rare Side Effect of Pemetrexed

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Introduction: Pemetrexed was approved by FDA in 2004 to treat local or advanced metastatic non-small cell lung cancer. It works by disrupting folate dependent processes. It is histologically delineated by coagulative necrosis of the renal papilla and medullary regions along with severe mouth pain and odynophagia. The chemotherapy regimen was changed from pembrolizumab to pemetrexed two days prior. Severe odynophagia limited his oral intake. His BP on arrival was 86/60 and was fluid resuscitated. CBC was unremarkable except for platelet count of 56,000/μL and absolute neutrophil count of 372 cells/μL. CMP demonstrated BUN of 38 mg/dL and serum Creatinine of 4.2 mg/dL. His baseline Creatinine one month prior to presentation was .6. MRI of his abdomen was unremarkable. Initial treatment included aggressive fluid hydration, a granulocyte colony stimulating factor (THO-Filgrastim) and empiric IV antibiotics given the severe neutropenia. Additionally, 5mg of folic acid intravenously was started to counter the anti-folate effects of pemetrexed. Due to high suspicion of toxic volatile substance ingestion, Fomepizole was administered and a urine sample was viewed under the microscope. Needle shaped crystals were noted to be present. Patient underwent 1 session of hemodialysis and significantly improved clinically. Ethylene glycol level, drawn prior to hemodialysis, came back at 24.9 μmol/L. He received 4 additional doses of fomepizole. He also received high dose thiamine and pyridoxine to enhance the metabolism of ethylene glycol. Labs drawn the following morning resulted in an undetectable ethylene glycol level.

Discussion: Toxin ingestion needs to be considered in any obtunded patient. Workup should include careful assessment of acid-base status and osmolar gap. Prompt Treatment may need to be initiated prior to confirmatory lab results. Simple methods including urine microscopy and fluoresce the urine with Wood’s lamp can assist in prompt diagnosis. In our case, crystalluria was present. A teaching point is that the crystals need not be the classic “envelope shape” as a six-sided needle-like structure often occurs as noted in our patient. While labs may confirm the diagnosis, the answer can be found in the urine.

PO284

An Unusual Presentation of Type 1 Cryoglobulinemic GN in Monoclonal Gammopathy of Undetermined Significance (MGUS)

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Introduction: Type I cryoglobulinemia can develop in the setting of monoclonal gammopathy of undetermined significance (MGUS) and can have renal involvement in a third of cases. We present an unusual case of Type I cryoglobulinemic glomerulonephritis (GN).

Case Description: An 83-year-old woman with a history of IgG Kappa MGUS presented with decreased urine output and nausea. During the previous six months, the patient was hospitalized three times for acute kidney injury (AKD) requiring dialysis. Two renal biopsies had been performed during those admissions, which showed GN with scant immune deposit. One glomerulus had intraluminal staining for IgG and Kappa suggesting Type I cryoglobulinemia. Additional Type I cryoglobulinemic GN secondary to her MGUS (Figure 1, A-C). She declined chemotherapy at the time, however, each time her renal function improved spontaneously and she was discharged without requiring dialysis. In the ED, her blood pressure was 182/69 but her vitals were otherwise normal. The physical exam was unremarkable. Labs were notable for sodium 122 mg/dL, potassium 5.2 mg/dL, creatinine 4.5 mg/dL, albumin 3.4 g/dL, low C3 and C4, and positive MPO-ANCA. The urinalysis showed 50 red blood cells, 15 white blood cells, and random urine protein > 2000 mg/dL. Other serologic and infectious labs, including serum cryoglobulin, were negative. The renal ultrasound was normal. The patient’s renal function worsened and was started on dialysis. This time the patient agreed to chemotherapy and immunosuppression with the aim to prevent further recurrences of AKI. The patient was started on clone-directed therapy with cyclophosphamide, bortezomib, and dexamethasone. Plasma exchange therapy was also performed for the clearance of light chains. The patient’s renal function improved and she was discharged without requiring dialysis. Her two-month follow up creatinine was 1.08 mg/dL.

Discussion: This case of type 1 cryoglobulinemic GN is unusual in that the patient developed cyclical but self-resolving episodes of AKI-D that was successfully treated with clone-directed therapy.
A Rare Case of Evans Syndrome with Systemic Lupus Erythematosus and Pulmonary Nocardiosis

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Introduction: Evans syndrome (ES) is a rare autoimmune disorder characterized by the simultaneous or sequential development of autoimmune hemolytic anemia (AIHA) and immune-mediated thrombocytopenic purpura (ITP). The exact pathophysiology is unknown but is initiated by having autotibodies attacking body’s own red blood cells and platelets.

Case Presentation: A 25-year-old male with history of autoimmune dysregulation including SLE (diagnosed when he was 13), Evan’s Syndrome, class 5 lupus nephritis, presented to the Hospital for difficulty breathing, dry cough and 30-pound weight loss. He was admitted to ICU for acute hypoxic respiratory failure requiring intubation. His lab work showed anemia, thrombocytopenia, AKI, ANA+, low C3, C4, elevated LDH, high uric acid, UA showing 3+ blood and 6 grams of proteinuria. A chest CT on admission also noted extensive LAD, splenomegaly, ground glass opacities and interstitial prominence in lungs. He underwent a lung biopsy which showed DAH. The patient was also treated with pulsed steroids, plasmapheresis and Cytoscan. He had also MSA bacteraemia treated with antibiotics and rehab course complicated with pulmonary nocardiosis.

Discussion: Although ES is an extremely rare case, it is important to keep broad differentials as renal dysfunction is common from different pathologies. Usually the most common cause of AKI associated with ES is ATN from intravascular hemolysis and had differentials as renal dysfunction is common from different pathologies. Usually the most common cause of AKI associated with ES is ATN from intravascular hemolysis and had widespread intratrabular hemoglobin casts but it is essential to consider other etiologies as in our case of previous lupus flare.

Acute Myositis Complicated by Rhabdomyolysis in Setting of COVID-19 Infection in a Patient with Rosuvastatin: A Case Report

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Introduction: Viral illnesses are uncommon cause of rhabdomyolysis and AKI. A few cases of rhabdomyolysis have been reported with Covid-19 infection previously. However, Covid-19 presentin solely with rhabdomyolysis in absence of respiratory symptoms is rare. There is also paucity of data supporting steroids use in such cases. We present a case of COVID-19 related rhabdomyolysis who recovered in response to steroid therapy.

Case Description: This is a 78-year-old female with history of dyslipidemia and chronic kidney disease III who presented with generalized weakness and myalgias. Home medications included Rosuvastatin. She was diagnosed with Covid-19 virus. Rosuvastatin was held, however her myalgia muscle weakness worsened, and she was no longer able to stand without support. She denied fever, chills, rash, or respiratory symptoms. At presentation, physical exam revealed diffuse muscle tenderness and diminished strength: 1/5 and 2/5 in bilateral upper and lower extremities respectively. WBCs 11.13. K 5.7, Cr 5.72, ANA, HMG CoA reductase antibody assay and myositis panel (SSA-52, SSA-60, Smith/RNP antibodies, anti-SM-RNP, anti-SS-A, anti-SS-B, & RF) were negative. CK 14, 085 U/L, granular and muddy brown casts on urine microscopy. Lower extremities MRI showed bilateral muscular edema, EMG was consistent with myopathic changes characterized by fibrillation, positive sharp wave, and a prominent type 2 fiber atrophy, and mild neurogenic changes, consistent with rhabdomyolysis. Immunohistochemistry showed rare perivascular B lymphocytes and plasma cells. CK continued to rise and peaked at 98,383 U/L. At that point steroid therapy was initiated.

Care Unit. Continuous renal replacement therapy is a lesser known cause of acquired thrombocytopenia.

**Case Description:** In this retrospective case series, four patients that developed thrombocytopenia while receiving continuous renal replacement therapy (CRRT) in the Intensive Care Unit were evaluated. The temporal relationship between onset of thrombocytopenia, timing of CRRT, and subsequent trend in platelet counts were analyzed. The patients had a variety of risk factors for thrombocytopenia including septic shock, presence of chronic kidney disease, mechanical support therapies, and anticoagulation with heparin. Despite these characteristics and interventions, each of the patients demonstrated a pronounced drop in platelet count within 72 hours of initiating CRRT, with a subsequent improvement in platelet count following cessation of CRRT.

**Discussion:** Thrombocytopenia is a complication of critical illness that, in extreme cases, can lead to further cost and resources to evaluate and possibly delay necessary interventions. Anticoagulation with heparin may also contribute to the development of thrombocytopenia. Nephrologists and hemotologists in critical care cases, can lead to further cost and resources to evaluate and possibly delay necessary interventions.

**Data**

CRRT = Continuous Renal Replacement Therapy

**PO0291**

**Successful Utilization of Hemodialysis for Treatment of Vancomycin Nephrotoxicity**

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**Introduction:** Vancomycin is frequently used as empiric antimicrobial therapy for septic shock. At supratherapeutic levels, vancomycin can potentially cause nephrotoxicity. Nephrotoxicity often resolves on discontinuing the medication, but recovery may be prolonged and injury severe, requiring dialysis. The role of hemodialysis is limited, and evidence suggests that standard membrane dialysis provides poor clearance. However, the current use of high flux dialysis can eliminate vancomycin faster, promoting quicker renal recovery.

**Case Description:** A 49-year-old female admitted for septic arthritis received vancomycin 1.5g q8h and piperacillin/tazobactam. After two days, she developed an oliguric acute kidney injury (AKI). Urine sediment revealed few tubular cells without casts. Vancomycin trough level was 42 μg/mL, and the random level was 101.3μg/mL. We suspected vancomycin toxicity, and for quicker clearance of the drug, we initiated high flux dialysis. She received five sessions of HD in addition to the random vancomycin level dropped to 18 μg/mL. Gradually her urine output improved with resolution of AKI.

**Discussion:** Discerning vancomycin nephrotoxicity can be a challenge as higher levels can result from decreased GFR from AKI. The rise of creatinine coinciding with elevated vancomycin levels and the absence of an alternative explanation for renal injury supports the diagnosis of vancomycin nephrotoxicity. The odds of developing vancomycin nephrotoxicity are three times higher when combined with piperacillin/tazobactam. Incidence of AKI increases with higher dosage (>4g vancomycin/day), higher trough levels (>15 mg/L), and longer treatment time (>1 week). Treatment is aimed at discontinuation of the drug. In severe AKI, with oliguria and poor clearance, strikingly elevated serum vancomycin levels may further escalate the risk of renal injury. In our case, the use of HD to increase the clearance of vancomycin may have expedited renal recovery. Faster removal of vancomycin with HD should be considered in patients with severe AKI.

**PO0292**

**Atypical Hemolytic Uremic Syndrome: A Case Report**

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**Introduction:** Thrombotic microangiopathy is a pathological condition comprised of microvascular thrombosis involving any organ of the body leading to thrombocytopenia, Coombs-negative hemolytic anemia, and end-organ damage. The most common forms of thrombotic microangiopathies are Shiga toxin-producing Escherichia coli mediated hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and atypical hemolytic uremic syndrome. The atypical hemolytic uremic syndrome occurs due to genetic and acquired mutations in complement regulatory factors and to complement activation factors in the immune system, mainly the alternative pathway. Clinical manifestations and outcomes differ with the prevalent mutations of the patient. Currently, available treatment modalities are therapeutic plasma exchange and a monoclonal antibody against C5, eculizumab.

**Case Description:** 43-Year-Old African American female with past medical history significant for type 2 Diabetes Mellitus with 2-day history of fever and altered mental status. On presentation, she has BP 264/133. Her blood investigations showed acute kidney disease, thrombocytopenia, hemolytic anemia with negative Coombs’s test. Coagulation profile was normal. Schistocytes were noted on peripheral smear. Received plasmapheresis for 3 sessions. Diagnosis of Thrombotic thrombocytopenic purpura with no clinical improvement. Initiated on hemodialysis. Adams TS 13 level returned at 27%, ruling out Thrombotic thrombocytopenic purpura. Genetic complement testing was sent on the patient and was initiated eculizumab for presumed Atypical hemolytic uremic syndrome. After giving 6 doses of eculizumab patient is deceased and necropsy revealed eculizumab off dialysis. Genetic complement testing is negative however, next generation sequencing revealed no coverage for the CFHAI and CFHRS genes which may be a risk factor for FH autoantibody development and needs further testing.

**Discussion:** Atypical hemolytic uremic syndrome is a rare disease entity requiring a high index of suspicion to diagnose. It is a diagnosis of exclusion. Early diagnosis with prompt treatment will render a better outcome. The atypical hemolytic uremic syndrome needs to be considered in all patients with thrombotic microangiopathy.
PO0295

Patient with Refractory Acquired Thrombotic Thrombocytopenic Purpura Treated with a Novel Agent Caplacizumab
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Introduction: Acquired or immune-mediated TTP is characterized by thrombocytopenia and anemia caused by autoantibody-mediated inhibition of the von Willebrand factor (vWF) cleaving protease, ADAMTS13. This results in a microangiopathic hemolytic anemia and severe thrombocytopenia, resulting in tissue ischemia, multiorgan failure, and, potentially, death. Up until now, treatment for TTP included therapeutic plasma exchange (TPE) and immunosuppression. Recently, caplacizumab, the first targeted nanobody-based therapeutic agent that prevents adhesion of platelets to vWF, has been approved for use in acquired TTP. We present a case of acquired TTP that was refractory to high dose, steroids, therapeutic plasma exchange (TPE) and rituximab but responded well to caplacizumab.

Case Description: A 53-year-old man with HIV, complicated by cryptococcal meningitis and PCP pneumonia, intermittent confusion, headache, and multiple falls, presented with anemia, thrombocytopenia, an elevated LDH, and a peripheral blood smear with numerous schistocytes with acute kidney injury with an initial serum creatinine of 1.7 mg/dl which peaked up to 5.5 mg/dl. Further testing revealed a positive ADAMTS13 inhibitor with high titer of 3.4 and less than 5% ADAMTS13 enzyme activity, consistent with TTP. He was treated with high dose steroids, TPE, and rituximab but did not respond. He was initiated on caplacizumab on hospital day 14 and by day 18 his platelet counts began to normalize and mentation improved. He suffered only mild epistaxis as a side effect from caplacizumab. In span of few days, his neurologic symptoms resolved and he was discharged home to complete thirty days of caplacizumab treatment. At the time of discharge, his creatinine level was 1.7 mg/dl which peaked up to 5.5 mg/dl. Further testing revealed a positive ADAMTS13 inhibitor. His peripheral smear showed anisocytosis, poikilocytosis, target cells, and Howell-Jolly bodies. His bone marrow biopsy showed hyperplasia of erythroid lineage with scattered megakaryocytes. ADAMTS13 level was done again and confirmed to be positive. His platelet counts regressed to normal levels with a normal differential and a platelet count of 247k. His creatinine level normalized to 1.7 mg/dl and he was discharged home to complete thirty days of caplacizumab treatment.

Discussion: Though conventional therapy has reduced the mortality of TTP, it is not always effective and there are a fair number of cases refractory to conventional treatment. Caplacizumab, the first nanobody-based therapeutic agent, has shown marked efficacy in treating TTP and its complications and is a therapeutic option for patients with refractory TTP.

PO0296

Use of Eculizumab in Thrombotic Microangiopathy (TMA) Associated with PM/SCL100 and 75 and RP 155 Antibody-Positive Autoimmune Overlap Syndrome with Renal Crisis
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Introduction: TMA with associated PM/SCL100 & 75 and RP 155 antibody positive autoimmune overlap syndrome with renal crisis has a very poor prognosis and limited therapeutic options. Use of Eculizumab has been reported in only a few cases in literature.

Case Description: A 44 years old female with hypertension and Raynaud's phenomenon presented with hypertensive emergency, recent sclerodactyly, hemolytic anemia, thrombocytopenia and renal failure. Routine serum markers including DsDNA Ab, complements, ANCA, SSA, SSB, Scl 70 Ab, Anti-centromere Ab, RNA polymerase 3 Ab, U-3 RNP Ab, lupus anticoagulant, beta 2 glycoprotein Ab and ADAMTS-13 were all negative. Pulse Steroids and plasmapheresis were initiated due to concern of aHUS. Renal biopsy showed onion skinning of arterioles with near complete occlusion of arterioles as shown in the figure. ACE1 was added. Later she was found to have positive PM/SCL 100 & 75 and RP 155 antibodies. She was started on Eculizumab secondary to poor hematological response to the above measures. Our patient showed improvement of her thrombotic microangiopathy which helps to support the use of this drug in this rare disorder.

Discussion: Very limited therapeutic options are available for cases of Autoimmune Overlap Syndrome. Our use of Eculizumab; an anti-C5D monoclonal antibody, also supports the benefits of blocking the activation of the classical complement pathway which may suggest the underline mechanism in this disease process.
Discussion: Eosinophilic cystitis is a rare disease. Association with history of allergy and urinary tract infection is variable. Radiological finding are usually consistent with thickened bladder wall. In a case series of 10 Chinese patients, only one patient had bilateral hydropnephrosis. Medical treatment is mainly by non-steroidal anti-inflammatory drugs, corticosteroids, anti-histamines and antibiotics. Surgical modalities of treatment include transurethral resection of the lesions, partial cystectomy or total cystectomy. Response to different modalities of treatment is variable.

PO0299
Treatment of FSGS and Hemophagocytic Syndrome with Tocilizumab
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Introduction: Hemophagocytic syndrome (HPS) is a rare and often life-threatening condition characterized by an overreaction of the immune system. HPS has a variety of triggers including: malignancy, infection, and rheumatologic conditions. Clinically, it is characterized by acute fever, cytopenia, lymphadenopathy, hepatosplenomegaly, intravascular coagulation, hyperferritemia, and elevated liver associated enzymes. We present a case of reactive HPS complicated by focal segmental glomerulonephritis (FSGS) secondary to a febrile gastrointestinal illness in an otherwise healthy 36 year old male.

Case Description: A 36 year old male presented to the ER with a 3 day history of fevers, nausea, vomiting, and diarrhea. Labs demonstrated hyponatremia to 126 and acute renal injury. He was admitted for presumed viral gastroenteritis and treated supportively. He then developed elevated liver associated enzymes and pancytopenia. An infectious work up was unrevealing. Flow cytometry was negative for lymphoma or leukemia. Ferritin was elevated at 4450 ng/ml. A bone marrow biopsy demonstrated hemophagocytosis. He then developed multiple pulmonary embolisms, lower extremity edema, new onset ascites, and nephrotic range proteinuria. A renal biopsy showed diffuse podocyte effacement with rare Focal Segmental Glomerulosclerosis (FSGS) associated with a febrile gastrointestinal illness in an otherwise healthy 36 year old male.

Discussion: The pathogenesis of HPS is excessive activation and proliferation of T lymphocytes and macrophages leading to phagocytosis of hematopoietic cells in the bone marrow and hyperssecretion of proinflammatory cytokines causing multi organ dysfunction. Due to the difficulty in diagnosis, the Hscore was developed to estimate bone marrow and hypersecretion of proinflammatory cytokines causing multi-organ dysfunction. Due to the difficulty in diagnosis, the Hscore was developed to estimate

PO0300
Transition of Portal Vein Doppler Waveform with Improving Venous Congestion: A Case Study
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Introduction: The diagnostic accuracy of physical examination, weight, laboratory parameters such as BNP is limited for the assessment of fluid status. Point-of-Care Ultrasonography (POCUS) is emerging as a valuable bedside tool for evaluation of hemodynamics at the bedside. Herein, we present a case which illustrates the practical utility of portal vein Doppler.

Case Description: A 78-year-old woman with a history of heart failure (HF) with reduced EF (<20%) and pulmonary hypertension was brought to the hospital for altered mental status. She was found to have acute kidney injury (AKI) with a serum creatinine of 2.2 mg/dL (baseline ~1.1) and urinalysis was suggestive of UTI. Urine sodium and chloride were ~20 mmol/L. Antibiotic therapy was started. AKI was presumed to be secondary to volume depletion as her diuretic regimen was recently intensified. There was no significant weight gain. Admitting physician noted mild pedal edema and no jugular venous distension. NT-pro-BNP level was 8118 pg/mL (last available value 10,537). 1 liter of isotonic fluid was administered, and diuretics were held. Her mental status eventually improved; nephrology consulted for AKI. POCUS-assisted physical examination demonstrated severely impaired left ventricular systolic function, a D-shaped left ventricle suggestive of pressure and volume overload and a plethoric inferior vena cava (IVC) suggestive of elevated right atrial pressure. Portal vein Doppler waveform was pulsatile with intermittent flow reversal consistent with severe venous congestion. Based on these findings, diuretic therapy was restarted. Serum creatinine improved to 1 mg/dL at discharge. While IVC continued to be dilated, portal vein waveform showed consistent improvement during the course of decongestive therapy [Fig.1].

Discussion: While IVC POCUS is relatively easy to perform, it may be chronically dilated in patients with pulmonary hypertension. Portal vein Doppler offers an additional datapoint to assess the severity of venous congestion and monitor the efficacy of decongestive therapy.

PO0301
Skin Biopsy in Diagnosis of Acute Interstitial Nephritis
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Introduction: Acute Interstitial Nephritis (AIN) is a common cause of Acute Kidney Injury (AKI). It is often caused by drugs, systemic diseases, and infectious diseases. The diagnosis is elusive, as the triad of fever, rash, and peripheral eosinophilia is rarely seen. Other diseases, such as atheroembolic renal injury, could present similarly. Hallmark findings on urinalysis (leukocytes, WBC casts) and urine eosinophils are also nonspecific. Hence, a definitive diagnosis only comes from renal biopsy. The case presents a patient with AKI and rash, highlighting the utility of skin biopsy in diagnosing AIN as an alternative to renal biopsy.

Case Description: A 72 year old female with a history of hypertension and chronic kidney disease was treated with Keflex in-hospital for a urinary tract infection. Within four days of beginning the medication, she developed a maculopapular rash on the trunk, back, and extremities with AKI (creatinine rose to 3.05 mg/dL, while creatinine on admission remained below baseline of 1.9 mg/dL). Keflex was discontinued and replaced with Ciprofloxacin. Urinalysis had 2+ proteinuria and 3+ hematuria with 113 red blood cells and 24 white blood cells. Urine eosinophils was positive. Autimmune workup was unremarkable. Renal ultrasound showed kidneys of normal size and echogenicity. The patient began empiric prednisone 60 milligrams daily. Dermatology performed a skin biopsy showing inflammation consistent with drug erosion. Immunostaining was unremarkable. Meanwhile, the patient’s creatinine began to improve after treatment and reached baseline by discharge. The rash also began to improve.

Discussion: AIN is a very common cause of AKI, particularly in the hospital setting. Current lab tests used for workup are neither sensitive nor specific for the disease. Often, the testing for AIN is not even performed. A definitive diagnosis requires tissue sampling, traditionally via renal biopsy. However, the procedure has particular risks, such as retroperitoneal bleed. In this case, skin biopsy showed inflammation characteristic of drug eruption in a patient with AKI and rash correlating in time with initiation of an antibiotic, lending credence to the diagnosis of AIN. Therefore, in patients with suspected AIN involving skin rash, skin biopsy could prove to be a safer mode of tissue sampling for diagnosis, averting the complications traditionally associated with renal biopsy.

PO0302
Oxandrolone-Induced Acute Tubular Necrosis
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Introduction: Oxandrolone is an anabolic-androgenic steroid (AAS) indicated as adjunctive therapy to promote weight gain in chronic wasting conditions. It is also used traditionally via renal biopsy. However, the procedure has particular risks, such as retroperitoneal bleed. In this case, skin biopsy showed inflammation characteristic of drug eruption in a patient with AKI and rash correlating in time with initiation of an antibiotic, lending credence to the diagnosis of AIN. Therefore, in patients with suspected AIN involving skin rash, skin biopsy could prove to be a safer mode of tissue sampling for diagnosis, averting the complications traditionally associated with renal biopsy.

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Underline represents presenting author.
Case Description: A 30-year-old previously healthy male presented to the ED with complaints of intense nausea and vomiting. He reported intentional caloric restriction and intense exercise over the past month, along with using under-the-counter oral Oxandrolone. Labwork revealed AGMA and ketosis (CO2 17.2mmol/L, AG 24.4 mmol/L, β-hydroxybutyrate 48.97 mg/dL) elevated Creatinine (2.8 mg/dL). Glucose, LFTs and CK levels were normal. Ketones, Protein 100 mg/dL, BHC 10-25. US and CT of abdomen and pelvis were unremarkable. He was started on IVF and anti-emetics with resolution of symptoms and starvation ketoacidosis. Renal function, however, progressively worsened. BUN/Cr < 20, FeNa 14% and no improvement with IVF was reported. Further work up revealed K+, Na+, creatinine > 200 mg/dL and low T3/T4. Urinalysis revealed 10+ proteinuria, blood, ketones and acetoacetate. Blood, UA revealed K+ 7.3mEq/L, Cr 1.3mg/dL, ESR 22 mm/hr and urine protein/creatinine ratio of 0.35mg/mg友情. She has subsequently been started on a prednisone taper to which she has responded well.

Discussion: TIN is associated with a number of systemic illnesses inclusive of pSS. Renal disease in pSS is as high as 42%, with TIN accounting for approximately 10-20% of cases. TIN usually presents after the initial diagnosis of pSS but in our patient it occurred concurrently with the diagnosis. The renal involvement in pSS is usually chronic and it typically shows mononuclearic TIN with minimal glomerular involvement. However, there is a wide range of renal pathology including TIN to MPGN, membranous nephropathy, and focal sclerotic GN. Even though renal impairment does not typically precede pSS it is imperative to biopsy as early as possible so that treatment can be initiated to prevent chronic disease.

PO0305

Excess Vitamin C Leading to Hyperoxaluria and AKI
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Introduction: Secondary hyperoxaluria is caused by increased ingestion of oxalate or oxalate precursors, increased oxalate enteric absorption due to fat malabsorption, or changes in intestinal microflora and can manifest as end stage renal disease or hyperuricemia.

Case Description: A 55-year-old female with history of hyperparathyroidism and hyperuricemia (not med compliant) presented with myxedema coma secondary to uncontrolled hyperthyroidism. Initial workup revealed elevated potassium (7mmol/L), BUN (194mg/dL), SCr (55mg/dL) and TSH <100IU/mL. She was given IV levothyroxine, IV lithium, insulin, calcium gluconate and hydrocortisone, and started hemodialysis in the setting of acute kidney injury (AKI) with no known underlying CKD, nephroliathiasis or nephrocalcinosis. Autoimmune, gastrointestinal, and hepatobiliary AKI etiologies were ruled out. A renal biopsy revealed renal oxalosis (Fig 1). Investigation of possible secondary causes of renal oxalosis revealed consumption of large quantities of vitamin C in hopes of preserving her health during the COVID-19 pandemic. The patient remained dependent on hemodialysis was discharged on levothyroxine 150mcg sublingual daily followed by nephrology and endocrinology. At time of discharge, TSH remained 1-200IU/mL, but free T4 was 0.86 ng/dL without any hypothyroid symptoms. High dose vitamin C consumption was discontinued.

Discussion: The combination of severe hyperuricemia resulting in myxedema coma and the excessive intake of vitamin C, a precursor for oxalate stones in the kidney, was likely the cause of AKI in our patient. We recommend considering secondary oxalosis in cases of dialysis-dependent AKI in the setting of high dose vitamin C consumption or increased exogenous oxalate ingestion and confirming this diagnosis with renal biopsy.

Figure 1: Left: Rhomboid shaped calcium oxalate crystals distending renal tubule with attenuated and disruption of epithelial lining. Right: Calcium oxalate crystals characterized byfibrinefugent under polarized light microscopy.

PO0306

Candida parapsilosis Endocarditis Presenting as Acute Glomerulonephritis: A Case Report
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Introduction: Candida species is an uncommon cause of left sided endocarditis that traditionally associated with high morbidity rate. In a few rare cases, Candida endocarditis may present as a cause of glomerulonephritis. Here we present a case of Candida parapsilosis endocarditis that presented as acute glomerulonephritis.

Case Description: A 52 y/o Caucasian female with history of antiphospholipid syndrome, intravenous drug use history on suboxone who presented with 3 weeks of acute renal failure. She was on anticoagulation, and combination therapy with acenocoumarol and rivaroxaban. UA showed +3 blood. She was referred for kidney biopsy due to acute kidney injury with proteinuria. UA revealed 3+ proteinuria. Bloodwork revealed normal creatinine and CRP. She was started on anticoagulation therapy and she was transferred to the nephrology unit.

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mildly elevated ANA at 1:80 and negative double strand DNA, smooth muscle antibody level, PR3/MPO and extractable nuclear antigen antibody including SSA/SSB, RnP, Scl-70 and Jo-1 antibody level. A CRP was 33 and ESR was 47. Blood cultures revealed Candida parapsilosis. MRI spine with inflammatory changes of L4-L5 suggesting osteomyelitis. Patient received micafungin but remained persistently fungemic. A TEE revealed a large mitral valve vegetation. While under evaluation for mitral valve surgery, she suffered from a large right MCA stroke and deceased within 48 hours from brain herniation. No autopsy performed due to family’s request.

Discussion: Fungal associated GN is a rare clinical entity that usually mentioned only as a foot note in textbooks. The mechanism of kidney injury is likely immune complex deposition. Given the high mortality rate with Candida endocarditis and its associated complications, heightened clinical suspicion and early aggressive treatment with antifungal and surgery are important. Corticosteroid in one case report improved renal function indicating a possible role in patients with controlled infection.

PO0307

Linezolid-Associated Interstitial Nephritis
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Introduction: Acute Interstitial Nephritis (AIN) accounts for 15-27% of renal biopsies performed for Acute Kidney Injury (AKI). Drug induced AIN remains the most common cause. We present a case of Linezolid induced AIN, a rare entity.

Case Description: Elderly male patient with type 2 diabetes, hypertension and normal renal function was initiated on linezolid for osteomyelitis. Two weeks later, he reported a maculopapular rash on his arms and chest. Labs were significant for a serum creatinine (Scr) of 3.6mg/dl. Immunological and infectious work up for AKI was unremarkable. Scr continued to increase to 7.2mg/dl and absolute serum eosinophil count was 1800 cells/μl. Interstitial nephritis was suspected and empiric prednisone was initiated. Renal biopsy showed Acute Tubular Injury with Interstitial Nephritis and moderate interstitial fibrosis. The AIN was associated with several eosinophils, and was consistent with a drug induced reaction. Linezolid was stopped, and the patient continued a steroid taper with which Scr improved to 2.0mg/dl and remained stable. The patient did not meet diagnostic criteria for DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) as he had no other systemic involvement, and the rash was not associated with desquamation or infiltration.

Discussion: This patient developed a rash and interstitial nephritis after the initiation of linezolid. He reported no Non-Steroidal Anti-Inflammatory Drug (NSAID) intake and was on vancomycin and piperacillin- tazobactam for less than 48 hours, during which renal function remained stable. Linezolid associated Interstitial Nephritis is rare, and only 4 cases have been reported in the literature. As the prevalence of Methicillin Resistant Staphylococcus Aureus increases, we must be wary of this complication before initiating treatment. Renal function must be monitored, and prompt initiation of steroids can ensure improvement of renal function.

Case Description: A 43 year old male was treated with Rifampicin for Mycobacterium marinum infection 3 years ago. He recently injured his hand and took two pills of Rifampicin leftover from 3 years ago to prevent another infection. He took them about 12 hours apart and a few hours after taking the second pill he developed severe nausea, vomiting, flank pain and dark colored urine. He presented to emergency department and labs showed elevated LDH(lactate dehydrogenase) and bilirubin, thrombocytopenia, anemia and elevated creatinine. He was transferred to our hospital for further management. Upon arrival creatinine was 7.5mg/dl. Bilirubin had normalized and haptoglobin was in normal range. ADAMTS13 level was 56%. Peripheral smear did not show schistocytes. He underwent kidney biopsy which showed moderate acute tubular injury and focal thrombotic microangiopathy. It was determined that he had AKI from type 2 hypersensitivity to Rifampicin. His creatinine continued to worsen to 18mg/dl before improving. He did not require renal replacement therapy. On follow up three weeks later, his creatinine had improved to 1.7mg/dl.

Discussion: Rifampicin hypersensitivity can manifest with hepatitis, hemolytic anemia and AKI. It is most often seen when the drug is re-administered or used intermittently. The outcome of AKI is usually favorable after discontinuation of the drug, with most patients achieving full recovery within 90 days. As the hypersensitivity reaction is infrequent, prompt recognition and withdrawal of drug is important to prevent irreversible injury.

PO0308

Rifampicin: An Infrequent Cause of AKI
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Introduction: Rifampicin is used to treat Mycobacterium infection. Hypersensitivity reaction to rifampicin resulting in acute kidney injury (AKI) is infrequent. Here we describe rifampicin hypersensitivity in a patient presenting with AKI who was treated for Mycobacterium marinum infection.
Atypical Hemolytic Uremic Syndrome Secondary to Homozygous CFHR1-CFHR3 Mutation
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Introduction: Atypical hemolytic uremic syndrome (aHUS) is a disease of complement dysregulation characterized by microangiopathic hemolytic anemia, thrombocytopenia, and multisystem end organ damage commonly affecting the kidneys. About two thirds have identifiable genetic abnormalities. Mutations cannot be identified in 30% of the time. A strong association has been observed between anti-FH autoantibodies and a homozygous deletion of CFHR1 and CFHR3. Factor H autoantibodies can impair complement regulation, resulting in aHUS. We report a case of aHUS secondary to a homozygous CFHR1 – CFHR3 mutation.

Case Description: A 35-year-old gentleman with no significant past medical history presented with acute worsening of his kidney function of unclear etiology (creatinine 2.5mg/dl). Kidney biopsy was performed showing thrombotic microangiopathy without evidence of vasculitis. Two days post-biopsy, he developed acute weakness and slurred speech. MRI of the brain was compatible with multiple acute cerebral infarcts. Initial laboratory values were nonspecific but follow up labs showed evidence of hemolysis with worsening renal function (creatinine 3.8 mg/dL) and thrombocytopenia (platelet count 120,000 from 283,000 per microliter). Further workup showed undetectable haptoglobin, elevated lactic acid dehydrogenase, low C3 levels and normal ADAMS-T13 activity. Given high index of suspicion for aHUS and the absence of other causes of thrombotic microangiopathy, he was started on eculizumab. After 6 doses his renal function improved and repeat MRI showed improving cerebral vasculopathy suggesting that the process was likely thrombotic. The aHUS susceptibility panel was positive for a homozygous CFHR3-CFHR1 gene deletion with elevated Factor H autoantibody 74.2 mg/dL (normal 37-68 mg/dL). The patient’s renal function stabilized with complete neurologic recovery. He remains on maintenance dose of eculizumab.

Discussion: Atypical HUS is a rare cause of thrombotic microangiopathy. Many cases have identifiable genetic mutations that lead to dysregulation of alternative complement pathway. Delayed or inappropriately treated cases lead to increased morbidity and mortality. Early screening for aHUS related genetic mutations in patients with acute kidney injury and microangiopathic hemolytic anemia is essential for prompt diagnosis of aHUS and help guide treatment duration.
Unexplained AKI: Never “Brush” Off the Role of a Renal Biopsy

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Introduction: Anti-Brush Border Antibody Disease (ABBAD) is a rare condition typically seen in elderly individuals and presents with acute kidney injury (AKI) and sub-nephrotic proteinuria. Patients often progress rapidly to ESKD despite treatment.

Case Description: A 73-y/o man with a PMH of HTN, a-fib and CKD (serum creatinine SCr 1.5 mg/dl 4 mo ago and 2.3 mg/dl 2 mo ago) was found to have a SCr of 3.2 mg/dl. His medications were tamsulosin, apixaban, losartan and metoprolol tartrate. He denied NSAID usage. His vital signs were normal and his physical exam was unremarkable. His urinalysis was normal and his physical exam was unremarkable. His renal ultrasound was normal. A renal biopsy demonstrated 50% global sclerosis with remaining glomeruli normal. There was moderate interstitial fibrosis and tubular atrophy, and significant tubular calcium oxalate crystal deposition. At the time of discharge, she had poor creatinine clearance and remained on hemodialysis.

Discussion: ABBAD occurs from formation of IgG antibodies against low density lipoprotein-related protein 2 (LRP2) megalin which deposit on the tubular BM of the PCT. This approach requires a low renal threshold for biopsy in AKI. It is however unknown if early treatment can alter the typical abysmal renal outcome.

Lamotrigine-Induced Acute Interstitial Nephritis


Introduction: Medications such as penicillins, cephalosporins, vancomycin, ibuprofen, and ketorolac are the most common cause of acute interstitial nephritis (AIN), accounting for more than 75% of cases. Recently, antiepileptic drugs such as lamotrigine have been reported to cause AIN. Here, we report a case of a 39-year-old female who was on lamotrigine and admitted to the hospital with abdominal pain and acute renal failure.

Case Description: A 39-year-old female with a history of Hepatitis C, history of meth and heroin abuse, overactive bladder, hypothyroidism, and bipolar disorder presented to the emergency department with a week of abdominal pain. In the emergency department, she complained of nausea, constipation, and five days of hematuria. The patient was admitted after labs showed BUN/Cr of 48/3.69. Two weeks prior to presentation, she was started on lamotrigine 100 mg daily, which was held upon admission. Patient was started on IV fluids but her condition acutely worsened with thrombocytopenia, anemia, and leukopenia. She was started on methylprednisolone 500 mg IV daily due to concern for AIN vs vasculitis. Her blood and urine cultures resulted positive for E. coli, and she was subsequently started on IV ceftriaxone. The patient underwent a left kidney biopsy demonstrating AIN without crescentic glomerulonephritis, which was likely an allergic reaction secondary to lamotrigine use. Her biopsy also showed neutrophilic infiltration, likely secondary to pyelonephritis. She was discharged in stable condition on prednisone oral 20 mg daily.

Discussion: In summary, we present an adult patient on lamotrigine who was admitted due to acute renal failure. There have only been four reported cases of AIN induced by lamotrigine use. The patients had few commonalities other than lamotrigine use, but notably half of them were being treated for bipolar disorder. Our patient had a history of drug abuse with uncertainty on last use, which could represent another cause of
her AIN. After cessation of lamotrigine and treatment with methylprednisolone 500 mg IV, her urine output improved and renal biopsy confirmed AIN. Our case is significant because it substantiates the need for corticosteroid management of lamotrigine-induced AIN.

PO0316
A Case of Abrupt Anuria from Bilateral Kinked Ureters
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Introduction: Urinary tract obstruction is a well-known cause of reversible AKI. In patients with 2 functioning kidneys, bilateral ureteral obstruction is rare and unilateral ureteral obstruction rarely causes anuria and often does not result in a noticeable worsening of renal function. Here we describe a case of abrupt anuria and severe AKI secondary to bilateral kinked ureters resembling parenchymal renal failure.

Case Description: A 58-year-old female with metastatic epithelial mesothelioma underwent debulking peritoneectomy, bilateral salpingo-oophorectomy, and omentectomy with hyperthermic intraperitoneal chemotherapy with cisplatin at 50 mg/m². Bilateral ureteral catheters were placed preoperatively to avoid ureteral injury during surgery. The catheters were removed on post-operative day (POD) 0. Post-operative course was initially uncomplicated with stable renal function and more than 2L urine output a day. On POD 2, she was noted to have abrupt anuria despite the presence of a functioning foley catheter. Her creatinine increased from 0.7 mg/dL to 2.3 mg/dL. Renal ultrasound revealed normal sized, ecchogenic kidneys with mild bilateral hydropnephrosis. A CT cystogram with contrast was negative for a urinary leak. On POD 3, she remained anuric. At this point there was concern for a dense ATN caused by cisplatin and initiation of renal replacement therapy was considered. Given a high degree of suspicion for ureteral obstruction, the patient underwent cystoscopy with bilateral retrograde pyelogram revealing significant bilateral ureteral kinking (see image). Bilateral ureteral stents were placed with brisk urine output noted intraoperatively and her renal function improved back to baseline.

Discussion: Obstruction can occur at any point in the urinary tract but tends to only cause anuric AKI with an obstruction below the level of the bladder for patients with 2 functioning kidneys. Obstruction at the level of the ureter generally does not cause anuric AKI except in rare bilateral cases. This case may represent reflex anuria in the setting of a cause anuric AKI with an obstruction below the level of the bladder for patients with 2 functioning kidneys, bilateral ureteral obstruction is rare and unilateral ureteral obstruction rarely causes anuria and often does not result in a noticeable worsening of renal function. Here we describe a case of abrupt anuria and severe AKI secondary to bilateral kinked ureters resembling parenchymal renal failure.

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Recreation with a Concerning Diagnosis

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Introduction: Sarcoidosis is a systemic granulomatous disease of unknown etiology, characterized by non-necrotizing/non-caseating granuloma. The diagnosis of sarcoidosis requires stepwise approach to identify organs that may be affected and are amenable to biopsy, exclusion of other causes of granulomatous histopathology with special stains for mycobacteria and fungi, documentation of involvement of at least one additional organ system, and exclusion of other multisystem granulomatous diseases.

Case Description: A 73-year-old male with history of chronic kidney disease stage 2 received serum creatinine 1.4mg/dl, T2DM, hypertension, history of lymphoma presented to the clinic. He was noted to have a black ink tattoo on his shoulder, present for > 40 years. Blood work showed wbc 8.66, Hb 12/8.39, platelets 210, BUN/Cre 3.4/2.86, GFR 21. Na 139, K 3.6, Hco 26, Ca 10.9, P 3.5, Mg 2.2, HgbA1c 6.3%, Ua++protein. Follow up: Further work up for hypercalcemia and acute kidney injury showed Ca 11.2, iPTH 10.2, PTHrP 4.7, 25 vitamin D 78.2, 25 D 41, ACE 84, SPEP/UPEP: no monoclonal gammopathy. CXR negative for hilar lymphadenopathy. Renal ultrasound normal size kidneys with mild echogenicity. Chest CT showed calcified enlarged left lower lobe, supracavicular, chest wall and axillary lymph nodes and reticul/mixed mild pleural thickening. He underwent axillary lymph node biopsy which showed granulomatous lymphadenitis, with extensive infiltration by pigment laden macrophages, multiple non-caseating granuloma with foreign body type giant cell, some with intracellular pigment particles staining. Staining was negative for any mycobacterial or fungal organism, melanoma cocktail had negative staining, the immunostains showed increased background due to pigment. The differential included non-infectious granulomatous lymphadenitis and sarcoidosis.

Discussion: Our patient had a tattoo placed > 40 year ago and developed non-caseating granuloma with extensive infiltration by pigment laden granuloma. In an unexplained case of hypercalcemia in the setting of granulomatous histopathologic finding containing tattoo pigment, it is prudent to consider the diagnosis of sarcoidosis. Granulomatous reaction to tattoo pigment histologically can be sarcoïdal or foreign body type. These sarcoïdal granuloma usually involve the tattooed skin and may represent first manifestation of systemic sarcoidosis.

Liraglutide-Induced Hypercalcemia with AKI

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Introduction: Iatrogenic hypercalcemia from Vitamin D analogues and Calcium supplements is well-described. We present a patient who developed AKI and hypercalcemia on stable doses of these agents in CKD after being started on Liraglutide. This diabetic agent is a GLP-1 agonist, used for weight loss and glycemic control. We postulate the decreased gastric and intestinal motility caused by Liraglutide as the cause of increased enteric absorption and bioavailability of CaCO3 + Calcitriol leading to hypercalcemia-induced AKI.

Case Description: A 60 YO man with PMH of DM-2, Obesity and Multiple Myeloma (MM) presented for evaluation of AKI on CKD. He had CKD stage 3b due to MM with a b/l sCr of 3.5 mg/dl. Two years prior, he developed severe symptomatic hypocalcemia after treatment with Denosumab for osteolytic lesions. He was started on Calcitriol 1 mcg QD and CaCO3 2000 mg TID with stable serum Calcium, phos, iPTH and Cr for the next two years. He presents now with fatigue, paresthesias and weight loss, one month after being started on Liraglutide by his PCP. Labs: serum Cr 4.3 mg/dl (b/l 3 mg/dl), Ca 13 mg/dl (b/l 9.5 mg/dl), Phos 5.5 mg/dl, iPTH 25 pg/ml. AKI was deemed secondary to hypercalcemia and thus Liraglutide, Calcitriol and CaCO3 were discontinued with resolution over two weeks (Fig 1).

Discussion: Liraglutide improves glycemic control and reduces weight by slowing gastric and intestinal motility inducing early satiety. It modifies the enteric absorption of drugs and can increase the bioavailability of lipophilic drugs such as Calcitriol. Longer contact with gastric acid pH can potentially render agents more lipophilic with increased absorption. In our case, the temporal relationship between Liraglutide and onset of hypercalcemia, in a patient previously stable on unchanged doses of Calcitriol and CaCO3 suggests increased enteric absorption and calcium uptake caused by the GLP-1 agonist. We suggest close monitoring and potential reduction of Calcitriol and CaCO3 dose prior to starting gastroparetic agents like Liraglutide. Further studies are recommended to better elucidate the pharmacokinetics of Calcitriol and Liraglutide.

Rifampin-Induced Hemolytic Resulting in Pigment Nephropathy

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Introduction: Rifampin is an antibiotic that is a key component of multidrug regimens used to treat mycobacterial infections. The toxicity profile including hepatotoxicity is relatively well known, however some other complications including hemolysis, is a rare side effect. Pigment nephropathy is an abrupt deterioration of renal function as a consequence of the toxic action of endogenous heme-containing pigment on the kidney. We present a case of pigment nephropathy in the setting of rifampin-induced hemolysis requiring renal replacement therapy.

Case Description: A 74 year old female with a history of bronchiectasis, cavitary lung lesion due to pulmonary nocardiosis, mycobacterium avium-intracellulare infection (MAI) and atrial fibrillation presented with multi-organ dysfunction and anuria while recently restarting rifampin, azithromycin and ethambutol for the treatment of MAI infection. She was on laborator[y findings for a creatinine of 3.7 mg/dL and BUN 62 up from a baseline creatinine of 0.65 mg/dL with severe thrombocytopenia, platelet count 36 x 10^9/L and hemoglobin of 10.4g/dL. This coupled with liver dysfunction evidenced by INR 1.4, indirect bilirubin 6.2 mg/dL, AST 1311 U/L, ALT 506 U/L, elevated lactate dehydrogenase 2074 U/L, low haptoglobin 16 mg/dL, gave an initial suspected diagnosis of thrombotic microangiopathy (TMA). Peripheral blood smear revealed few schistocytes. Negative ADMATS13 antibody and a low PLASMIC score guided us not to initiate plasmapheresis. Serological work up including ANA, dsDNA, ANCA were negative, while C3 was low at 76 mg/dL and C4 14 mg/dL. The patient remained anuric and was initiated on hemodialysis. As the platelet count improved, she underwent kidney biopsy showing diffuse acut tubular injury with prominent casted casts. Immunofluorescence was negative without any evidence of TMA. After approximately two months of dialysis, renal function recovered back to serum creatinine of 1.14 mg/dL and the patient no longer required hemodialysis.

Discussion: Rifampin induced hemolysis is rare complication but can mimic TMA and cause renal dysfunction due to pigment nephropathy. Nephrologists should be aware of this possible rare complication of rifampin therapy.

Paraneoplastic Manifestations of Mantle Cell Lymphoma

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Introduction: Mantle cell lymphoma (MCL) is a rare and aggressive form of Non Hodgkins Lymphoma. Pathological patterns involving extra nodal sites are either the result of local infiltration or systemic dissemination. Our patient had a tattoo placed > 40 year ago and developed non-caseating granuloma with extensive infiltration by pigment laden granuloma. In an unexplained case of hypercalcemia in the setting of granulomatous histopathologic finding containing tattoo pigment, it is prudent to consider the diagnosis of sarcoidosis. Granulomatous reaction to tattoo pigment histologically can be sarcoïdal or foreign body type. These sarcoïdal granuloma usually involve the tattooed skin and may represent first manifestation of systemic sarcoidosis.

Page Kidney Secondary to Ruptured Myctic Pseudoaneurysm of Renal Artery: An Unusual Complication of Infective Endocarditis

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Introduction: Myctic pseudoaneurysms of renal artery following infective endocarditis are uncommon and rupture is the most feared complication. This can lead to subcapsular hematoma and development of Page kidney, an uncommon cause of secondary hypertension and renal dysfunction. We present a unique case of ruptured...
mycotic pseudoaneurysm of the renal artery that resulted in subcapsular hematoma and Paget’s kidney in an intravenous (IV) drug user.

**Case Description:** A 36-year-old female IV drug user presented with fever and hemoptysis. She denied history of kidney disease or preceding trauma. Admission blood pressure was 116/61 millimeter of mercury. Initial serum creatinine was 1.6 milligrams per deciliter (mg/dL). Renal ultrasound was unremarkable. She was found to have septic emboli on computed tomography (CT) of the chest, and methicillin-resistant Staphylococcus aureus (MRSA) grew in her blood cultures. Patient was diagnosed with infective endocarditis based on Duke’s criteria. She was started on IV antibiotics. On the third day of admission, she developed severe right flank pain and hematuria. She had worsening acute kidney injury and was started on hemodialysis. She was persistently hypertensive and progressively anemic. Hb dropped to 6.5 g/dL requiring transfusion of packed red cells. CT abdomen showed a new aneurysm and subcapsular hematoma of the right kidney. The bleeding pseudoaneurysm of the superior pole branch of the right renal artery was embolized by interventional radiology. She subsequently improved and no longer required hemodialysis. Plasma renin activity level returned elevated at 12.26 nanograms per milliliter per hour (reference 0.16-5.8 ng/mL).

**Discussion:** Renal artery aneurysm has a reported incidence of 0.1%. Subcapsular hematoma from rupture of mycotic pseudoaneurysm is a very rare complication of infective endocarditis. Page kidney is a hyperplasticinic phenomenon that results from the renal ischemia secondary to external compressive forces from subcapsular hematoma. Elevated renin level and activation of the renin-angiotensin-aldosterone system usually occurs, as in our patient. For this reason, angiotensin converting enzyme inhibitors and relief of external compression are great treatment options in these patients.

**PO0325**

A Case of AKI with ANCA Vasculitis Associated Retroperitoneal Fibrosis

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**Introduction:** Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) refers to a group of multi-system autoimmune small vessel diseases that can give rise to a broad array of clinical signs and symptoms. AAN-associated retroperitoneal fibrosis (RPF) is an exceptionally rare condition characterized by fibroinflammatory changes in the retroperitoneal space. Most RPF cases are idiopathic, or can be secondary to other medical conditions, the rarest association is with AAV. We present a case of AAN-associated RPF in a patient with recurrent acute kidney injury (AKI).

**Case Description:** A 57-year-old male with a history of reactive arthritis presented to the hospital with acute left lower quadrant abdominal pain and found to have AKI due to obstruction by a soft tissue nodule on the left pelvic sidewall with mild-moderate hydronephrosis. He underwent left ureteral stent placement and his hydronephrosis resolved. Left iliac lymph node pathology was consistent with RPF. He was started on pulse steroids, Rituximab, and IVIG. He was admitted for sudden onset of anuric AKI: Clinical Case Reports. He subsequently had a series of repeat admissions to the hospital with fevers, hypotension, shortness of breath, and recurrent AKIs. Each time, he was treated with antibiotics and stress-dose steroids with resolution of his symptoms. He was advised to return to the hospital if his symptoms progressed to include hemoptysis and epistaxis. He was found to have proteinase-3 antibodies (PR-3) consistent with granulomatosis with polyangiitis and was started on rituximab.

**Discussion:** RPF in association with AAV is an extremely rare condition with very few cases documented in the literature. RPF is an uncommon collagen vascular disease characterized by inflammation of the retroperitoneal space which can produce obstruction notably affecting the abdominal aorta, iliac arteries and ureters. Mostly idiopathic, RPF can be associated with vasculitis, infections, medication, and neoplasms. As highlighted in this case, AAV should be considered with a recently diagnosed RPF and recurrent AKI. A hallmark is improvement of symptoms with steroids. This is important with reference to patient outcomes as delayed treatment, especially when renal disease is present, portends a higher risk of end stage renal disease and early mortality.

**PO0327**

IV Immunoglobulin Triggering Renal Cortical Necrosis


**Introduction:** Renal cortical necrosis is a rare cause of acute kidney injury mostly seen in infants and young women with obstetric complications accounting for >50% of cases. Intravenous immunoglobulin (IVIG) is used for treatment of various conditions and one of the complications associated with its use is thromboembolism. We report the case of a patient that developed thrombotic microangiopathy with renal cortical necrosis after receiving IVIG.

**Case Description:** A 50-year-old man with Alport syndrome status post renal transplant in 2008 complicated by nasal Natural Killer T-cell lymphoma in 2017, had cutaneous recurrence in 2020 and was started on treatment with Brentuximab. He subsequently developed Immune Thrombocytopenic Purpura (ITP) and was started on pulse steroids, Rituximab, and IVIG. He was admitted for sudden onset of anuric renal failure after receiving the first dose of IVIG. He was off anticoagulation since diagnosis of NK/T-cell lymphoma in 2008 and Tacrolimus was held after he developed thrombocytopenia raising concern for alloagraft rejection. The patient was started on dialysis. Evaluation including C3, C4, ANA, anti-GBM antibodies, ANCA, rheumatoid factor, cryoglobulins, HIV, Hepatitis B and C, blood and stool cultures, stool Shiga toxin, echocardiogram, CMV PCR, peripheral smear, BK virus, ADAMTS 13, and DSA were unremarkable. He underwent renal biopsy that showed extensive cortical necrosis and thrombotic microangiopathy. A follow up ultrasound showed no blood flow to the kidney allograft. He did not had renal recovery and was discharged on outpatient dialysis.

**Discussion:** Thrombosis is a well-known complication of IVIG. IVIG increases blood viscosity and reduced blood flow promoting thrombogenesis. This can manifest as acute coronary syndrome, stroke, or venous thromboembolism. In our patient, it has manifested as thrombotic microangiopathy with cortical necrosis. IVIG, although, a very useful drug in treatment of various medical conditions should be used with caution, ensuring adequate hydration while monitoring baseline viscosity in patients at risk of hyperviscosity, prior to administration.
**PO0328**

**Bilateral Renal Artery Stenosis**

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**Introduction:** We present a patient with renal failure and accelerated hypertension while on a chronic stable dose of an angiotensin-converting enzyme inhibitor (ACEI) due to progression of renal artery stenosis (RAS).

**Case Description:** A 73-year-old Caucasian male with DM2, HLD, CKD2 was referred for evaluation of resistant HTN. Initial visit, blood pressure (BP) was controlled on stable doses of metoprolol XR 50 mg qd, amldipine 10 mg qd, hydrochlorothiazide 25 mg qd and lisinopril 40 mg qd. Ultrasound revealed bilateral 11 cm kidneys, left proximal RAS with peak systolic velocities (PSV) of 2.6 m/s, globally elevated resistive indices (RI) >0.83-0.86. Given controlled HTN, stable renal function with baseline Scr range of 1.1-1.2, he was conservatively managed with above medications and statin. On 4 month follow up, BP 160-200/60s, despite stable medication doses and compliance, unexplained elevated Scr 2.1 mg/dL. Given suspicion of RAS progression, renin and aldosterone level were drawn measuring 3000 pg/ml (6 mo prior 1800) and 16 ng/dL (prior 12), respectively. Patient underwent renal artery duplex with noted bilateral RAS: >60% diameter reductions and RI averaging 0.85. ACEI was promptly discontinued and within 48 hours, the patient’s Scr improved to 1.5, and he underwent CT-Angiogram (CTA) abdomen to determine if intervention needed. CTA noted bilateral moderate ostial RAS (left 50%, right 30%) due to progression of atherosclerotic calcifications. At follow up, Scr normalized to 1.2, BP controlled on amldipine 10 mg qd and carvedilol 3.125 mg BID. Given the resolution of uncontrolled resistant HTN, and return to baseline Scr, renal artery stenting was not pursued and the decision remained continued monitoring.

**Discussion:** ACEI are indicated as effective anti-HTN therapy in unilateral RAS. However, when accelerated hypertension and/or renal failure occurs while on an ACEI in an elevated risk individual with RAS, a high index of suspicion for RAS progression must be entertained and the ACEI promptly discontinued. Individuals at risk for progression of atherosclerotic lesions are elderly individuals, especially those with HLD and DM. Elevated renin levels and Scr, which were rapidly obtained during our clinic visit, were suggestive of pronounced renal ischemia and prompted quick action of ACEI discontinuation, definitive imaging and overall clinical improvement.

**PO0329**

**The Role of KYNU in Mediating Sex Dimorphism of AKI**

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**Background:** Acute kidney injury (AKI) is a disorder that is associated with high mortality and a high risk for development of chronic kidney disease. It is well documented that female gender is associated with relative resistance to kidney injury, the underlying mechanism is incompletely understood. Mounting evidence suggests that NAD+ levels are associated with enhanced tolerance of kidney to injury, and exogenous supplement of NAD+ precursor NMN alleviates AKI. The present study examined NAD+ synthesis pathways and their association with gender related susceptibility to AKI.

**Methods:** IRRI AKI model was performed on 8 weeks old wild-type C57BL/6 female and male mice, bilateral renal pedicles were clamped for 22 minutes. The animals were euthanized 48 hours after reperfusion. Prepubertal (3 weeks old) wild-type C57BL/6 female or male mice were ovariectomized or castrated respectively and were euthanized after 5 weeks for renal KYNU expression analysis. The metabolites of NAD+ de novo pathway were examined by HPLC.

**Results:** Following IRRI, female mice had less severe kidney injury, manifested as lower BUN and Cr levels, lower kidney injury marker (NGAL) expression and alleviated tubule damage. Further study revealed renal KYNU, but not other enzymes involved in the NAD+ synthesis pathways, was 5 fold higher in female mice compared to male at age 8 weeks, despite that it is comparable between female and male mice at age 7 days. Prepubertal oophorectomy in female mice did not significantly decrease renal KYNU expression, in contrast, prepubertal castration of male mice increased renal KYNU levels to that seen in female, demonstrating KYNU is regulated by testosterone other than estrogen. HPLC result showed no difference in the metabolites concentration between male and female mice under physiological condition, however, following IRRI, 3-HAA and QA concentration, which are precursors for NAD+, were significantly upregulated in the female urine but remained unchanged in the male urine, so as QA concentration in the female urine, both 3-HAA and QA increase. Therefore, the NAD+ synthesis pathway is more activated in the female kidney under AKI condition, which may contribute to NAD+ synthesis and improve AKI.

**Conclusions:** We propose a KYNU-dependent mechanism, which contributes to the relative renoprotection of female after IRRI by regulating renal NAD+ level. NAD+ de novo synthesis pathway may be a potential target for IRI-AKI treatment.

**Funding:** Government Support - Non-U.S.

**PO0330**

**β-Estradiol Protects from Ferroptosis and Explains the Higher Sensitivity of Murine Male vs. Female Kidney Tubules to Acute Tubular Necrosis**

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**Background:** In several preclinical models of acute kidney injury (AKI), male mice are known to exhibit a higher sensitivity compared to females, but mechanistic insights to explain this observation have been lacking over decades. Acute tubular necrosis (ATN) is a common feature of AKI the sensitivity to which might explain this long-standing obstacle.

**Methods:** Isolated murine kidney tubules were assessed with cell death assays (e.g. LDH release assay).

**Results:** Here, we demonstrated in isolated murine kidney tubules that spontaneous ATN is a regulated event. While tubules isolated from combined necroptosis- and pyroptosis-deficient mice (NLKL/GSDMD<sup>−/−</sup>) did not show different LDH release levels compared to control, inhibition of ferroptosis by the ferroptosis inhibitor ferostatin 1 (Fer-1) significantly protected wild type tubules. Importantly, we detected less spontaneous necrosis in female versus male tubules. While female tubules exhibited resistance to LDH release, male tubules were sensitive but could be protected by co-incubation with Fer-1. Tubular sex specific differences could not be explained by potential pro-ferroptotic effects of testosterone but rather by anti-ferroptotic effects of β-estradiol.

**Conclusions:** In summary, while these data confirm the involvement of ferroptosis in spontaneous tubular necrosis, our findings strongly identified β-estradiol as a general inhibitor of ferroptosis. This anti-ferroptotic effect explains the difference in sensitivity toward ATN of renal tubules of male and female mice.

**Funding:** Government Support - Non-U.S.

**PO0331**

**Pharmacological Validation of HDAC8 as a Therapeutic Target for AKI**

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**Background:** Treatment for acute kidney injury (AKI) remains a significant unmet medical need and there are few validated targets on which to base therapeutic development and drug discovery programs. Our work has revealed histone deacetylase 8 (HDAC8) as a promising new candidate.

**Methods:** Known potent, selective HDAC8 inhibitors, as well as negative control compounds within the same scaffold, were evaluated in gentamicin-induced AKI in zebrafish (zAKI), ferroptosis injury AKI (IRI-AKI) in mouse, and in human kidney organoid-derived tubule cells subjected to hypoxia.

**Results:** Known potent, selective HDAC8 inhibitors such as PCI-34051, tetrahydroxysobutane hydroxamic acids and an isoxindol amide were effective in the zAKI assays, while control compounds (i.e. HDAC8 inactive compounds of the same scaffold) were not effective. Testing of PCI-34051 in the IRI-AKI mouse model showed improvements in kidney function markers (BUN, GFR) and while there was no significant reduction in renal fibrosis as measured by Sirius red staining, expression of the renal fibrosis markers Collagen 1α1 and Loxl2 were reduced. Further evaluation of PCI-34051 and the isoxindol amide in primary renal epithelial cells from human kidney organoids showed that HDAC8 inhibition is associated with a pronounced suppression of interstitial myofibroblasts and one mechanism of action may be inhibition of ferroptosis.

**Conclusions:** Our data supports that pharmacological inhibition of HDAC8 ameliorates AKI injury in multiple in vivo models and validates this target as a promising therapeutic lead to treat AKI.

**Funding:** NIDDK Support

**PO0332**

**Class IIa Histone Deacetylase Inhibition Blunts AKI by Suppressing Apoptosis, Enhancing Autophagy, and Promoting Cellular Proliferation**

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**Background:** Expression and function of histone deacetylases (HDACs) vary with cell types and insults. Our recent studies have shown that class IIa HDACs contribute to renal fibrosis chronically, but their roles in acute kidney injury (AKI) remain unknown.

**Methods:** In this study, we examined the effect of TMP269, a potent and selective class IIa HDAC inhibitor on follic acid (FA) and ischemia/reperfusion (IR)-induced AKI in mice.

**Results:** Protein levels of four class IIa HDAC isoforms (4, 5, 7, 9) were increased in kidneys of IR-induced AKI mice. TMP269 treatment showed improvements in kidney function markers (BUN, tGFR) and while there was no significant reduction in renal fibrosis as measured by Sirius red staining, expression of the renal fibrosis markers Collagen 1α1 and Loxl2 were reduced. Further evaluation of TMP269 and the isoxindol amide in primary renal epithelial cells from human kidney organoids showed that HDAC8 inhibition is associated with a pronounced suppression of interstitial myofibroblasts and one mechanism of action may be inhibition of ferroptosis.

**Conclusions:** Our data supports that pharmacological inhibition of HDAC8 ameliorates AKI injury in multiple in vivo models and validates this target as a promising therapeutic lead to treat AKI.

**Funding:** NIDDK Support

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**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Cisplatin AKI: Localization of Cell State Injury Clusters with Spatial Transcriptomics

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Background: Clinical and preclinical studies revealed that damage to proximal tubular (PT) epithelial cells after severe acute kidney injury (AKI) is a critical mechanism underlying the development of chronic kidney disease (CKD). Recent advancements of single-cell RNA sequencing (scRNA-seq) approach identified that PT cells adopt heterogeneous molecular states after injury and contribute to maladaptive repair. However, their cell fate after mild versus severe AKI remains poorly understood.

Methods: Single-cell transcriptomics and genetic fate-mapping approaches were used in a mouse model of unilateral ischemia-reperfusion injury (IRI) to investigate PT cell dynamics after short (20 min) and prolonged ischemia (30 min). For scRNA-seq analyses, we analyzed a total of 18,258 cells from the damaged kidneys harvested on 6 hours, and 1, 7, and 21 days after 30 min ischemia and the homeostatic normal kidneys. We used Seurat’s integration and label transfer to create the integrated dataset. To infer the dynamic cellular process during injury and repair, we used two computational tools (Monocle 3 and Velocyt).

Results: Our single-cell mouse atlas of maladaptive repair shows that PT cells develop a more clearly distinct, pro-inflammatory state following injury. These cells are characterized by reduced expression of homeostatic genes (ex. Lyp2, Slc34a1) and enrichment of genes associated with kidney development (ex. Sow, Cdh8) and kidney injury (ex. Vcam1, Hic1). Gene ontology analysis of these cells revealed high enrichment of pro-inflammatory signaling. Our genetic fate-mapping using a Sox18CreERT2, Rosa26-tdTomato mouse line showed these inflammatory PT cells transiently appear after short ischemia and return to their original state without inducing fibrosis. However, they accumulate and contribute to persistent inflammation after prolonged ischemia.

Conclusions: Our single-cell transcriptomic and genetic fate-mapping approaches identify that the accumulation of inflammatory PT cells after severe injury underlies the maladaptive repair process. Future studies of how this pathologic cell state persists and contributes to inflammation will inform us to develop novel therapeutic approaches for AKI and its transition to CKD.

Funding: NIDDK Support, Private Foundation Support

Cisplatin AKI: Localization of Cell State Injury Clusters with Spatial Transcriptomics

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Background: Human acute kidney injury (AKI) is a multifactorial process and severity varies between individuals. The murine cisplatin model is a reproducible example of AKI with limited confounding variables. We determined the pathways and injury markers dysregulated across the nephron in cisplatin AKI. We localized relevant human cell state signatures with spatial transcriptomics (ST) to determine which were most prevalent in cisplatin AKI and where these cells reside.

Methods: Six 129S6-SVE mice received vehicle or cisplatin (0.5 mg/g). After 72 hours, mouse kidneys were harvested and preserved for histology, single cell sequencing (scRNAseq), and ST. Gene mapping was completed with Cell Ranger 5.0.1 (scRNAseq) or Space Ranger 1.2.0 (ST). Human scRNAseq data was downloaded from the Scanpy org, clustered by cell state (injured, adaptive, degenerative, transitioning, cycling, or reference) and mapped to mouse orthologs in Enemb database. Seurat clustered and integrated scRNAseq data as well as performed spatial mapping. Visualizations were created with R Studio.

Results: Cisplatin mice had increased BUN and tubular atrophy. scRNAseq identified 32 cell clusters, merged across common cell types. Cell cycle genes (Cdh11a) were upregulated across epithelial cell types, but injury markers (Lcn2 and Spp1) were on Space Ranger 1.2.0 (ST). Human scRNAseq data was downloaded from the Scanpy org, clustered by cell state (injured, adaptive, degenerative, transitioning, cycling, or reference) and mapped to mouse orthologs in Enemb database. Seurat clustered and integrated scRNAseq data as well as performed spatial mapping. Visualizations were created with R Studio.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Unraveling Single-Cell Responses in Human AKI
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Background: Acute kidney injury (AKI) is frequently observed in critically ill patients and is associated with a poor prognosis. AKI has recently moved into the focus of interest during the SARS-CoV-2 pandemic as high rates of AKI have been reported in severe COVID-19. We aimed to delineate cell type-specific molecular phenotypes associated with human AKI, including COVID-associated AKI. Methods: We analyzed human kidney tissue morphology and single-nucleus RNA sequencing. Samples included kidney biopsies obtained within 2 hours post mortem from patients who succumbed to critical illness with and without evidence of AKI. Samples also included tumor-adjacent normal kidney tissues obtained during surgeries. AKI cases included patients with severe courses of COVID-19 (COVID-AKI) and patients with other types of critical illness associated with systemic inflammation (Non-COVID-AKI). Post-mortem kidney tissues obtained 30 min, 1 hour and 2 hours after death from a brain-dead patient without AKI were analyzed to assess the impact of post-mortem effects. Results: Single-nucleus sequencing from kidney tissues yielded data of high transcriptome and spatial resolution, which allowed transcription-based identification and de-novo spatial reconstruction of kidney cells. Principal component and differential gene expression analyses indicated that the presence of clinically confirmed AKI was the primary driver of global kidney transcriptomes and that different molecular subtypes of AKI existed. In contrast, the sampling time post-mortem and the presence of COVID-19 had minor effects. Subclustering analyses of different kidney cell types identified subclasses of cells representing injured kidney tubular cells, which were marked by distinct biomarker expression and expression signatures signifying intrinsic responses to inflammation, an induction of epithelial-to-mesenchymal transition, and an upregulation of hitherto unrecognized novel receptor-ligand pairs.

Conclusions: We provide the first cell type-specific molecular atlas of human AKI, revealing unanticipated disease subtypes and cell type-specific injury patterns.

Mechanisms of Nucleophosmin-Mediated Regulated Cell Death During Renal Ischemia
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Background: Nucleophosmin (NPM) is a protein chaperone that potentiates Bax-mediated cell death during ischemic AKI by an unknown mechanism. In contrast, heat shock protein 70 (Hsp70) is a potent anti-apoptotic agent that promotes renal cell survival and preserves organ function. In this study, we characterize for the first time the intracellular events in which NPM and Hsp70 compete to regulate cell survival during ischemic stress.

Methods: Hsp70 wild type (WT) or Hsp70 mutants either restricted to the cytosol (Hsp70 985A) or unable to enter the nucleolar region (Non-AKI). Hsp70 null PTEC that expressed a cytosol-restricted NPM mutant.

Results: Equivalent, selective over-expression of the hsp70 proteins significantly improved cell survival after ischemic stress in the following rank order: WT > M45 > 985A (each P < 0.05 vs. control). Only Hsp70 mutants with nuclear access (WT and M45) inhibited 985A Hsp70 phosphorylation that mediates NPM translocation and reduced cytosolic NPM accumulation. Neither WT nor the Hsp70 mutants inhibited stress-induced NPM de-oligomerization. In contrast, WT > 985A > M45 Hsp70 significantly improved survival in Hsp70 null PTEC that expressed a cytosol-restricted NPM mutant, interacted with cytosolic NPM, and reduced NPM-Bax complex formation required for mitochondrial injury and cell death. Hsp70 knockout prevented the cytoprotective effect of suppressing NPM in ischemic PTEC and also increased cytosolic NPM accumulation after acute renal ischemia in vivo, emphasizing the protective effects of Hsp70 on NPM-mediated renal cell toxicity.

Conclusions: These observations identify key steps that mediate NPM toxicity during ischemia-induced cell death: (1) nuclear NPM de-oligomerization, (2) NPM translocation into the cytosol and (3) cytosolic NPM-Bax complex formation. Hsp70 promotes renal cell survival during ischemic acute kidney injury partly by inhibiting two of these toxic events in distinct cell compartments: nuclear NPM translocation and NPM-Bax interaction in the cytosol. Renal cell survival during ischemic AKI is substantially improved by interfering with events that render NPM toxic.

Funding: NIDDK Support
Methods: Kidney ischemia-reperfusion injury (IRI) was employed to induce AKI in mice. We subjected mice to IRI. A molecular docking study, and thermal shift assays were performed to determine the binding capacity between Limonin and key targets. In vivo and in vitro molecular experimental pathology studies were applied.

Results: After ischemic AKI, pretreatment of Limonin preserved kidney functions, ameliorated tubular injury, and repressed inflammation in the diseased kidneys, compared to the vehicles. In structure, we identified Limonin has active binding sites for 38 cell-free extracellular nucleic acid, the potential of transfer RNA (tRNA) encapsulated within extracellular vesicles as a new class of urine biomarkers for kidney injury has not been explored.

Methods: Using rat renal ischemia-reperfusion and tubular cell injury models, we tested if extracellular release of tRNA encapsulated in extracellular vesicles responds to kidney injury and determined the mechanism of tRNA packaging into extracellular vesicles under oxidative stress.

Results: We detected a set of tRNAs present in urine that was packaged inside extracellular vesicles. We then identified extracellular vesicle-loaded tRNAs differentially released after ischemia-reperfusion injury and oxidative stress, in a reproducible manner. Next, we determined post-transcriptional methylation of these tRNA as a response to oxidative stress present in extracellular vesicle tRNAs. Mechanistically, oxidative stress decreases tRNAs loading into intracellular vesicles, mobilizes tRNAs to endosomes destined to extracellular vesicles, suppresses release of extracellular vesicles from the cell surface, and induces Mti-mediated transcriptional repression of the tRNAs, all of which affect the availability of tRNAs in the cytoplasm.

Conclusions: Our data support that decreased release of non-fragmented tRNAs via extracellular vesicles reflects oxidative stress of kidney tubules, which might be a new source of urine biomarkers for ischemic kidney injury and could lead to reparation protein translation in response to oxidative stress.

Funding: NIDDK Support

PO0341

Inhibition of miR-155 Ameliorates AKI by Protecting Tubelomerase and Reducing DNA Damage of Renal Tubular Cells

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Background: Acute kidney injury (AKI) is associated with significant morbidity and mortality, and currently there is no therapy to prevent or treat established AKI. miR-155 is significantly up-regulated in diabetic nephropathy, IgA nephropathy, bilateral renal ischemia-reperfusion injury (IRI) or drug-induced AKI. However, the molecular mechanism of miR-155 in AKI remains to be studied.

Methods: We subjected miR-155−/− mice and wild-type controls, as well as human proximal tubule cells, to cisplatin-induced AKI models. We assessed kidney function and injury with standard techniques and measured telomere by the fluorescence in situ hybridization.

Results: The expression level of miR-155 was upregulated in both cisplatin-induced AKI mice model and cisplatin-treated HK2 cells. Inhibition of miR-155 expression protected cisplatin-induced AKI both in vivo and in vitro. A molecular docking study, and thermal shift assays were performed to determine the binding capacity between Limonin and key targets. In vivo and in vitro molecular experimental pathology studies were applied.

Conclusions: We demonstrated that inhibition of miR-155 ameliorates AKI involving the targeting and regulation of TRF1 and CDK12, indicating a novel regulatory mechanism and elucidating a potential target for cisplatin induced AKI treatment.

Funding: Government Support - Non-U.S.

PO0342

Evaluation of Urinary NHE3 in Rats with AKI

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Background: Acute kidney injuries (AKIs), caused by hypovolemia, ischemia-reperfusion, or nephrotoxins, are concerned with high morbidity and mortality. Urinary N-tau exchanger isoform 3 (NHE3) has been demonstrated as a non-invasive marker of acute tubular necrosis. However, the ideal diagnostic biomarker in AKI is still lacking.

Methods: In order to determine the potential role of urinary NHE3 in early diagnosis of AKI, we evaluated the expression of NHE3 in daily urines from rat models of AKI, including low NaCl (0.1%) plus candesartan (1mg/kg/day, IP) for 7 days, ischemia-reperfusion (ischemia for 40min, reperfusion for 2h) and cisplatin (20mg/kg for 7 days) in Sprague Dawley rats (male, 2-3 months old, 4-7 rats per group). Urine exosomes were isolated by a series of centrifuges including ultracentrifuges.

Results: NHE3 levels (western blotting) were increased at day 1, which was 1 day before serum creatinine increased in low NaCl/candesartan rats and reperfusion rats (day 1) relative to controls. They were also increased in cisplatin rats at day 2 (1 day before serum creatinine increased). Furthermore, NHE3 in original urines from 6 patients diagnosed with AKI (Scr 249.83 ± 166.93 umol/L) and 6 volunteers with normal renal function (Scr 68.67±13.20umol/L) were assessed without ultracentrifuge isolation. NHE3 was increased remarkably in AKI patients (333±28, % of controls) compared with volunteers (100±30, %, t-test, P<0.05).

Conclusions: Our results in rats and patients suggest that assessment of urine NHE3 may be a potential non-invasive biomarker for early detection of various acute kidney injuries.

Funding: Government Support - Non-U.S.

PO0343

Tubular β-Catenin Ameliorates AKI by Restoring Mitochondrial Biogenesis

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Background: Renal tubular β-catenin signaling plays a protective role in acute kidney injury (AKI), but the underlying mechanisms remain unclear. Mitochondrial dysfunction is responsible for the pathogenesis of AKI. This study aims to investigate the role of β-catenin activation on mitochondrial biogenesis in tubular cells upon AKI and its underlying mechanism.

Methods: Loss- and gain-of-β-catenin function was established in mice with tubular-specific β-catenin stabilization (TubCat mice) and knockout (TubCatKO mice). Septic and aseptic AKI was induced by exposure to LPS or ischemia/reperfusion, respectively. Kidney injury was examined by NGAL immunohistochemical staining. Markers of mitochondrial biogenesis were determined by Western blot, real-time quantitative PCR and immunofluorescence staining. Signal cascade was examined by Western blot.

Results: Compared to the controls, TubCat mice under septic and aseptic AKI had significantly alleviated kidney injury and enhanced mitochondrial biogenesis as indicated by (i) reduction of NAD+ positive tubules; (ii) restoration of mitochondrial mass protein TOMM20 and mitochondrial biogenesis molecules PGC-1α and NRF1; (iii) increasing co-localization of PGC-1α and β-catenin in renal tubules and (iv) increasing FOXO3A signaling against septic and aseptic injury. Consistently, kidney injury, and mitochondrial dysfunction were aggravated in TubCatKO mice versus their control littermates.

Conclusions: In both septic and aseptic AKI, tubular β-catenin stabilization restores mitochondrial homeostasis through the FOXO3A/PGC-1α signaling pathway.

Funding: General Research Fund (HKU 1719818), RGC Collaborative Research Fund (Ref: C7018-16G) and Hong Kong Society of Nephrology Research Grant (2019)

PO0344

CB11: Mitochondrial Effects in Renal Proximal Tubular Cells

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Background: Oxidative stress and mitochondrial dysfunction are characteristic of many acute and chronic conditions such as acute kidney injury and chronic kidney disease. Renal proximal tubular cells (RPTC) are mitochondria dense, dependent on oxidative phosphorylation, and are particularly susceptible to injury. Identifying compounds that modulate mitochondrial biogenesis (MB) is of increasing importance for the treatment of renal diseases associated with metabolic dysfunction. We investigated the effects of 1-buty-3-hydroxy-1-[2-oxo-2-(pyridin-2-ylthyl)-1,3-dihydory-2H-indol-2-one, (CB11), on MB, mitochondrial dynamics, antioxidant response, and apoptosis in RPTC using a model of renin-angiotensin-induced in some NHE3 phosphorylation.

Methods: In primary cultures of renal proximal tubular cells, we used uncoupled oxygen consumption rate (FCCP-OCR), transmission electron microscopy, immunoblotting, oxidant-induced injury with tert-butyl hydroperoxide (TBHP), and flow cytometry.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

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**Results:** CB11 (0.1 nM) treatment increased FCCP-OCR and mitochondral number after 24h. CB11 increased control or CB11 exposed samples 48h post-injury. TBHP-induced injury increased Amv+; while exposure of CB11 did not attenuate Amv+.

**Conclusions:** CB11 represents a new and highly potent inducer of MB with a unique signaling pathway in RPTC. Our data reveal that CB11 pretreatment does not prevent oxygen-induced cell death but acts as a RPTC protector. Future studies will test this compound in AKI and CKD models.

**Funding:** Commercial Support - University of Arizona

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**PO0345**

**Title:** FDA-Approved Drug Lasmiditan Stimulates Mitochondrial Biogenesis and Promotes Recovery of Vasculature and Renal Function After Ischemia-Reperfusion Injury in Mice

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**Background:** Acute kidney injury (AKI) is induced by multiple mechanisms (e.g. ischemia/reperfusion (IR), drugs, sepsis) and results in tubular and vascular dysfunction. Mitochondrial fission is a key mediator of injury and recent studies have shown that pharmacological-induced mitochondrial biogenesis (MB) can provide renal recovery. Activation of the 5-HT1F receptor has been demonstrated to induce MB in the mouse kidney and the absence of said receptor results in greater renal injury from I/R, demonstrating the importance of the 5-HT1F receptor in the kidney. The goal of this study was to test the efficacy of the potent, selective, and FDA-approved 5-HT1F receptor agonist lasmiditan in a mouse I/R-induced AKI model.

**Methods:** Male mice were subjected to I/R-induced AKI. After 24h, serum creatinine was collected for analyses. I/R and I/R+lasmiditan were divided into two groups and dosed with lasmiditan (0.3 mg/kg) daily. Vascular leakage was determined using Evan’s blue dye and tight junction proteins.

**Results:** Treatment with lasmiditan increased renal cortex mitochondrial number by 33%. Serum creatinine levels were similar in the I/R+vehicle group and I/R+lasmiditan group at 24h. At 44h, serum creatinine markedly decreased by 72% and KIM-1 decreased by 75% in I/R+lasmiditan group compared to I/R+vehicle group, respectively. PGC-1α and electron transport chain complexes IV and V were restored in I/R+lasmiditan group. Vascular permeability increased 2.5-fold in the I/R+vehicle group and was restored to control levels in the I/R+lasmiditan group. The tight junction proteins occludin, ZO-1, and Claudin 5 decreased in the I/R+vehicle group and was restored to control levels in the I/R+lasmiditan group.

**Conclusions:** In this study we demonstrate that FDA approved lasmiditan restores mitochondrial function and renal and vascular function after I/R injury in mice. Lasmiditan could be repurposed for the treatment of AKI in humans.

**Funding:** Veterans Affairs Support

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**PO0346**

**Title:** Treprostinil Improves Mitochondrial Dynamics and Reduces Oxidative Stress During Renal Ischemia-Reperfusion Injury in Rats

Maewen Ding,1 Evelyn Tolbert,2 Mark Birkenbach,2 Reginald Y. Gohh,2 Nisanne S. Ghomem,1 University of Rhode Island, Kingston, RI.1 Rhode Island Hospital, Providence, RI.

**Background:** Renal ischemia-reperfusion injury (IRI) is a major factor that contributes to acute kidney injury (AKI). Mitochondria enriched in renal proximal tubular cells are particularly susceptible to IRI-induced oxidative stress. Currently, there is no treatment for IRI available. We recently demonstrated the efficacy of treprostinil (RotaCare®) as a prophylactic agent in reducing AKI demonstrated in rat renal IRI. This study investigates the role of treprostinil in improving mitochondrial dynamics and reducing oxidative stress during rat renal IRI.

**Methods:** Male Sprague Dawley rats were subjected to 45 minutes of bilateral renal ischemia followed by 1-72 hours reperfusion. Placebo or treprostinil (100 ng/kg/min) was administered subcutaneously via an osmotic mini-pump. Blood and kidney tissue were collected for analyses.

**Results:** Treprostinil significantly reduced renal injury and peak elevated serum creatinine in both 24-48 h post-reperfusion compared to placebo-treated animals. PAS staining revealed that treprostinil markedly reduced epithelial cell necrosis and partially attenuated apical brush border loss at 6 hours post-IRI vs. placebo, with near reconstitution of normal architecture by 48-hours post-reperfusion. Also, treprostinil reduced renal antioxidant levels, including catalase, superoxide dismutase activity, and glutathione content vs. placebo (p<0.001). In parallel, treprostinil improved the mRNA expression of Nqo1 and Gclc, that encode NAD(P)H dehydrogenase [quinone] 1 and glutamate-cysteine ligase catalytic subunit (Gclc) to 45% (p<0.05) and 32% (p<0.01) of sham at 48 hour post-IRI vs. placebo. Treprostinil reduced the renal mitochondrial fission proteins Drp1 and Mff by 61% and 44% relative to placebo (p<0.001) and restored the phosphorylation of mitochondrial fusion marker Sirt3 along with the mRNA expression of Mfn1, Mfn2, and Opal to that of sham (vs. placebo, p<0.0001).

**Conclusions:** Treprostinil reduced renal oxidative stress as well as Drp1-mediated mitochondrial fission and upregulated Sirt3-mediated mitochondrial fusion, thereby improving renal mitochondrial dynamics and protecting against renal IRI. These results support the clinical investigation of treprostinil as a viable therapy to reduce renal IRI.

**Funding:** Other NIH Support - The material presented herein is supported by Institutional Development Award (IDeA) U54GM115677 from the National Institute of General Medical Sciences of the National Institutes of Health, which funds Brown University Advance-CTR (U54GM115677), and the University of Rhode Island Core Lab (P20GM103430).

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**PO0347**

**Title:** A Mitochondrial Cardiolipin Targeting Peptide Ameliorates Kidney Oxidative Damage

Soje Kwon,1 Semin Cho,1 Jong moo Jun,1 Kyu hong Kim,1 Jae Woo Lee,2 Dong Ki Kim,1 Yon Su Kim,1 Seung Hee Yang,1 Sevilla National University Hospital, Jongno-gu, Seoul, Republic of Korea; 2National Cancer Center, Goyang, Gyeonggi-do, Republic of Korea.

**Background:** Mitochondria is a major organelle of adenosine triphosphate production and O2 consumption. Also, kidney is mitochondria abundant organ. Many mitochondria-targeting agents were developed, though there is no single agent approved in clinical practice. We investigate renoprotective effect of newly invented mitochondrial cardiolipin targeting peptide, the SNU-RD, in hypoxic condition.

**Methods:** Based on our experience that dimer formation by bisulfate bond of cell penetrating peptide accelerates its stability, we synthesized 15 candidate tetra-peptides which target inner mitochondrial membrane specific phospholipid, the cardiolipin. After cell viability, distribution and mitochondrial functional test, we selected best candidate and tentatively named as SNU-RD. As hypoxic damage, bilateral ischemia-reperfusion injury (IRI) and primary cultured human proximal tubular epithelial cells (pTECs) with H2O2 were chosen. Wild-type mice were divided into four groups: sham, IRI, IRI with low dose or high dose SNU-RD. After SNU-RD treatment with various concentration (10nM, 100nM, 1000nM), high dose H2O2 stress was done. Mitochondrial function was tested and mitochondrial oxygen consumption rate (OCR) was measured.

**Results:** In IRI, serum BUN and creatinine were significantly decreased without SNU-RD dose dependency. Pathologic findings (NGAL and cytochrome C) were improved. Also, mitochondrial anti-oxidative enzyme (NQO-1, SOD-1), ATP6 and IL-10 mRNAs were over-expressed after SNU-RD treatment. Cell viability was increased with dose dependently decrease of early and late apoptosis. H2O2 stress was done. Mitochondrial function was tested and mitochondrial oxygen consumption rate (OCR) was measured.

**Conclusions:** Mitochondrial cardiolipin targeting peptide, SNU-RD can protect kidney from hypoxic injury by restoring mitochondrial function.

**Funding:**

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**PO0348**

**Title:** Regulation of Mitochondrial Metabolism in T-Regulatory Cells by Programmed Cell Death Protein 1 in AKI

Murat Dogan, Vikram Sabapathy, Rajkumar Venkatadri, Christopher O’Neill, Sandhya Xavier, Didier Portilla, Rahul Sharma. University of Virginia School of Medicine, Charlottesville, VA.

**Background:** The regulatory cells (Tregs) are important for suppressing inflammation and for resolution of injury during acute kidney injury (AKI). Absence or blocking of programmed cell death 1 (PD-1) mitigates the Treg-mediated protection in AKI. The mechanisms, however remain unknown. Here we test the hypothesis that PD-1 regulates mitochondrial metabolism of Tregs during AKI.

**Methods:** Bilateral renal ischemia reperfusion injury (IRI) was used to investigate the role of PD-1 function in Tregs. Adoptive transfer of splenic CD4 +CD25+ Tregs with or without blocking of PD-1 was performed in recipient mice. Also 24h prior to IRI, renal structure and function was assessed by plasma creatinine, kidney, and NGAL expression, histopathology and flow cytometry. Mitochondrial

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Protect the recipient mice from IRI-induced AKI. The oxygen consumption rate (OCR), was also significantly reduced in the PD-1 Brf2, Tfam, Drp1, Mfn1, Mfn2 and Mff reduced mitochondrial mass, lower mitochondrial membrane potential, and greater

Maria

Induced AKI

Urinary UDP-Glucose as a Novel Actionable Biomarker of Dehydration-

Shixuan

Exaggerates Cisplatin-Induced Injury by Suppressing Autophagy

AKI: Mechanisms of Injury

related to mitochondrial dynamics. Scanning Electron microscopy (SEM) was performed using Seahorse Metabolic Flux membrane potential and ROS production respectively, as well as RT-PCR for genes at baseline and under maximal respiration as compared to WT. PD-1

at 100nM and 200nM. Cells were harvested 48 hours post-transfection for mRNA and

and sex-matched WT mice were harvested 48 hours post-transfection for mRNA and

AQP1 localization was examined in kidney cortex of mice that have undergone 35 minutes

and sex-matched wild type ones. Furthermore, we used cultured cells to examine whether autophagy was involved.

Results: It was found that more severe AKI occurred in IFT88 knockout mouse than controls. Mechanistically, IFT88 stimulation autophagy in kidney tubular cells as an intrinsic protective mechanism. However, renal autophagy was severely impaired in IFT88 knockout mouse. In cultured HK-2 cells, cisplatin induced more apoptosis when IFT88 was knocked down. Tatemichi 1 peptide, a specific autophagy activator, could partially prevent IFT88-associated cell death during cisplatin treatment, although ilium length was not improved significantly.

Conclusions: These results indicate that defective autophagy in IFT88-deficient kidney cells and tissues contributes to the exaggerated AKI following cisplatin exposure.

Funding: NIDDK Support, Veterans Affairs Support

P00350

Intralflagellar Transport Protein 88 Deficiency in Proximal Tubular Cells Exaggerates Cisplatin-Induced Injury by Suppressing Autophagy

Shixuan Wang, Zheng Dong, August University, Augusta, GA.

Background: Primary cilias are widely regarded as specialized sensors in differentiated cells that have been implicated in the regulation of cell proliferation, differentiation, and apoptosis. We previously showed that shortening of primary cilium sensitizes cultured kidney tubular cells to cisplatin-induced apoptosis. IFT88 is an essential component for ciliogenesis and maintenance.

Methods: To study the effect of proximal tubule-specific IFT88 ablation on cisplatin-induced kidney injury (AKI), we took advantage of conditional IFT88 knockout mice to study how differently cisplatin affected renal function in knockout mice and age- and sex-matched wild type ones. Furthermore, we used cultured cells to examine whether autophagy was involved.

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Funding: NIDDK Support, Veterans Affairs Support

PO0349

Intralflagellar Transport Protein 88 Deficiency in Proximal Tubular Cells Exaggerates Cisplatin-Induced Injury by Suppressing Autophagy

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Conclusions: These results indicate that defective autophagy in IFT88-deficient kidney cells and tissues contributes to the exaggerated AKI following cisplatin exposure.

Funding: NIDDK Support, Veterans Affairs Support

PO0351

Role of Collagen Receptors in Radiation-Induced Nephrotoxicity

Anis Ahmad,1 Jumana Afaghani,2 Junwei Shi,3 Saba Ansari,1 Jin Ju Kim,1 Yan Shi,3 Sandra M. Merscher,2,4 Alan Pollack,2,4 Youssef Zeidan,2,3 Alessia Fornoni,2,5 Brian Marples,1,6 Radiation Oncology 1University of Miami School of Medicine, Miami, FL; 2American University of Beirut (AUB) School of Medicine, Beirut, Lebanon; 3University of Rochester Medical Center, Rochester, NY.

Background: Radiation therapy represents a severe late complication for cancer patients that induces radiation nephropathy (RN). Collagen receptor 1Discoidin domain receptor 1 (DDR1) and integrin α2 are involved in the pathogenesis of renal fibrosis. However, the mechanisms is largely unknown. We hypothesized that radiation therapy (RT)-induced collagen 1 accumulation in podocytes activates DDR1, integrin α2, and matrix metalloproteinases (MMPs) signaling leading to changes in the laminin and collagen homeostasis in GBM thus inducing RN.

Methods: 10–14-weeks old C57BL/6 male and female mice received a single dose (SD) 40g, 10g, and 14g or fractionated dose (FD) 60g/3 and 24g/4X irradiations. Kidney function parameters (estimated glomerular filtration rate (eGFR), urinary albumin-to-creatinine ratio (ACR), serum BUN and creatinine), histopathological changes (determined by H&E, Periodic Acid-Schiff (PAS), Picrosirius red (PSR)), gene expression analysis (by nanostraf), ultrastructural changes (by transmission electron microscopy (TEM), were measured at 10- and 20-weeks post-SD and FD.

Results: IHC and nanostrafing showed a significant upregulation of Col I, pDDR1, and integrin α2 expression (p<0.001) and reduction in integrin α1 (p<0.001) in kidney cortices 10 and 20 weeks post-SD and FD. Western blot and gene expression analysis showed that several MMPs expression increased significantly in a dose- and time-dependent manner in cultured human podocytes and mouse kidney cortex post-RT. Significant reductions were seen in collagen type IV (Col4A3, Col4A4, Col4A5), laminin β5(2y) (LM-521) and a substantial increase in the expression of collagen type I (Col1A1, Col1A2), collagen type V (Col5A1, Col5A2), and laminin α1(1y) (LM-111) and laminin α2(2y) (LM-211) in radiated mice kidney cortex (p<0.001). TEM data demonstrated time and dose-dependent increases in GBM thickness and foot process width (p<0.001). Significant increases in fibrosis (PSR), mesangial expansion (PAS), ACR in association with collagen type II fibrous nodules post 20 weeks post-RT were observed.

Conclusions: Our data suggest that targeting collagen receptors (DDR1 and integrin α2) with specific small molecule inhibitors and genetic or pharmacological induction of integrin α3 may prevent the RN.

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PO0352

Leucine Metabolism and Ketone Bodies Role in AKI

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Background: Renal ischemia reperfusion (IR) results in injury caused by dynamic process that includes inflammation and extensive cell death. The increase in oxidative stress appears to play a great role in the inflammatory process causing acute kidney injury (AKI) during IR. Oxidative stress activates p53 and promotes cell death. On the other hand, ketones were shown to decrease oxidative stress and are renal protective under different pathological conditions including AKI. Acetoacetate, one of the major ketone bodies, is a product of leucine catabolism. The means through which ketone bodies could play a protective role still requires further understanding. Computational studies in our bodies, is a product of leucine catabolism. The means through which ketone bodies could play a protective role still requires further understanding. Computational studies in our

Results: To study proximal tubule-specific IFT88 ablation on cisplatin-induced kidney injury (AKI), we took advantage of conditional IFT88 knockout mice to study how differently cisplatin affected renal function in knockout mice and age- and sex-matched wild type ones. Furthermore, we used cultured cells to examine whether autophagy was involved.

Methods: To study the effect of proximal tubule-specific IFT88 ablation on cisplatin-induced kidney injury (AKI), we took advantage of conditional IFT88 knockout mice to study how differently cisplatin affected renal function in knockout mice and age- and sex-matched wild type ones. Furthermore, we used cultured cells to examine whether autophagy was involved.

Conclusions: These results indicate that defective autophagy in IFT88-deficient kidney cells and tissues contributes to the exaggerated AKI following cisplatin exposure.

Mice that were subjected to dehydration showed body weight loss. Water deprivation induced elevations in Scr and BUN after 48 and 72 hours, relative to control. Dehydration also promoted albuminuria and the redistribution of AQP1 from the plasma membrane into the PT cell by lowering PT injury, an increase in urinary UDGlc concentration, and renal recruitment of macrophages (CD64+/F4/80+) were detected at 48 and 72 hours of dehydration. In particular, infiltration of CD11c-positive renal macrophages after dehydration was observed. Conclusions: This study supports the hypothesis that UDGlc, released by damaged cells during severe dehydration, induces the renal recruitment of inflammatory macrophages leading to PT injury. Blocking the UDGlc-Glc/PY214 pathway represents, therefore, a new therapeutic avenue for the attenuation of dehydration-induced renal inflammation and dysfunction. In this context, urinary UDGlc is a promising actionable biomarker for dehydration-induced AKI.

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Kidney Protection by Caloric Restriction Depends on De Novo NAD+ Synthesis Activation

**Background:** In the basal phenotyping and 24 h after IRI, KYNU null mice showed significantly worse AKI than the wild type (wt). The changes in the murine transcriptome, proteome and tryptophan metabolism in KYNU null and wt mice showed no differences from p53 and fox3a signaling pathways and preserved expression of Sirt3 and PGC-1α in protection. Moreover, EED226 also enhanced renal tubular cell proliferation and suppressed inflammatory responses and phosphorylation of STAT3 and NF-kB, two transcriptional factors associated with inflammation.

**Conclusions:** These results indicate that targeted inhibition of PRC2 can improve renal function and promote the survival and proliferation of renal tubular cells through mechanisms associated with inhibition of p53 and fox3a signaling pathways and preserved expression of Sirt3 and PGC-1α.

**Funding:** Government Support - Non-U.S.

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Lack of Gb3 Elevated Renal Tubular Injury in a Mouse Model of Aristolochic Acid Nephropathy

**Background:** Globotriaosylceramide (Gb3) is a glycosphingolipid serving as the receptor for Shiga toxin (Stx) and is responsible for mediating binding of Stx onto kidney tissues. However, the normal physiological function of Gb3 in kidney remains unknown. Under normal circumstances, Gb3 plays a role in AA-induced kidney damage and repair by comparing renal function and pathological changes of wild type (WT) versus AAGALT KO mice after AA challenge.

**Methods:** WT and AAGALT KO C57 mice were intraperitoneally injected with AA (5mg/kg) for a total of 8 days. Mice general status and body weight were monitored. The urine, blood, kidney and bladder tissues of the mice were collected on the 9th day to determine the function and pathological changes.

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Results: Compared with WT C57 mice, A4GALT KO mice were more sensitive to AA. A total of 30 mice were divided into three groups: Sham, Cisplatin + vehicle, and Cisplatin + Limonin. Limonin was administered once daily via oral gavage started 3 days before cisplatin injection. At 72 h after cisplatin injection, kidney tissues were collected for metabolomics. Metabolomics was performed using Trace 1310 Gas Chromatograph coupled with an AS 1310 autosampler connected to a TSQ 8000 triple quadrupole mass spectrometer.

Conclusions: Our data suggested that Limonin mitigates cisplatin-induced AKI through alternating multiple metabolic pathways.

Funding: Government Support - Non-U.S.

PO0359

Role and Regulatory Mechanism of Adropin in AKI by Regulating PDK4

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Background: Oxidative stress and inflammation are the important biological mechanisms of the development of ischemic acute kidney injury (AKI). Pyruvate dehydrogenase kinase 4 (PDK4) is a key enzyme in the process of glucose oxidation, which can inhibit glucose oxidation. Adropin, a secreted protein encoded by Energy homeostasis Associated (ENH) gene, is involved in the pathogenesis and pathological process of metabolic and inflammatory diseases and other diseases, can inhibit oxidative stress and inflammation, but its mechanism is unclear in AKI.

Methods: In vitro, HK2 cells were incubated with rotenone to mimicked Ischemia Reperfusion Injury (mIRI) and treated with Adropin, the changes of mitochondrial function and autophagy, antioxidant protein, ROS levels and PKD4 were detected. In vivo, we established AKI model with IRI, and Adropin was given intravenously to detect the changes of renal injury indexes, antioxidant protein (SOD2), Adropin and PKD4 in mice.

Results: 1. Adropin up-regulated the antioxidant enzyme SOD2 and decreased the ROS level in HK-2 cells with mimicked Ischemia Reperfusion Injury. 2. The expression of PDK4 was significantly up-regulated and SOD2 was down-regulated in AKI mice induced by IRI. With the treatment of Adropin, the expression of SOD2 was up-regulated, and renal injury was alleviated.

Conclusions: Adropin can reduce the production of ROS by down-regulating the expression of PDK4 and up-regulating SOD2, thus alleviating renal injury in AKI.

PO0360

Targeting Myeloid Ferritin Heavy Chain (FTH) in Rhabdomyolysis-Induced AKI

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Background: Acute kidney injury (AKI) is defined as an abrupt decrease in kidney function and significantly impacts mortality. During rhabdomyolysis, muscle injury leads to release of myoglobin, causing an increased hem/iron delivery to the kidney, leading to AKI. Iron exacerbates oxidative stress and causes cell death. Kidneys respond to increased iron by inducing ferritin heavy chain (FTH) expression. FTH is a ferrooxidase which can inhibit glucose oxidation. Adropin, a secreted protein encoded by Energy homeostasis Associated (ENH) gene, is involved in the pathogenesis and pathological process of metabolic and inflammatory diseases and other diseases, can inhibit oxidative stress and inflammation, but its mechanism is unclear in AKI.

Methods: In vitro, HK2 cells were incubated with rotenone to mimicked Ischemia Reperfusion Injury (mIRI) and treated with Adropin, the changes of mitochondrial function and autophagy, antioxidant protein, ROS levels and PKD4 were detected. In vivo, we established AKI model with IRI, and Adropin was given intravenously to detect the changes of renal injury indexes, antioxidant protein (SOD2), Adropin and PKD4 in mice.

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Conclusions: Adropin can reduce the production of ROS by down-regulating the expression of PDK4 and up-regulating SOD2, thus alleviating renal injury in AKI.

PO0358

Metabolomics Reveals the Efficacy of Limonin on Mitigating Cisplatin-Induced AKI

Xia Zeng, XiaoKe Zhou, DaiChang Xiang, Yudan Chen, Haiyan Fu. State Key Laboratory of Organ Failure Research, National Clinical Research Center of Kidney Disease, Renal Division, Nanfang Hospital, Southern Medical University, Guangzhou, China.

Background: In the clinic, acute kidney injury (AKI) is one of the most severe cisplatin side effects, limiting its use in cancer therapy. Our previous study demonstrated that Limonin, a triterpenoid compound extracted from citrus, alleviated cisplatin-induced AKI. However, the involved mechanisms remain largely unknown. In this study, we elucidated how Limonin mitigates cisplatin-induced AKI from a new perspective, metabolomics.

Methods: A total of 30 mice were divided into three groups: Sham, Cisplatin + vehicle, and Cisplatin + Limonin. Limonin was administered once daily via oral gavage started 3 days before cisplatin injection. At 72 h after cisplatin injection, kidney tissues were collected for metabolomics. Metabolomics was performed using Trace 1310 Gas Chromatograph coupled with an AS 1310 autosampler connected to a TSQ 8000 triple quadrupole mass spectrometer.

Results: After AKI, Limonin significantly preserved serum creatinine and blood urea nitrogen levels and ameliorated kidney tubular injury, compared with vehicles. Kidney samples from mice were used for metabolomics. A total of 302 metabolites were detected. The principal component analysis indicated that these metabolites could be well separated, reflecting the changes of metabolite distribution after treatment of Limonin. Multivariate statistical analysis further identified 34 endogenous differentially expressed metabolites within the day 5 of administration. A4GALT KO mice began to show significant weight loss. On day 9, More severe renal tubular injury pathological changes, significantly increased urine leukocytes and ketones were detected in A4GALT KO mice. The proliferation of bladder transitional epithelial cells was significantly increased in AA treated WT and A4GALT KO C57 mice, accompanied with fibrin deposition, vascular dilatation and a small amount of inflammatory cell infiltration in the bladder compared with that in the untreated group. There was no significant difference in bladder changes between WT and A4GALT KO groups after AA administration. Multivariate analysis showed a clear separation of metabolic profiles between WT and A4GALT KO mice. The water contents of the cortex and medulla were determined to allow GSH levels to be expressed as nmol/ g kidney dry weight. A Student’s T-test was used to compare the groups, and statistical significance was determined at p < 0.05. All data shown as X ± SEM.

Conclusions: Our findings uncovered that GSH is protective in AA-mediated renal tubular necrosis and its presence reduces kidney injury. We will further explore its specific mechanism in the following study.

Funding: Other NIH Support - Burroughs Wellcome Fund
that converts ferrous iron into ferric form. Distinct myeloid populations promote injury and depletion of macrophages protect against rhabdomyolysis. Myeloid cells express high levels of IFN and mediate iron recycling. Therefore, we tested the hypothesis that myeloid F4H confers protection against rhabdomyolysis-induced AKI.

Methods: To induce rhabdomyolysis, female mice (10-12 weeks) deficient in F4H (F4Hfl/fl) and floxed controls (F4Hf/f) were deprived of water for 16 h and administered 50% glycerol via intramuscular injection into hindlimbs (7.5 or 11 ml/kg body weight). Mice were harvested at 1-, 3-, or 7-days post-glycerol. Kidney function and injury were evaluated by serum creatinine, and kidney injury marker 1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) expression, respectively. Kidneys were analyzed for markers of cell injury/death (KIM-1, calcium-binding protein A8 (S100A8)), cleaved caspase 3 (CC3) and TUNEL positivity and fibrosis.

Results: Rhabdomyolysis led to a significant loss in kidney function and an increase in kidney injury (NGAL and KIM-1) in all groups of mice. However, at 7 days, while these markers returned to baseline in F4Hfl/fl mice, there was a persistent tripling of creatinine and elevated KIM-1 levels only in F4Hf/f mice. This was associated with increased activation of JNK, and markers of cell death. Additionally, F4Hf/f kidneys expressed higher levels of aSMA and collagen when compared to F4Hfl/fl kidneys. This was associated with increased expression of TGFβ and Gal-3, which mediate myofibroblast activation and promote fibrosis.

Conclusions: Our findings demonstrate that while myeloid F4H deletion does not impact acute injury following rhabdomyolysis, it mitigates injury progression and promotes recovery. Current studies are aimed at using single cell RNA sequencing approaches to identify key pathways that are activated during the resolution phase following rhabdomyolysis.

Funding: NIDDK Support

PO0361
Nicotinamide Retains Klotho Expression and Ameliorates Rhabdomyolysis-Induced AKI
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Background: Acute kidney injury is a severe complication of rhabdomyolysis. Inflammation plays a critical role in the pathogenesis of rhabdomyolysis-induced AKI. Nicotinamide, a form of vitamin B3 and a precursor of nicotinamide adenine dinucleotide, has been shown potent anti-inflammation effects. Klotho is a tubular highly expressed renoprotective protein. Therefore, we explored the effect of nicotinamide on rhabdomyolysis-induced AKI and the underlying mechanisms.

Methods: We used glycerol-induced rhabdomyolysis mouse model to observe the effect of nicotinamide on kidney injury. Western blot, chromatin immunoprecipitation and small interfering RNA were used to evaluate the role of Klotho in nicotinamide-related renoprotection.

Results: The results showed that nicotinamide attenuated kidney injury in rhabdomyolysis. Moreover, nicotinamide effectively blocked the recruitment of NF-kB, NCoR and HDAC1 to the promoter of Klotho and preserved Klotho expression. More importantly, renoprotection effect of nicotinamide was abrogated when Klotho was knockdown by small interfering RNA.

Conclusions: Our study demonstrates that Klotho preservation is essential for the renoprotection effect of nicotinamide and provides a new preventive strategy for rhabdomyolysis-induced AKI.

Funding: Government Support - Non-U.S.

PO0362
Defective Clearance of Nucleic Acids Exacerbates AKI
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Background: Extracellular nuclear DNA and RNA released from dying cells can act as damage associated molecular pattern (DAMP) to trigger inflammatory pathology during acute kidney injury (AKI). Cell-free or cytoplasmic DNA can activate immune cells through the interferon stimulatory DNA (ISD) pathway to contribute to tissue damage. We aimed to understand immune dysregulation due to defective DNA clearance in AKI, we utilized Three prime repair exonuclease (TREX1) deficient mice.

Methods: C57BL/6J (B6) mice or bone marrow derived macrophages (BMDM) were treated with poly (I:C) (pIC) to mimic elevated nucleic acid DAMPs, Bilateral ischemic reperfusion injury (IRI) or treatment of TREX1 deficient (TREX1 KO and TREX1 D18N) and STING KO mice with cisplatin (Csp), which causes DNA damage-induced AKI was employed. Renal function was assayed using plasma creatinine (Pcr) and blood urea nitrogen (BUN) levels. Levels of proinflammatory cytokines (IFNg, TNFa) renal injury markers (Kim1 and Ngal) and pro-inflammatory genes (Il1b, Mx1, Nos2, Ifi44, Tnfa and Il6) were measured by Flow cytometry, ELISA and RT-PCR.

Results: Treatments of wildtype (WT) B6 mice with pIC upregulated proinflammatory cytokines leading to a Th1 predominance, indicative of excessive inflammatory predisposition. Csp and IRI induced significantly higher injury and dysfunction in TREX1 deficient (TREX1 KO and TREX1 D18N) mice. Kidney injury markers Kim1 and Ngal were also significantly elevated along with elevated proinflammatory cytokines. The TREX1 D18N mice subjected to IRI also exhibited upregulated recently activated (CD4/CD69+) and elevated T effector memory (CD4/CD44/CD62L+) phenotype confirming immune dysregulation. CD4 T cells in TREX1 D18N mice also had reduced levels of the anti-inflammatory cytokine IL-10. Interestingly, STING KO and TREX1 D18N-STING double KO mice also had exacerbated injury levels indicating the role of unclered DNA and the cGAS-STING DNA sensor pathway in AKI as a result of TREX1 deficiency.

Conclusions: The study presents evidence of the role of TREX1 and uncleared DNA to cause immune dysregulation in AKI and supports employing approaches that can target DNA scavenging to counteract the burden of AKI.

Funding: NIDDK Support, Other NIH Support - National Institute of Allergy and Infectious Diseases

PO0363
Heme Oxygenase 1 Is a Key Player in Arsenical-Induced AKI
Amie Traylör, Ritesh Srivastava, Stephanie Esman, Jasim Khan, Anna A. Zmiewska, Bini Mathew, Laurence M. Black, Mark J. Suto, Mohammad Athar, Anupam Agarwal. University of Alabama at Birmingham, Birmingham, AL; ’Southern Research, Birmingham, AL.

Background: Arsenicals, such as Lewisite, are a class of warfare vesicants that cause immediate and painful blistering of the skin and mucous membranes upon contact. Systemic absorption of arsenicals results in “Lewisite shock,” which is characterized by hypovolemia due to capillary damage, and multi-organ dysfunction. There is an ongoing risk of exposure from arsenical weaponization, but accidental exposures from underground storage of these compounds in several countries including the US, Italy, Russia, and Japan also pose a risk. Molecular mechanisms of arsenical-induced injury

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involve oxidative and endoplasmic reticulum (ER) stress, inflammation, and cell death. We characterized a single cutaneous exposure to arsenicals causes acute kidney injury (AKI) in mice as evidenced by increased serum and urinary biomarkers of AKI. Intrarenal heme oxygenase-1 (HO-1), a protective anti-oxidant enzyme, is also upregulated as a response to injury in addition to ATF4 and CHOP, molecules involved in regulation of ER stress and cell death.

Methods: To interrogate the precise role of HO-1 in arsenical-induced AKI, we exposed HO-1 knockout mice (HO-1-/-) and wild-type controls to phenylarsine oxide (PAO), an analog of Levistein that is commonly used due to the restricted use of this vesicant. Employing in vitro techniques, we further tested the efficacy of a novel small molecule inducer of HO-1, SR-37618 after PAO treatment.

Results: Our data show that HO-1 deficiency results in worse kidney damage post-PAO exposure, suggesting it is a targetable enzyme for intervention. Utilizing a novel small molecule inducer of HO-1 created in collaboration with Southern Research, we demonstrate that 1 hour pre-treatment with SR-37618 diminishes PAO-induced ATF4 and CHOP expression in HEK-293 cells.

Conclusions: While further studies to assess the efficacy of SR-37618 in mouse models are ongoing, the data presented here provide evidence that HO-1 induction by SR-37618 is protective against arsenical-induced AKI. Moreover, small molecule inducers of HO-1 could potentially serve as a novel therapeutic for intervention in other forms of AKI.

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PO0364 Quantitative Systems Toxicology (QST) Modeling of Drug-Induced Acute Kidney Proximal Tubule Epithelial Cell Injury and Associated Renal Hemodynamic Responses

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Background: Renal proximal tubule epithelial cells (RPTEC) are vulnerable to drug-induced toxicities which often result in acute kidney injury (AKI). Drug toxic effects range from mild sub-lethal RPTEC injuries to cellular death via multiple cellular damage mechanisms. At the systems level, decline in glomerular filtration rate (GFR) is a common manifestation of AKI. The complexity of pathophysiological responses (cellular, neurohormonal, hemodynamic) that lead to impaired filtration pose a challenge for reliable prediction of AKI. QST modeling is a promising method for translating cellular- level renal damage to clinical manifestations of AKI.

Methods: We developed RENAsym, a QST model of drug-induced AKI that includes key cellular injury mechanisms and renal hemodynamic responses. At the cellular level, RENAsym represents RPTEC life cycle, bioenergetics, and immune responses to renal toxicity. In vitro assays were used to parameterize key cellular injury mechanisms. At the systems level, RENAsym model represents renal function and feedback mechanisms including tubuloglomerular feedback (TGF) and renin-angiotensin-aldosterone systems (RAAS). RENAsym was employed to characterize the renal hemodynamic responses of drugs inducing RPTEC injury in humans treated with cisplatin.

Results: At the cellular level, urinary biomarkers such as KIM-1 and oGST were used to represent cellular injury and death following cisplatin exposure. RENAsym was able to capture the elevations in KIM-1 and oGST. The model also captured GFR decline and demonstrated that it occurs due to 1) increased Bowman’s pressure, 2) reduced GFR caused by vasoconstriction due to RAAS activation and TGF mechanisms, and 3) lower renal perfusion pressure from excess sodium and water excretion. The model quantitatively relates cellular injury and biomarker changes with renal hemodynamic responses.

Conclusions: RENAsym represents kidney function at cellular and organ levels in healthy and pathologic states caused by toxic drug effects. By describing drug induced cellular injury and subsequent hemodynamic changes it can predict clinical responses during AKI.

Funding: NIDDK Support

PO0365 Elastin-Like Polypeptide Vascular Endothelial Growth Factor (ELP-VEGF) Improves Renal Function and Decreases Inflammation Following Ischemia-Reperfusion Injury in Mice

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Background: Acute Kidney Injury (AKI) represents a significant clinical concern and significant risk factor for the development of chronic kidney disease (CKD). AKI is associated with impaired renal function, increased inflammation and microvascular congestion. In a single cell fusion protein between the elastin-like and VEGF domains causes acute kidney injury (AKI) in mice as evidenced by increased serum and urinary biomarkers of AKI. Intrarenal heme oxygenase-1 (HO-1), a protective anti-oxidant enzyme, is also upregulated as a response to injury in addition to ATF4 and CHOP, molecules involved in regulation of ER stress and cell death.

Methods: To interrogate the precise role of HO-1 in arsenical-induced AKI, we exposed HO-1 knockout mice (HO-1-/-) and wild-type controls to phenylarsine oxide (PAO), an analog of Levistein that is commonly used due to the restricted use of this vesicant. Employing in vitro techniques, we further tested the efficacy of a novel small molecule inducer of HO-1, SR-37618 after PAO treatment.

Results: Our data show that HO-1 deficiency results in worse kidney damage post-PAO exposure, suggesting it is a targetable enzyme for intervention. Utilizing a novel small molecule inducer of HO-1 created in collaboration with Southern Research, we demonstrate that 1 hour pre-treatment with SR-37618 diminishes PAO-induced ATF4 and CHOP expression in HEK-293 cells.

Conclusions: While further studies to assess the efficacy of SR-37618 in mouse models are ongoing, the data presented here provide evidence that HO-1 induction by SR-37618 is protective against arsenical-induced AKI. Moreover, small molecule inducers of HO-1 could potentially serve as a novel therapeutic for intervention in other forms of AKI.

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PKM2-Specific Deletion in Myeloid Cells Ameliorates Renal Impairment by Alleviating Metabolic Changes in CaOx-Induced AKI

Background: MPC1 was disrupted in tubular epithelial cells by generating PKM2fl/fl;LysM-Cre mice. At steady state, this fueled adaptations in carbohydrate, fatty acid, and amino acid metabolism. Interestingly, pathway analysis identified glutathione metabolism as significantly altered in Tub-MPC1-KO mice. Glutathione biosynthetic precursors were decreased and NADPH/NADP was increased in Tub-MPC1-KO kidney. This implies that the renal redox environment was potentially primed to be better able to respond to renal oxidative stress. To test this idea, rhabdomyolysis-induced AKI was initiated by injecting Tub-MPC1-KO WT and Tub-MPC1-KO mice intramuscularly with glycercol. Following AKI, Tub-MPC1-KO mice lost less weight and had significantly decreased serum cytatst C and BUN compared to Tub-MPC1-WT mice.

Conclusions: In vivo disruption of tubular MPC1 results in metabolic changes that favor a reduced cellular environment and protects from glycercol-induced AKI.

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PO0370
Ginsenoside Rg3 Attenuates Ischemia Reperfusion-Induced Renal Injury in Mice via Induction of Autophagy Flux

Background: Ginsenoside Rg3 (Rg3) has been shown as protective effects via various mechanism. However, the renoprotective effect and the role of autophagy are not clearly evaluated. This study investigate Rg3 induces autophagy flux and reduces renal cell death in renal ischemia reperfusion injury (IRI).

Methods: C57Bl/6 mice were divided into the following groups: sham; Rg3 treated sham; saline treated IRI mice; Rg3 treated IRI mice. Kidneys and blood were collected 24h after operation of mice (sham and IR operation). Renal function, kidney histology, and the protein expression of autophagy signals were evaluated.

Results: In IRI mice, the levels of BUN and s-Cr were increased, compared to sham. The Rg3 treatment decreased the BUN and s-Cr in IRI mice. In addition, Rg3 treatment decreased the renal injury score including the renal tubular cell detachment and necrosis in IRI mice. Rg3 treated IRI mice showed significantly less oxidative stress and autophagy impairment, greater amounts of LC3 and Beclin-1, lower amounts of p62, and higher levels of renal ATP6E compared to saline treated IRI mice. Rg3 treatment also increased phosphorylation of AMPK in IRI mice kidney.

Conclusions: Rg3 has renoprotection against renal IR injury via enhancement of autophagy flux.

PO0371
A Novel Immunomodulatory Peptide Suppresses Inflammatory Macrophages and Mitigates AKI

Background: Monocytes/macrophages are known to play a critical role in the pathology and progression of acute kidney injury (AKI), as large numbers of monocytes are recruited to the kidney and differentiate into pro-inflammatory macrophages (M1 phenotype) after injury. Although targeting macrophages has emerged as a promising therapeutic strategy for AKI, the effective treatment is still limited. We previously identified a novel peptide, the MPS peptide, which targets the signaling molecule myristoylated alanine-rich C-kinase substrate (MARKCS), a central inducer of M1 macrophages. In this study, we have employed this novel peptide to determine if MARKCS inhibition reduces kidney injury.

Methods: High-dimensional single-cell mass spectrometry was used to reveal immune profiling in an AKI mouse model. Both commercial macrophage cell lines and primary macrophages isolated from peripheral blood mononuclear cells were utilized in this study for gene expression analysis. In vitro and in vivo inflammatory activities of the MPS peptide were confirmed by Western blots, real-time reverse transcription-polymerase chain reaction (RT-qPCR), flow cytometry, ELISA cytokine assays, and immunohistochemistry.

Results: Analysis of the single-cell RNA sequencing data has identified that the immunomicroenvironment of injured kidneys is associated with the expansion of monocytes/macrophages, particularly M1 macrophages. We next show that an elevated abundance of phospho-MARKCS in macrophages upon cisplatin treatment and this increase occurred in parallel with an increase of M1 markers as well as upregulation of inflammatory cytokines and markers of nephrotoxicity in cisplatin-exposed kidneys. Mechanistically, we demonstrate that MPS peptide had an inhibitory effect on cisplatin-induced phospho-MARKCS, p65 phosphorylation, and NF-kB activation in macrophages. Targeting of MARKCS phosphorylation using MPS peptide not only downregulated kidney-infiltrating M1 macrophages but also suppressed levels of serum creatinine and blood urea nitrogen in mice exposed to cisplatin.

Conclusions: Our results suggest that MARKCS phosphorylation is a novel NF-kB activator in pro-inflammatory macrophages and also presents a proof of concept for the use of MPS peptide as a renal protection agent for AKI.

Funding: Other U.S. Government Support

PO0309
Tubular MPC1 Deletion Protects from Glycerol-Induced Kidney Injury

Methods: MPC1 was disrupted in tubular epithelial cells by generating Pax8- Mpfc1 (Tub-MPC1-KO) mice and was tested against Mpc1fl/fl (Tub-MPC1-WT) littermates. 13C-tracer and steady state metabolomics were performed in 4 hour-fasted mice. Rhabdomyolysis-induced AKI was initiated by injecting 10 ml/kg of 50% glycercol into the hind limb of Tub-MPC1-WT vs Tub-MPC1-KO mice and we evaluated toxicity and kidney function prior to sacrifice.

Results: 13C enrichment into TCA cycle intermediates demonstrated decreased glucose-driven PDH- and PC-dependent pyruvate metabolism in Tub-MPC1-KO. At steady state, this fueled adaptations in carbohydrate, fatty acid, and amino acid metabolism. Interestingly, pathway analysis identified glutathione metabolism as significantly altered in Tub-MPC1-KO mice. Glutathione biosynthetic precursors were decreased and NADPH/NADP was increased in Tub-MPC1-KO kidney. This implies that the renal redox environment was potentially primed to be better able to respond to renal oxidative stress. To test this idea, rhabdomyolysis-induced AKI was initiated by injecting Tub-MPC1-WT and Tub-MPC1-KO mice intramuscularly with glycercol. Following AKI, Tub-MPC1-KO mice lost less weight and had significantly decreased serum cystatin C and BUN compared to Tub-MPC1-WT mice.

Conclusions: In vivo disruption of tubular MPC1 results in metabolic changes that favor a reduced cellular environment and protects from glycercol-induced AKI.

Funding: NIDDK Support, Other NIH Support - NICHID K12 HD027748

PO0368
PKM2-Specific Deletion in Myeloid Cells Ameliorates Renal Impairment by Alleviating Metabolic Changes in CaOx-Induced AKI

Results: In PKM2fl/fl;LysM-Cre mice, the number of F4/80+CD11b+ cells in kidneys were similarly elevated by but less impairment of renal function, inflammation/injury and renal lactate content changes and inflammation/injury. FAPESP (2019/02893-9 and 2017/05264-7), CNPq and Pernacast Silva, Niels O. Camara. 12 Universidade de Sao Paulo, Sao Paulo, Brazil; 1 Universidade Federal de Sao Paulo, Sao Paulo, Brazil.

Conclusions: Myeloid-specific PKM2-knockout mice (PKM2 fl/fl;LysM-Cre) and their Cre-negative littermates (PKM2fl/) underwent AKI by a single i.p. injection of NaOx (100mg/kg) and 3% NaOx in drinking water for 24hr before sacrifice. Expression of PKM2 in bone marrow-derived macrophages was assessed by FACS. Serum creatinine, blood urea, renal CaOx crystal deposition (Pizzolato staining), IL-6, NGAL, KIM-1, HK2, CPT1a and CPT2 mRNA expression (quantitative PCR), macrophage number/phenotype (FACS), and lactate levels all were all measured.

Conclusions: Pro-inflammatory macrophages rely mainly on glycolysis in oxalate-induced AKI. Deletion of PKM2 in myeloid cells partially prevents renal metabolic changes and inflammation/injury. FAPESP (2019/02893-9 and 2017/05264-7), CNPq and FAPES (Financial Code 001).

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PO0372
Renal NG2-Expressing Cells Have Phagocytic Activity and Facilitate Renal Recovery After Ischemic Injury
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Background: Pericytes play an important role in the recovery process after ischemic injury of many tissues. Brain pericytes in the peri-infarct area express macrophage markers in response to injury stimuli and are involved in neovascularization. In the kidney, pericytes around the renal glomerulus express NG2 antigen 2 (NG2) pericytes have been found to accumulate after renal injury. However, the role of accumulated NG2+ cells in injured kidneys remains unknown.

Methods: A reversible ischemic reperfusion model, we found that renal NG2+ cells were increased in injured kidneys and expressed macrophage markers (CD11b or F4/80) on day 3 after reperfusion. Isolated NG2+ cells from ischemia/reperfusion (IR) kidneys also had phagocytic activity and expressed anti-inflammatory cytokine genes, including mannose receptor and IL-10. These macrophage-like NG2+ cells did not likely differentiate into myofibroblasts because they did not increase α-SMA expression. Intravenous transfusion of renal NG2+ cells isolated from donor mice on day 3 after reperfusion into recipient mice on day 1 after I/R surgery revealed that NG2+ cell-injected mice had lower plasma kidney injury during LPS sepsis.

Results: Isolated NG2+ cells from ischemia/reperfusion (IR) kidneys also had phagocytic activity and expressed anti-inflammatory cytokine genes, including mannose receptor and IL-10. These macrophage-like NG2+ cells did not likely differentiate into myofibroblasts because they did not increase α-SMA expression. Intravenous transfusion of renal NG2+ cells isolated from donor mice on day 3 after reperfusion into recipient mice on day 1 after I/R surgery revealed that NG2+ cell-injected mice had lower plasma kidney injury during LPS sepsis. Our data suggest that while kidney-specific Hmgcs2 deletion results in a significant attenuation of circulating ketones during fasting and LPS sepsis, while kidney-specific Hmgcs2 deletion has no effect. Preliminary data show that the loss of Hmgcs2 in the kidney results in an increase in KIM1 protein, a marker indicative of kidney injury, up to 48 hours after LPS injection.

Conclusions: It is well-established that the liver is the main source of circulating ketones; however, data support this notion and demonstrate that although fasting and LPS sepsis induce an upregulation of renal Hmgcs2, the expression of this enzyme in the kidney does not appear to contribute to circulating ketones. Our data suggest that while renal Hmgcs2 does not produce systemic ketones, it may be important for mitigating kidney injury during LPS sepsis.

Funding: NIDDK Support, Other NIH Support - NGMS, Private Foundation Support

PO0373
The Role of Renal Hmgcs2 in Fasting and Bacterial Inflammation
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Background: The purpose of inflammatory anorexia during states of acute illness or infection (e.g., sepsis), remains incompletely understood. We have found that glucose supplementation during bacterial sepsis suppresses ketogenesis and increases mortality, suggesting a potential protective effect of fasting metabolism. Gene expression analysis of the liver and kidney during fasting and after lipopolysaccharide (LPS) challenge, to model sterile bacterial inflammation, revealed that Hmgcs2, the rate-limiting enzyme of ketogenesis, is suppressed in the liver while upregulated in the kidney during LPS sepsis. This expression pattern differs from fasting, during which Hmgcs2 is induced in both the kidney and liver. The significance of renal Hmgcs2 upregulation during bacterial inflammation is unclear.

Methods: Liver-specific Hmgcs2 knockout mice (Alb-CreERT2: Hmgcs2fl/+), kidney-specific knockout mice (Six2-Cre; Hmgcs2fl/+), Ppara–/– and wild-type C57BL/6J mice were fed ad libitum, fasted or injected i.p. with 10 mg/kg LPS. Plasma was analyzed for lipids and ketones. Livers and kidneys were harvested for RNA and protein analysis.

Results: In wild-type mice, circulating ketones increase during fasting and LPS sepsis. While not expressed in the fed state, Hmgcs2 protein is induced in the proximal tubules in a PPARα-dependent manner during both fasting and LPS sepsis. Liver-specific Hmgcs2 deletion results in a significant attenuation of circulating ketones during fasting and LPS sepsis, while kidney-specific Hmgcs2 deletion has no effect. Preliminary data show that the loss of Hmgcs2 in the kidney results in an increase in KIM1 protein, a marker indicative of kidney injury, up to 48 hours after LPS injection.

Conclusions: In conclusion, our study confirmed the observations made in the CREDEENCE and the EMPA-REG OUTCOME trials. The empagliflozin effects on KIM-1 and miR-26a might indicate beneficial regulation of inflammation and innate immune response. Our data should stimulate clinical studies analyzing whether empagliflozin is a preferable SGLT-2 inhibitor in patients at high AKI risk.

Funding: Government Support - Non-U.S.

PO0374
Head-to-Head Comparison of Two SGLT-2 Inhibitors on AKI Outcomes
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Background: Sepsis-associated acute kidney injury (AKI) is associated with high mortality. Cell-free hemoglobin (CFH) is reduced in patients with severe sepsis and higher levels are independently associated with mortality. CFH is toxic to HK-2 cells, suggesting that CFH can directly injure the renal tubular epithelium. Treatment with ascorbate (Vitamin C) or acetylaminocephalin provides protection from CFH-induced toxicity in endothelial cells. Therefore, renal expression of CFH is toxic to HK-2 cells, suggesting that CFH can directly injure the renal tubular epithelium. Treatment with ascorbate (Vitamin C) or acetylaminocephalin provides protection from CFH-induced toxicity in endothelial cells. Therefore, renal expression of CFH is toxic to HK-2 cells, suggesting that CFH can directly injure the renal tubular epithelium. Treatment with ascorbate (Vitamin C) or acetylaminocephalin provides protection from CFH-induced toxicity in endothelial cells. Therefore, renal expression of CFH is toxic to HK-2 cells, suggesting that CFH can directly injure the renal tubular epithelium.

Methods: We then treated mature human kidney organoids with CFH (1 mg/ml) for 48 hours and evaluated cell toxicity, viability, reactive oxygen species (ROS), and mitochondrial fragmentation. To study the protective effects, CFH-exposed organoids were co-treated with ascorbate (200 μM) or acetylaminophen (1000 μM) for 48 hours.

Results: Urinary glucose excretion was comparable in both treatment groups indicating comparable SGLT-2 inhibition. Comparing GFR surrogate markers after IRI (sCr and BUN). At all investigated time points after IRI, sCr and BUN were higher in the IRI+canagliflozin group than placebo-treated rats, whereas the empagliflozin group did not differ from the placebo group. IRI led to tubular dilatation and necrosis. Empagliflozin was able to reduce that finding whereas canagliflozin had no effect. Renal expression of KIM-1 increased after IRI and empagliflozin but not canagliflozin normalized KIM-1 expression (Figure). IRI reduced urinary microRNA-26a excretion. Empagliflozin but not canagliflozin was able to restore normal levels of urinary mIR-26a.

Conclusions: In conclusion, our study confirmed the observations made in the CREDEENCE and the EMPA-REG OUTCOME trials. The empagliflozin effects on KIM-1 and miR-26a might indicate beneficial regulation of inflammation and innate immune response. Our data should stimulate clinical studies analyzing whether empagliflozin is a preferable SGLT-2 inhibitor in patients at high AKI risk.

Funding: NIAMS Support, Other NIH Support - NIGMS, Private Foundation Support

PO0375
Modeling Sepsis in Human Kidney Organoids: Cell-Free Hemoglobin-Induced Cytotoxicity Is Attenuated by Ascorbate or Acetaminophen
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Background: Sepsis is a leading cause of mortality. We then treated mature human kidney organoids with CFH (1 mg/ml) for 48 hours and evaluated cell toxicity, viability, reactive oxygen species (ROS), and mitochondrial fragmentation. To study the protective effects, CFH-exposed organoids were co-treated with ascorbate (200 μM) or acetylaminophen (1000 μM) for 48 hours.

Results: Urinary glucose excretion was comparable in both treatment groups indicating comparable SGLT-2 inhibition. Comparing GFR surrogate markers after IRI (sCr and BUN). At all investigated time points after IRI, sCr and BUN were higher in the IRI+canagliflozin group than placebo-treated rats, whereas the empagliflozin group did not differ from the placebo group. IRI led to tubular dilatation and necrosis. Empagliflozin was able to reduce that finding whereas canagliflozin had no effect. Renal expression of KIM-1 increased after IRI and empagliflozin but not canagliflozin normalized KIM-1 expression (Figure). IRI reduced urinary microRNA-26a excretion. Empagliflozin but not canagliflozin was able to restore normal levels of urinary mIR-26a.

Conclusions: In conclusion, our study confirmed the observations made in the CREDEENCE and the EMPA-REG OUTCOME trials. The empagliflozin effects on KIM-1 and miR-26a might indicate beneficial regulation of inflammation and innate immune response. Our data should stimulate clinical studies analyzing whether empagliflozin is a preferable SGLT-2 inhibitor in patients at high AKI risk.

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organs compared to control group (n=3; p<0.05). LDH assay also revealed that the addition of acetaminophen attenuated the impact of CFH on organs by decreasing the toxicity by ~23% within the organs (p value <0.0001).

Conclusions: Human kidney organs can be used to model sepsis-induced AKI. CFH treatment induced toxicity and reduced viability of the human kidney organs. Both ascorbate and acetaminophen had protective effects on CFH-induced organ injury.

Funding: Private Foundation Support

PO0376

Pulsed Ultrasound Reduces Oxidative Stress-Induced Disruption of Epithelial Barrier in Sepsis-AKI

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Background: Oxidative stress disrupts epithelial junctions leading to increased paracellular permeability and kidney dysfunction. We previously showed that pulsed ultrasound (pUS) reduced inflammatory and kidney injury. We hypothesized that pUS mitigates renal injury by maintaining epithelial tight junctions. Here, we utilized lipopolysaccharide (LPS)-induced sepsis to create acute kidney injury (S-AKI) in a mouse model and RAW 264.7 cells to investigate the effects of pUS on the epithelial tight junction barrier and renal macroporosity.

Methods: C57BL6 mice received pUS 24 hrs before LPS treatment. The parameters of pUS therapy followed the protocol previously published by us (PMID: 23907510). Following pUS treatment, mice received a single injection of LPS (5 mg/kg, ip). Animals were euthanized at increasing time intervals for measurement of mRNA expression and kidney histology. Kidney morphological changes were observed by using PAS staining. Co-staining with TUNEL and cleaved caspase-3 was used to assess kidney injury. For in-vitro assays, RAW cells were seeded onto 4-well plates and incubated for 24 hrs at a density of 5 x 10^4 per well. Cells were treated with LPS (100 ng/ml) in serum-free DMEM for 2 hrs.

Results: LPS induced kidney injury and apoptosis, as observed by PAS and TUNEL staining, was attenuated by pUS. Co-staining with PDS95 (postynaptic scaffolding density protein 95) and ZO-1 (zonula occludens-1) showed both were expressed in kidneys. LPS also induced significant loss of PDS95 accompanied by a reduced mRNA expression of nuclear factor erythroid 2-related factor 2 (NRF2) and activated macrophages. The structural changes, extent of loss of PDS95 and Nrf2, as well as macrophage infiltrate were all partially reversed by prior pUS treatment. In cultured RAW cells, pUS upregulated the expression of NRF2 and heme oxygenase-1 (HO-1), and attenuated CD68-positive macrophage signals.

Conclusions: pUS protected kidneys from LPS-induced S-AKI by preserving antioxidant NRF2 expression and attenuating oxidative stress-induced disruption of epithelial tight junctions.

Funding: NIDDK Support

PO0377

Hypertensive Diabetic Kidney Disease Increases the Severity of Experimental AKI

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Background: Patients with diabetic kidney disease (DKD) are at increased risk of severe AKI and adverse outcomes. Since DKD may alter cellular and therapeutic responses in AKI, there is a need to establish a model to evaluate the mechanisms and therapeutics of AKI in the context of DKD. These studies address this deficiency by characterizing AKI in transgenic mice with renin-induced hypertension and progressive DKD.

Methods: Hypertensive male transgenic TTR transgenic (Tg) mice, which over-express renin in the liver, were treated with/− streptozotocin to induce diabetes (DM). Tail cuff BP; urinary albumin/creatinine ratio (ACR); BUN; and transdermal GFR (tGFR) were measured from 12 weeks of age in Tg and non-transgenic littermates (Wild type, WT) were given 10 mg/kg LPS. Wild type control (Con) received saline. Renal function tests, plasma BUN creatinine, proteinuria, and albuminuria were performed. Plasma, Kidney, and liver were harvested after 12 hours for western blots and ELISA. Electron microscopy (EM) was done to evaluate podocytes.

Results: Albuminuria were 3 and 5 fold higher than Con (p<0.05) these were attenuated in Tg (p<0.05). Cytokines (IL-1β, IL-6, and TNFα) in the liver, kidney, and plasma of WT after LPS injection was 2 to 4-fold higher than Con. However, in the liver of Tg+LPS, only TNFα was significantly reduced. Plasma and kidney cytokines of Tg+LPS were significantly lower than WT+LPS (Fig.). The reduction of cytokines in the kidney of Tg+LPS was more profound than the plasma of Tg+LPS. Podocyte effacement in Tg mice was less severe than WT. We could detect cmyc in plasma and kidney in Tg mice.

Conclusions: This study shows targeted increase of IAP in the kidney can abate LPS mediated deterioration of renal function, inflammation, and podocyte effacement. IAP has been shown to be released after LPS administration perhaps as a protective mechanism. An increase in plasma cmyc after LPS injection indicate that human IAP could have been secreted in the blood from the kidney or intestine. This may have decreased the inflammatory burden in the plasma.

Funding: Other U.S. Government Support

PO0378

Kidney-Specific Intestinal Alkaline Phosphatase (IAP) in Transgenic Mice Protects Lipopolysaccharide (LPS)-Induced Inflammation and Renal Failure

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Background: LPS is a major player in septic AKI. However, LPS can be dephosphorylated to an inactive form by IAP. We generated kidney specific IAP transgenic mice (Tg) to test whether the targeted increase in IAP can decrease inflammation and improve renal function.

Methods: Tg mice were developed in C57Bl6 background using human chimeric IAP under the control of villin promoter making them kidney specific albeit some expression was also observed in the intestine. The 3' prime end of the transgenic codon had a cri to distinguish human IAP from resident mouse IAP. Tg and non-transgenic littermates (Wild type, WT) were given 10 mg/kg LPS. Wild type control (Con) received saline. Renal function tests, plasma BUN creatinine, proteinuria, and albuminuria were performed. Plasma, Kidney, and liver were harvested after 12 hours for western blots and ELISA. Electron microscopy (EM) was done to evaluate podocytes.

Results: Serum creatinine and BUN were 2.5 and 3 fold higher in WT compared to Con (<0.01), the increases were attenuated in Tg (p<0.05). In WT proteinuria and albuminuria were 3 and 5 fold higher than Con (p<0.05) these were attenuated in Tg (p<0.05). Cytokines (IL-1β, IL-6, and TNFα) in the liver, kidney, and plasma of WT after LPS injection was 2 to 4-fold higher than Con. However, in the liver of Tg+LPS, only TNFα was significantly reduced. Plasma and kidney cytokines of Tg+LPS were significantly lower than WT+LPS (Fig.). The reduction of cytokines in the kidney of Tg+LPS was more profound than the plasma of Tg+LPS. Podocyte effacement in Tg mice was less severe than WT. We could detect cmyc in plasma and kidney in Tg mice.

Conclusions: This study shows targeted increase of IAP in the kidney can abate LPS mediated deterioration of renal function, inflammation, and podocyte effacement. IAP has been shown to be released after LPS administration perhaps as a protective mechanism. An increase in plasma cmyc after LPS injection indicate that human IAP could have been secreted in the blood from the kidney or intestine. This may have decreased the inflammatory burden in the plasma.

Funding: Other U.S. Government Support

PO0379

Pretreatment with Low-Dose Lipopolysaccharide Attenuates Ischemia Reperfusion-Induced Vascular Congestion Through Vasocostriction of the Outer Medulla During Reperfusion

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Background: Vascular congestion in the renal outer medulla (OM) is common in acute necrosis caused by ischemia and has been shown to protect renal injury. Evidence from our laboratory suggests that vascular congestion originates in the renal venous vessels during ischemia and backfills the outer-medullary circulation with red blood cells (RBCs) during the reperfusion phase. We have previously reported that pretreatment with low dose lipopolysaccharide (LPS) attenuates ischemia reperfusion (IR) induced vascular congestion, however the mechanisms mediating this effect remain unknown. In the current study, we hypothesized that pretreatment with LPS prevents vascular congestion by limiting early reperfusion of the OM capillaries following ischemia.

Methods: To test this hypothesis, male WKY rats (12wks) were pretreated (i.p) with 1mg/kg LPS (n=6) or saline control (n=7) daily for 3 days. Rats were then anesthetized, and Transonic Laser Doppler probes were inserted in the cortex and OM. Regional kidney blood flow was then measured for 10 minutes of baseline, 45 minutes of renal artery clamping and 30 minutes of reperfusion.

Results: There were no differences in baseline blood flow between rats pretreated with low dose LPS or saline control (n=7) daily for 3 days. Rats were then anesthetized, and Transonic Laser Doppler probes were inserted in the cortex and OM. Regional kidney blood flow was then measured for 10 minutes of baseline, 45 minutes of renal artery clamping and 30 minutes of reperfusion.

Conclusions: There were no differences in baseline blood flow between rats pretreated with low dose LPS or saline control (n=7) daily for 3 days. Rats were then anesthetized, and Transonic Laser Doppler probes were inserted in the cortex and OM. Regional kidney blood flow was then measured for 10 minutes of baseline, 45 minutes of renal artery clamping and 30 minutes of reperfusion.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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Conclusions: Our data indicate that LPS pre-treatment, paradoxically, slows the early injury process by activating the response of the endothelium. Inhibition of this effect attenuates mediul venous congestion by allowing RBCs in the shared venous circulation to clear. These findings support the hypothesis that backfilling of the renal medullary circulation before cortical reperfusion is restored, is responsible for the development of vascular congestion and tissue injury. We speculate this may prevent lung injury but can lead to impaired renal function by ameliorating alteration in intestinal permeability.

Methods: 12 weeks biweekly oral gavage (1mg/kg) of carbon tetrachloride (CCl4) in mice induced cirrhosis. AKI was precipitated by injecting 2 mg/kg IP LPS one day before culling. The dose of LPS, chosen after careful titration, precipitated AKI only in cirrhotic mice. Animals were divided into four groups (control (CO), CCI4, CCI4+LPS (CCl4+L), CCl4+LPS+Curcumin (CCl4+L+CU)). CCl4+L+CU received 100 mg/kg CU for 12 weeks. FITC-dextran was administered a day before culling orally and blood levels assessed to determine intestinal permeability. Blood, urine, liver, and kidney were harvested to measure various parameters.

Results: BUN and creatinine of CCl4 and CCl4+L were significantly higher than CO; however, a significant decrease of urinary sodium (50±8%, p<0.01) and urine output (70±9%, p<0.01) was seen only in the CCl4+L group. Liver injury markers SGOT and SGPT were significantly high in CCl4 and were even higher in CCl4+L. CU treatment (CCl4+L+CU) significantly improved all the liver and renal functions. Inflammamome markers NFκB, caspase 1, and IL-1β in the liver and kidney of CCl4 were significantly higher than the control which was further augmented in the CCl4+L group. There was a significantly increased absorption of FITC-dextran and decreased expression of tight junction proteins ZO 1 and claudin in the jejunum and ileum of CCl4 and CCl4+L cohorts suggesting increased intestinal barrier permeability. Curcumin treated, CCl4+L+CU group had decreased expression of inflammamome markers, decreased absorption of FITC-dextran, and increased expression of intestinal tight junction proteins.

Conclusions: Although curcumin has a significant anti-inflammatory property its systemic anti-inflammatory effect is limited by its poor bioavailability. We post that curcumin by mitigating intestinal permeability reduces inflammatory burden in the circulation which helps in preserving liver and kidney function.

PO0384 Identification of Hub Genes and Pathways of Ischemia-Reperfusion Injury and AKI by a Bioinformatics Method

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Background: Ischemia/reperfusion injury (IRI) is the most common cause of acute kidney injury (AKI). However, mechanisms underlying the rapid loss in kidney function and tissue injury are not fully elucidated. We aimed to explore the potential crucial genes and pathways involved in the pathogenesis of IRI/AKI by the bioinformatics method.

Methods: We extracted two gene expression profiles (GSE87024 and GSE34351) from the GEO database of wild-type mice and the early onset of the IRI-AKI. Differentially expressed genes (DEGs) were identified from the two expression profiles, enriched with its gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways of the DEGs. Then we applied Gene set enrichment analysis (GSEA) methods to detect the potential crucial gene sets, the string network to identify PPI, and Cytoscape with plugin-ins to find the hub genes and modules. We also used the robust rank aggregation (RRA) to the combined DEGs of the two datasets and analyzed the target genes for miRNA/TF, drug-gene interaction networks to find the potential therapeutic targets.

Results: We extracted a total of 239 and 384 DEGs in GSE87024 and GSE34351 separately, with the 73 same DEGs. GO and KEGG enrichment analysis of the DEGs were probed using flow cytometry, histology, immunohistochemistry, quantitative gene expression, and biochemical analyses. The in vitro analyses were performed using peritoneal and bone-marrow-derived macrophages. We used correlation analysis to ascertain the contribution of different cells involved in the inflammation and fibrosis process. Preliminary meta-analysis of single cell RNA seq data indicated high expression of ST2 on renal macrophages. Therefore, we performed acute and chronic studies on stroma cell specific deletion of ST2. Interestingly, loss of ST2 on myeloid cells also resulted in attenuation of acute renal injury. In vitro, effectorcytosis assays on both peritoneal and bone-marrow derived macrophages demonstrated that loss of ST2 on macrophages resulted in a decrease in functional phagocytosis of apoptotic cells. Intriguingly, results from the chronic injury model showed that the absence of myeloid-ST2 led to attenuated injury and fibrosis and a significant reduction in the immunoregulatory cells and cytokines.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
The most common cause of acute kidney injury (AKI) in critically ill patients is sepsis. There are currently no treatments for septic AKI. Intra-renal macrophages include both tissue-resident (CD11bhi, F4/80lo) and infiltrating (CD11b+,
F4/80hi) populations. The role of resident and infiltrative macrophages in septic AKI pathogenesis remains unclear. As resident macrophages are reported to contribute to tissue repair following injury, we hypothesized that selective depletion of resident macrophages would worsen septic AKI.

Methods: Resident macrophages were selectively depleted via diphtheria toxin injection in CD11cCre+;CX3CR1dtr/wt (RM KO) mice compared to CD11cCre-;CX3CR1dtr/wt (RM WT) mice. RM WT and RM KO mice were subjected to sham or cecal ligation and puncture (CLP) sepsis. Kidney injury was assessed by serum creatinine and histologic injury scoring. Cytokine mRNA and protein levels in the serum and kidney were measured by RT-PCR and ELISA. Fluorescent cell-sorting and single cell RNA sequencing were used to profile gene expression following CLP in various intra-renal cell lineages.

Results: After CLP, resident macrophages displayed high levels of anti-inflammatory genes including interleukin 1 receptor antagonist (IL1rn), known to suppress IL6 generation. Compared to RM WT mice, RM KO mice displayed worsened septic AKI at 24 hours as measured by serum creatinine (0.17 ± 0.08 vs 0.41 ± 0.17 mg/dl, p<0.001-Fig. 1) and histologic injury score (median injury score score vs 1 vs 1, p<0.02). Furthermore, RM KO mice elaborated higher circulating and kidney IL-6 levels. In turn, anti-IL6 therapy ameliorated septic AKI in RM KO mice (Fig. 1).

Conclusions: Resident macrophages protect against septic AKI by limiting IL6 generation. Production of anti-inflammatory IL1rn by resident macrophages may limit tissue damage by constraining IL-6 generation in the septic kidney.

Funding: NIDDK Support, Other NIH Support - K08 GM132689 to JRP, Veterans Affairs Support
Spatially Resolved Transcriptomics Reveal Temporal Dynamics of Gene Expression Changes in a Model of Female AKI

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Background: Preclinical studies of acute kidney injury (AKI) have focused on male rodents leaving a substantial gap in our understanding of AKI in females. Single cell transcriptomic studies are remarkably powerful, but the loss of positional information with tissue dissociation handicaps our interpretation. Therefore, we applied the 10X Genomics spatial transcriptomic solution, Visium, to investigate interactions between cell types in their physiological orientation during injury.

Methods: We performed bilateral ischemia reperfusion injury (Bi-IRI) on female C57BL/6J mice. Kidneys were collected at acute and late injury timepoints. The efficacy of IRI cross-clamp was validated by transdermal GFR measurements using FITC-sinistrin. Sequencing libraries were created from flash frozen kidney tissues, sequenced by NovaSeq, and integrated with corresponding images using SpaceRanger.

Results: New analytic pipelines SPOTlight and Giotto, enriched with gene expression data from our previously published single cell transcriptomic atlas of mouse injury, significantly enhanced the visualization and resolution of spatial data in our female Bi-IRI model. Spatial libraries detected 16,856 unique genes across all injury timepoints. Integration with scRNAseq increased resolution of specific underrepresented cell types, such as macrophages, T cells, and fibroblasts. Key visualization tools demonstrated changes in the temporal and spatial expression of differentiation markers, including Krt20 and Vim, after injury. Spatial interaction analyses of macrophages and T cell related genes, such as Lyn and Tmem30b, revealed dynamic cell type interaction changes in addition to specific interactions with a proinflammatory and pro-fibrotic proximal tubule injury-induced cell state. We prioritized cell-cell interactions based on physical proximity and validated these results by immunofluorescence. We curated an online data visualization tool to provide broad access of this dataset to the community.

Conclusions: We present the first comprehensive spatial transcriptomic atlas for a female mouse model of AKI along a time course after ischemic injury. We leveraged this spatial transcriptomic dataset to investigate cell type interaction changes, revealing previously unknown cellular dynamics of macrophages and T cells in the proximal tubule.

Funding: NIDDK Support

Single-Cell Sequencing of Immune Cells in AKI and Renal Fibrosis

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Background: Immune responses help determine outcome following acute kidney injury (AKI) and Chronic Kidney Disease (CKD) progression. Single Cell RNA Sequencing (scRNAseq) provides an unparalleled opportunity to uncover heterogeneity and provide new mechanistic understanding in AKI-CKD. We have performed scRNAseq of immune cells at specific timepoints mimicking human disease pathology in models of AKI and renal fibrosis.

Methods: Kidneys were harvested from three mice at each time point (Figure 1) mimicking disease states in AKI-CKD. Using a cell sorting strategy, CD45+ cells were sequenced in total. Analysis of gene expression profiles delineated transcriptomic profiles in distinct sub-clusters of immune cells across disease states. Comparison of these demonstrated dynamic changes in immune cell compositions, recruitment and patterns of gene expression, in line with an immune response to AKI recovery and fibrosis. Heterogenous clusters of macrophages were seen in disease states, revealing an inverse pattern of gene expression when comparing AKI-recovery and AKI-fibrosis.

Results: 21,734 CD45+ve Cells were sequenced in total. Analysis of gene expression revealed high levels of CD-31 and VE-Cadherin 10 days after isolation (EVOS-M500). We have identified a novel mechanistic target of injury/necrosis. While the functional restoration of the renal MV is crucial, the mechanisms by which MV angiogenesis improves renal recovery remain understudied. Unfortunately, primary cultures of renal microvascular endothelial cells (RMEC) exhibit variability in purity and outgrowth, and undergo phenotypic losses in monocultures. Thus, we focused on refining the isolation and phenotypic retention of monocultured mouse renal peritubular endothelial cells (MRPEC).

Methods: MRPEC were initially isolated using the method of Zhao et al (2014). MRPEC were then subjected to a second round of CD146+ magnetic bead purification. Twice purified MRPEC (TP-MRPEC) were seeded in cloning cylinders within 35mm culture dishes precoated with fibronectin or gelatin, and incubated overnight at 37°C with 5% CO2 in ScienceCell™ EC media. Cloning cylinders were removed the next day, and media was changed every 24h. After 48h, cells were placed onto a circular rotor in a 37°C incubator. After 10 days, purity and phenotype were assessed by flow cytometry analysis using a CD146-PE+ antibody (Biologend®) and confirmed by immunofluorescent (IF) staining of endothelial markers VE-Cadherin and CD31.

Results: Brightfield micrographs revealed that TP-MRPEC seeded in cloning cylinders increased seeding density, promoted faster outgrowth, and preserved MRPEC morphology. MRPEC seeded onto fibronectin exhibited faster outgrowth; however, MRPEC seeded onto gelatin reduced morphological variability. MRPEC placed onto a circular rotor set to ~45rpm enhanced endothelial cell polarization and paracrine signaling. Flow cytometry analysis revealed that standard MRPEC had an average PE+ purity of ~76% compared to the IgG isotype and unstained controls. Conversely, TP-MRPEC average purity was ~93% (N=5, Tis=829.09). Immunofluorescence staining confirmed high levels of CD-31 and VE-Cadherin 10 days after isolation (EVOS-M500).

Conclusions: In conclusion, we have developed a modified MRPEC isolation and cell monoculture protocol that enhances the uniformity, purity, and long-term phenotypic retention of primary MRPEC monocultures.

Funding: Veterans Affairs Support

Modeling Kidney Injury and Repair in Kidney Organoids Reveals an Intrinsic Repair Mechanism

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Background: Kidneys have the capacity for intrinsic repair, preserving kidney architecture with return to a basal state following tubular injury. When injury is overwhelming or repetitive, that capacity is exceeded and incomplete repair results in scar tissue replacing normal kidney parenchyma. Loss of nephronts correlates with reduced kidney function, which defines chronic kidney disease (CKD) and confers significant morbidity and mortality to the worldwide population. Despite the identification of pathways involved in intrinsic repair, limited treatments for CKD exist, in part due to the limited throughput and predictivity of animal studies.

Results: We focused on refining the isolation and phenotypic retention of monocultured mouse renal peritubular endothelial cells (MRPEC). Unfortunately, primary cultures of renal microvascular endothelial cells (RMEC) exhibit variability in purity and outgrowth, and undergo phenotypic losses in monocultures. Thus, we focused on refining the isolation and phenotypic retention of monocultured mouse renal peritubular endothelial cells (MRPEC).

Methods: MRPEC were initially isolated using the method of Zhao et al (2014). MRPEC were then subjected to a second round of CD146+ magnetic bead purification. Twice purified MRPEC (TP-MRPEC) were seeded in cloning cylinders within 35mm culture dishes precoated with fibronectin or gelatin, and incubated overnight at 37°C with 5% CO2 in ScienceCell™ EC media. Cloning cylinders were removed the next day, and media was changed every 24h. After 48h, cells were placed onto a circular rotor in a 37°C incubator. After 10 days, purity and phenotype were assessed by flow cytometry analysis using a CD146-PE+ antibody (Biologend®) and confirmed by immunofluorescent (IF) staining of endothelial markers VE-Cadherin and CD31.

Results: Brightfield micrographs revealed that TP-MRPEC seeded in cloning cylinders increased seeding density, promoted faster outgrowth, and preserved MRPEC morphology. MRPEC seeded onto fibronectin exhibited faster outgrowth; however, MRPEC seeded onto gelatin reduced morphological variability. MRPEC placed onto a circular rotor set to ~45rpm enhanced endothelial cell polarization and paracrine signaling. Flow cytometry analysis revealed that standard MRPEC had an average PE+ purity of ~76% compared to the IgG isotype and unstained controls. Conversely, TP-MRPEC average purity was ~93% (N=5, Tis=829.09). Immunofluorescence staining confirmed high levels of CD-31 and VE-Cadherin 10 days after isolation (EVOS-M500).

Conclusions: In conclusion, we have developed a modified MRPEC isolation and cell monoculture protocol that enhances the uniformity, purity, and long-term phenotypic retention of primary MRPEC monocultures.

Funding: Veterans Affairs Support

Poster PO0388
Methods: hPSC-derived kidney organoids were subject to repeated cisplatin injury twice weekly from differentiation days 49 to 63. Samples were harvested following each injury for immunostaining and qPCR to determine transition from intrinsic to incomplete repair. Single nuclear sequencing (snRNAseq) of pooled samples of control, intrinsic repair, and incomplete repair were compared to similar data sets of mouse UUO and IR, and human renal IRI. Transcripts results were validated with fibrotic human kidney biopsy samples by immunostaining. Targeted drug screening was conducted in kidney organoids to promote intrinsic repair for the identification of novel therapeutic candidates.

Results: snRNAseq from kidney organoids identified 159 differentially expressed genes and 29 altered signal pathways during intrinsic repair. Tabular atrophy and the induction of scar-forming myofibroblasts correlates with reduced expression of homology-directed repair genes in injured tubular cells, a finding supported by single cell transcriptomics in models of obstructive, hemodynamic, and immune-mediated kidney injury, as well as biopsy samples of patients with fibrotic kidney disease. We identified FANC/D2/RAD51-mediated repair as a critical determinant governing the transition between intrinsic and incomplete repair and identified a novel therapeutic target for the prevention of CRD onset and progression following AKI.

Conclusions: Our findings demonstrate the utility of kidney organoids in determining novel pathologic pathways, conducting mechanistic studies of human kidney disease and identifying druggable targets through translational studies.

Funding: NIDDK Support, Other NIH Support - NIH DP2EB029388 award, NIH U01EB028899, NCATS UCLA CTSI KL2, Private Foundation Support

**PO0394**

**T Cell Metabolic Reprogramming and Effect of Glutamine Blockade in Ischemic AKI**


Background: T cells play an important role in the pathogenesis of AKI. Metabolic programming of T cells regulates T cell function, is a rapidly emerging field, and has not been studied in detail during AKI. We aimed to elucidate dynamics of T cell metabolism as well as the effect of blocking glutaminolysis on ischemic AKI.

Methods: We induced ischemic AKI with 30 min ischemia followed by reperfusion in C57BL/6 mice and harvested kidneys and spleens at multiple early time points including during ischemia. Human nonischemic and ischemic kidney tissue was obtained from nephrectomy cases. T cells were isolated and analyzed by a flow cytometry-based immune-metabolic assay with interrogating metabolic programs. The data was evaluated by computational multidimensional analyses with machine learning. The glutamine antagonist JHU083, which targets T cell metabolism, was injected intraperitoneally and effects on AKI were evaluated.

Results: Unbiased high-dimensional analyses identified a distinct T cell subset with reduced expression of mitochondrial VDAC1 and phospho-S6 ribosomal protein (pS6) in posts ischemic kidneys. HK2M23e expression, regulated by TCA cycle, drove the segregation of ischemic kidney T cells from those of nonischemic kidneys in both humans and mice. Splenic T cells from post-AKI mice showed higher expression of GLUT1, hexokinase II (HKK), and CPT1a, indicating upregulation of glycolysis and fatty acid oxidation. Blocking glutamine uptake by JHU083 treatment attenuated renal injury at 24h (plasma creatinine 1.7±0.8 vs 1.0±0.5 mg/dL, P<0.03) and enhanced expression of pS6 (normalized MFI 0.38±0.07 vs 0.47±0.06, P<0.01) and HKII (0.31±0.04 vs 0.41±0.05, P<0.01) compared to vehicle-treated mice. Activation and proliferation were reduced in CD4 (CD44, 67±6% vs 84±7%, P<0.01; Ki67, 59±9% vs 51±6%, P<0.03) and CD8 T cells (Ki67, 73±7% vs 51±6%, P=0.03) in CD44, 61±11 vs 41±11%, P=0.03; CD69, 25±4% vs 18±4%, P=0.02; Ki67, 61±13 vs 48±12%, P=0.04) but increased in double-negative T cells (CD44, 94±2 vs 96±1%, P=0.04; CD8, 72±7% vs 77±1%, P=0.01) in post-AKI kidneys from the JHU083-treated group.

Conclusions: T cells undergo distinct metabolic reprogramming during ischemic AKI. Reconstitution of metabolism by targeting the T cell glutamine pathway could be a promising therapeutic approach for AKI.

Funding: NIDDK Support
recently found to be dysregulated in tubular epithelial cells (TECs) during renal ischemia/ reperfusion injury (IRI). However, the underlying mechanisms of circRNAs in the progression of renal fibrosis are largely unrevealed.

Methods: Mild-AKI (20 min-IRI) and severe-AKI (40 min-IRI) were performed in C57BL/6 mice. The expression of circRNA was analyzed in the freshly isolated tubules from these mice by RNA-seq. One of the dysregulated circRNA, circRNA2 was identified and analyzed by Northern blot, FISH and real-time qPCR in HK2 cells, mouse primary TECS and in mouse kidney. HK-2 cells were exposed to hypoxia as in vitro model. To study the function of circRNA2, we used the CRISPR-Cas9 genome editing system to create a knock out mouse model of circRNA2 in HK2, while our primary TECS were overexpressed by plasmid. To study the function of circRNA2 in vivo, we applied adenovirus-associated virus (AAV)-based circRNA2 overexpression in C57BL/6 mice 3 weeks before performing IRI model. G2/M cell cycle arrest and pro-fibrotic cytokine expression were evaluated in HK2 and primary TECS. Renal fibrosis was evaluated in mouse kidney sections.

Results: The un-biased sequencing showed significant down-regulation of circRNA2 in TECS from severe-IRI mice, as compared to the TECS from mild-IRI mice and control mice. Knockout circRNA2 in HK2 and primary TECS led to G2/M cell cycle arrest and pro-fibrotic cytokines expression. Overexpression of circRNA2 decreased hypoxia-induced G2/M cell cycle arrest of TECS. Preventative overexpression of circRNA2 in vivo ameliorated 40 min-IRI induced renal fibrosis.

Conclusions: Our results showed that circRNA2 regulated G2/M cell cycle transition of TECS and might be served as a therapeutic target for AKI-processed CKD.

Funding: Government Support - Non-U.S.; NIDDK Support

PO0398

Ischemia Reperfusion Activation of Kidney HDAC1 Results in Interstitial Fibrosis

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Background: Following a kidney ischemic event the chormatid remodeling enzyme, histone deacetylase-1 (HDAC1), is activated in many cell types of the kidney including fibroblasts/pericytes. Pharmacological inhibition of HDACs can attenuate ischemia-reperfusion-injury (IRI) mediated interstitial fibrosis. In this study, we tested the hypothesis that fibroblast/pericyte HDAC1 activation promotes interstitial fibrosis.

Methods: Tamoxifen inducible, fibroblast/pericyte HDAC1 knockout (KO) mice (HDAC1cre, Collα2-CreERT) and littermate controls (HDAC1cre0/0) were used. Male and female mice (8-10 wks of age) were given tamoxifen i.p. and IRI or sham surgery was performed after a 2-week tamoxifen washout period. A mild, 18 min, bilateral, warm IRI injury was used and samples collected over 4 weeks. Additional groups of mice underwent unilateral ureteral obstruction (UUO) for 48 h. In vitro experiments with kidney fibroblasts cells (NRK49F) overexpressing HDAC1 were used for RNA-sequencing studies.

Results: HDAC1 KO was confirmed in myofibroblast cells by co-immunolocalization of HDAC1 and platelet-derived growth factor receptor beta or α-smooth muscle actin (α-sm) in the kidneys of IRI mice. 24 h post ischemia there was a tripling of plasma creatinine (Pcr) in all IRI mice, regardless of sex or genotype. 2- and 4-weeks after IRI, Pcr were similar to sham values for all mice. However, the male control IRI mice had significant interstitial fibrosis but this was attenuated in the KO male IRI mice. The female mice, regardless of genotype, had very mild kidney damage and interstitial fibrosis at 4 weeks. The UUO male KO mice had reduced α-sm abundance compared to control male mice. Transcriptomes of NRK49F cells overexpressing HDAC1 had 15 genes upregulated (P<0.05) and 64 genes downregulated (0.5%). Upregulated genes included C3, Bmp6, Ccl12, and Fzd1. Downregulated genes included Clec4f, Il1b1. Gene ontology analysis determined significant enrichment in the regulation of Wnt signaling and innate immune response activating signal transduction.

Conclusions: For male mice, HDAC1 activation leads to pro-fibrotic programming of the myofibroblast and interstitial fibrosis. Future studies will determine the specific epigenetic pathways that may be significantly changed by HDAC1 activation leading to maladaptive interstitial fibrosis.

Funding: NIDDK Support

PO0399

Endothelial and Not Proximal Tubule Epithelial Pannexin 1 Plays a Critical Role in Fibrosis Progression After AKI

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Background: Activation of pannexin-1 (Panx1) channels during acute kidney injury (AKI) and Panx1-mediated release of tissue messengers facilitates the recruitment and activation of immune cells to the site of injury. Lack of Panx1 in the proximal tubules (PT) or in the endothelial cells (EC) significantly reduces AKI. Metabolites released from Panx1 affect a number of biological processes that regulate inflammation and cellular metabolism. Thus, we investigated the role of PT or EC Panx1 during AKI to chronic kidney disease (AKI-CKD) transition by inducing deletion of Panx1 from PT or EC before or after an established AKI.

Methods: AKI was induced by unilateral ischemia-reperfusion injury (IRI), folic acid, or bilateral IRI. Cell-type specific deletion of Panx1 was achieved by injecting tamoxifen before or after AKI to Panx1 floxed (Panx1flx) animals expressing either PT (Slc34a1Cre) or EC (Cd5Cre) specific inducible Cre-recombinase to generate either PT (Slc34a1Cre; Panx1flx) or EC

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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PO0401

Aprotic Exosome-Like Vesicles Aggravate Inflammation and Renal Injury After Ischemia-Reperfusion

Imane Kaci,1,2 Shanshan Lan,1,2 Hyunyun Kim,1,2 Annie Karakeusian Rimbaud,2 Francis Migneault,2 Julie Turgeon,1 Natalie Patey,1 Mélanie Dieudée,1 Marie-Josée Hebert,1 Université de Montréal Faculté de Médecine, Montreal, QC, Canada; 2Centre Hospitalier de l’Université de Montréal Centre de Recherche, Montreal, QC, Canada.

Methods: Post AKI, CD4+ T cells were also increased in ApoExo treated mice (p=0.01, p=0.009 and p=0.04, respectively) compared to controls that received ApoExo, characterized by the LG3 autoantigen, active 20S proteasome and a specific pattern of immunogenic RNAs, can prompt the production of anti-LG3. Here, we test the hypothesis that ApoExo drive renal inflammation after renal IRI leading to anti-LG3 production, defective microvascular repair and loss of renal function.

Conclusions: Collectively, these results identify ApoExo as novel regulators of inflammation after renal IRI, driving anti-LG3 formation, complement activation and fibrosis. These results suggest that autoimmune pathways triggered by ApoExo can contribute to microvascular rarefaction and renal fibrosis.

Funding: Private Foundation Support - Non-U.S.

PO0402

Probiotics Supplementation Protects the Transition from AKI to CKD in Aged Mice via the Kidney-Gut Axis

Myung-Gyu Kim,1 Yina Fang,1 Kyo Yoon Sook, Lee Hee Young, Jihyun Yang, Sewon Oh, Sang-Kyung Jo, Won-Yong Cho. Korea University Anam Hospital, Seoul, Republic of Korea.

Background: Several epidemiological studies have reported that acute kidney injury (AKI) is more frequent in the elderly and they often progress to chronic kidney disease (CKD). Chronic inflammation has recently been reported as an important mechanism mediating CKD progression after AKI in the elderly. This study investigated how kidney and intestinal crosstalk is involved in exacerbation of inflammation in AKI and whether microbial targeted therapy could modulate the transition from AKI to CKD in aged mice.

Methods: In young and aged C57BL/6 mice, 25min bilateral ischemia reperfusion injury protocol was applied, and then colon inflammation, histological changes and intestinal barrier integrity were compared for 28 days post-IRI. To determine the role of the microbiome on kidney-gut crosstalk, we analyzed microbiome from feces in young and aged mice and examined the effects of probiotics supplementation.

Conclusions: Our data indicate that while Panx1 from PT or EC play crucial role during AKI, Panx1 from EC is vital for limiting extent of fibrosis during AKI-CKD potentially by releasing metabolites that regulate immune cell function and fibrosis/repair.

Funding: NIDDK, Support, Government Support - Non-U.S.

PO0403

The Proteomic Landscape of Liver After AKI

Yuan Gui,1 Yanbao Yu,2 Dong Zhou,1 University of Connecticut School of Medicine, Farmington, CT; 2University of Delaware, Newark, DE.

Background: Acute kidney injury (AKI) was traditionally viewed as an ‘innocent bystander’ in various critical illnesses that reflected disease severity in the clinic. Emerging evidence suggests that AKI is an independent protagonist that may cause acute diseases in other organs such as the liver. Thus far, the mechanisms of hepatic dysfunction in patients with AKI have not been well described. We have previously characterized the kidney proteome changes after septic AKI. Here, we further described the proteomic landscape of the liver and assessed the reno-hepatic communications after septic AKI.

Methods: Cecal ligation and puncture procedure was employed to construct the sepsis-induced AKI model. A high-resolution accurate mass-based quantitative proteomics approach was applied.

Conclusions: After septic AKI, alanine aminotransferase (ALT) levels were markedly increased in serum at day 2, while it then dropped, approaching the baseline at day 7, reflecting the process of liver damage and repair. PAS staining exhibited a consistent trend in liver morphological changes. To understand the molecular mechanisms in AKI-caused liver injury, we examined the global proteome and phosphoproteome of the liver on day 2 and day 7 after AKI using a recently developed ultrafast and economic filter-based sample processing approach. We identified and quantified a total of 1,673 proteins and 1,219 phosphosites in the liver. The principal component analyses indicated that the liver’s completely distinct protein expression patterns between day 2 and day 7 after AKI. The network analyses revealed that oxidation-reduction and metabolic processes are the top two processes in liver injury and repair. In the meantime, we identified a wide range of differential proteins in the liver after AKI, including Cyp7b1, cyp1a2, Hemopexin, Acss2, Orn1, Steap 4, and Haptoglobin. These proteins were further validated by western blot and immunostaining. Of particular interest, Steap4, a member of the six transmembrane epithelial antigens of the prostate, was significantly upregulated in the liver but not in the kidney upon septic AKI, suggesting a tissue-specific inflammatory response.

Funding: Support - Non-U.S.
Conclusions: Our results imply that describing the liver’s proteomic landscape after liver injury, or xenon-hapten-induced liver injury, and Steap4 may serve as a potential candidate to monitor AKI-caused liver injury in the clinic.

Funding: NIDDK Support

PO0404

COX-2-EP4-MaBβ Axes Protect Against Renal Fibrosis in Mice with Renal Ischemic Injury

Yu Pan,1,2 Shirong Cao,1 Juan Pablo Arroyo Ornelas,1 Andrew S. Terker,1 Yinqiu Wang,1 Aoei Niut,1 Sunaw Wang,1 Xiaofeng Fan,1 Raymond C. Harris,1 Ming-Zhi Zhang.1,3 Vanderbilt University Medical Center, Nashville, TN; 1Shanghai Jiao Tong University, Shanghai, China.

Background: The mammalian kidney is easily injured by ischemic or toxic insults but can often recover functional and structural integrity. Immune immunity is involved in both the injury and recovery processes, and its maladaptive response causes delayed recovery and development of kidney fibrosis. Cyclooxygenase 2 (COX-2) plays an essential role in antiinflammatory and tissue-reparative M2 polarization of macrophages, the major renal myeloid cells. Renal macrophage COX-2 increases after acute ischemic kidney injury (AKI). The current study investigated the role of renal macrophage COX-2 in ischemic AKI and subsequent development of fibrosis.

Methods: We developed myeloid COX-2-/- mice (CD11b-Cre; COX-2f/f), myeloid EP4-/- mice (CD11b-Cre; EP4f/f), and myeloid MaBβ-/- mice (Ly6C-MCre; Maβf/f). The animals were uninephrectomized, immediately followed by unilateral renal pedicle clamping for 32 min.

Results: Following ischemic AKI, COX-2 was selectively increased in renal macrophages as indicated by colocalization with CD68, and myeloid COX-2-/- mice exhibited delayed renal recovery and increased tubulointerstitial fibrosis, in association with augmented proinflammatory cytokines in isolated renal macrophages. In bone marrow derived monocytes, PGE2 is the major COX-2-mediated arachidonic acid metabolites and acts primarily via EP4 receptors. Myeloid EP4-/- mice mimicked the effects observed with COX-2-/- mice in response to ischemic AKI. We found that myeloid EP4 activation induced expression of MaBβ, a major transcription factor, to upregulate antiinflammatory genes and suppress proinflammatory genes in macrophages. Selective myeloid MaBβ deletion recapitated the effects seen with myeloid COX-2 or EP4 deletion, with delayed recovery and increased kidney fibrosis. Mice with myeloid deletion of COX-2, EP4, or MaBβ had similar impairment of renal macrophage effectorcytosis.

Conclusions: These studies show that COX-2/EP4-dependent MaBβ expression mediates renal macrophage antiinflammatory and pro-resolving polarization and identifies a potential therapeutic target for AKI and chronic kidney disease, a finding that is relevant to understanding detrimental effects of NSAIDs in the setting of renal dysfunction.

Funding: NIDDK Support

PO0405

Subcutaneous Adipose Stromal Cell-Derived Secretome Improves Renal Function and Inflammation in Established AKI

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Background: Previous studies demonstrated that human adipose derived stromal cells (ASC) attenuated the development of acute kidney injury (AKI) and preserved vascular density, when administered in the suprarenal aorta immediately following ischemia reperfusion injury (IRI). Recently, stem cell derived secretome, has received attention as a potential therapy for AKI. The secretome contains growth factors, cytokines and extracellular vesicles that could act on proximal tubule cells (PTCs) and mitigate renal injury.

Methods: ASCs were cultured in serum-free medium. Conditioned media (secretome) was collected at 2, 7, 14, 21, and 28 days after injury and BUN, creatinine, iron, and ferritin levels were measured. Kidney tissues were collected at each time point for histology, histology, immunohistochemistry, RNA isolation, and immunoblot analysis.

Results: Conditional KO mice were generated and deletion of Hepcidin1 and FPN specifically in PTCs was confirmed at the DNA and protein levels. Treatment of mice with secretome post AKI would help understand reno-hepatic crosstalk, and Steap4 may serve as a therapeutic target.

Funding: NIDDK Support

PO0406

The Role of Disrupted Iron Metabolism in AKI: Targeting Iron Trafficking via the Hepcidin-Ferroportin Axis in Renal Proximal Tubules

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Background: Acute kidney injury (AKI) and iron-related disorders remain major clinical challenges associated with significant morbidity and mortality. Ferroportin (FPN) is an iron exporter, identified as a modulator of iron balance. Hepcidin binds to FPN, causing its internalization and degradation. Though FPN and FPN are expressed in proximal tubule cells (PTCs) of the mouse kidney, their role in the pathogenesis of AKI is unclear. Through this work, we hope to determine if modulation of iron homeostasis by selective deletion of hepcidin or FPN in PTCs alters the response to AKI.

Methods: We generated PTC-specific Hepcidin1 and Ferroportin (FPN) knockout (KO) by selectively expressing Cre in PTCs and confirmation with a red-green reporter (mTmG; Peck-cross cre). We served these mice to either the Folic Acid induced injury model, or the ischemia-reperfusion injury model of AKI. Serum samples were collected at 2, 7, 14, 21, and 28 days after injury and BUN, creatinine, iron, and ferritin level were measured. Kidney tissues were collected at each time point for histology, histology, immunohistochemistry, RNA isolation, and immunoblot analysis.

Results: Conditional KO mice were generated and deletion of Hepcidin1 and FPN specifically in PTCs was confirmed at the DNA and protein levels. Treatment of mice with secretome post AKI would help understand reno-hepatic crosstalk, and Steap4 may serve as a therapeutic target.

Funding: NIDDK Support

PO0407

Noncanonical Wnt5a/CD146 Signaling Drives Renal Fibrosis by Activating Transcriptional Factor Snail in AKI

Xiaomei Li, Jiejun Fan, Jia Qunzi Zhang, Ting Zhou, Ying Fan, Xiping Wang, Shuangshuang Jiao Tong University Affiliated Sixth People’s Hospital, Shanghai, China.

Background: Acute kidney injury (AKI) with severe and persistent kidney cell injury will eventually progress to permanent damage, progressive fibrosis and chronic kidney disease (CKD). However, the exact cellular and molecular mechanisms mediating the progression of AKI to CKD remain incompletely understood. We recently reported that Wnt5a promotes renal tubular inflammation in diabetic nephropathy by binding to CD146, which is increase in the prevalence of AKI and illuminate new therapeutic strategies for progressive kidney disease and other syndromes of iron overload.

Methods: To examine whether Wnt5a mediated CD146/JNK pathway was involved in renal fibrosis, we performed changes in Wnt5a expression in AKI and investigated the role of CD146-mediated Wnt5a/JNK pathway in fibrosis.

Results: Wnt5a promotes renal tubular inflammation in diabetic nephropathy by binding to CD146, which increase in the prevalence of AKI and illuminate new therapeutic strategies for progressive kidney disease and other syndromes of iron overload.

Funding: NIDDK Support

PO0408

Hyperactivation of CDK5 Promotes Proximal Tubule Cell Dedifferentiation and Intestinal Fibrosis in CKD

Kensei Taguchi, Bertha C. Elias, Craig R. Brooks. Vanderbilt University Medical Center, Nashville, TN.

Background: Chronic kidney disease (CKD) effects ~15% of the world’s population. Recently, we demonstrated that Cyclin G1 (C1G) regulates proximal tubule cells (PTCs) growth and promotes fibrosis. Moreover, PT cell dedifferentiation, which occur in CKD, and PKD5, which regulates cell cycle exit and homeostasis in differentiated cells. Under
normal conditions, CDK5 activity is kept in check by p35; however, during cellular stress, p35 is cleaved to p25, leading to hyperactivation of CDK5, a driving leader of many neurodegenerative diseases. The aim of the current study is to determine if CDK5-induced hyperactivation of CDK5 plays a pathological role in PTCs’ dedifferentiation and pro-fibrotic signaling.

Methods: A novel CDK5/p25 inhibitor, Glxix, was utilized to inhibit hyperactivation of CDK5. Protocol 1; Aristolochic acid nephropathy (AAN) and low-dose cisplatin models were conducted as AKI-to-CKD model by repeated doses of AA and cisplatin in 8 to 12-week-old male wild-type (WT) and CDG1 globally knockout mice (CDG1KO). Protocol 2; To investigate the effect of CDK5 hyperactivation, unilateral ureter obstruction (UUO) was used with administration of Glxix. Protocol 3; CDK5 was overexpressed in cultured PTCs. Protocol 4; Primary PTCs of WT and CDG1KO mice were co-incubated with AA in the presence or absence of Glxix or roscovitine, a selective CDK inhibitor. Expression and cleavage of p35 to p25 was also reduced in CDG1KO compared to wild-type CDG1KO PTCs. Inhibition of CD5 or CDK5/p25 interaction (hyperactivation) prevents dedifferentiation and profibrotic cytokine secretion in AA treated primary PTCs. Overexpression of either CDG1 or CDK5 induces upregulation of dedifferentiation and profibrotic markers, which can be reversed through inhibition of CDK5. In vivo, inhibition of CDK5/p25 binding reduces fibrosis and prevents PTC dedifferentiation following UUO.

Conclusions: CGL expression induces hyperactivation of CDK5 in PTCs. Inhibition of CDK5 or CDK5/p25 binding prevent CDG1 induced dedifferentiation, profibrotic cytokine secretion and fibrosis. Targeting the CDG1/CDK5 pathway is a potential therapeutic target for inhibiting AKI-to-CKD transition.

PO0409 Clearance of Chronic Senescent Tubular Cells by ABT263 After Ischemic AKI Halts the Progression of Established Fibrosis and Restores Tubular Regeneration

Man J. Livingston, Zheng Dong, Augusta University Medical College of Georgia, Augusta, GA.

Background: Emerging studies from aging models demonstrate that increased senescent cell load causes kidney dysfunction and removal of senescent cells by senolytics may rejuvenate aged kidneys for renoprotection. Senescent cells may also accumulate in the kidney during maladaptive repair after AKI. However, the pathological role of cellular senescence in post-injury kidney and the therapeutic significance of targeting senescence to treat fibrosis during AKI to CKD transition remain less understood.

Methods: To induce post-ischemic kidney fibrosis, 10 to 12-week-old C57BL/6 mice underwent 30-minute unilateral or 22-minute bilateral renal ischemia followed by reperfusion for 2 weeks. The mice were then treated with either vehicle or ABT263 at 50 mg/kg/day, daily i.p. injection, 5 days/week for 2 weeks. One week after the completion of ABT263 treatment, the morphology and function of the fibrotic kidneys were examined.

Results: Following ischemic AKI, senescent cells accumulated in renal tubules, as indicated by upregulation of p16 and SASP factors, increased tubular staining of SA-β-gal, and induction of γ-H2AX nuclear foci. This injury-induced tubular senescent phenotypes was accompanied by persistent interstitial fibrosis. Compared with vehicle treatment, ABT263 significantly eliminated senescent tubular cells and partially suppressed the progression of post-ischemic kidney fibrosis. Along with fibrosis resolution, ABT263 also reduced the infiltration of macrophages in interstitial tissues and attenuated the chronic expression of KIM-1 in injured proximal tubules, therefore creating a pro-regenerative environment for tubular repair. As a result, the number of Ki67-positive tubular cells was promoted and tubular expression of LTL was restored to some extent as well, indicating increased tubular proliferation and dedifferentiation. Consistent with the morphological findings, renal function, as assessed by BUN, serum creatinine and eGFR, was also improved in mice treated with ABT-263.

Conclusions: These results support the pathological role of tubular injury-induced accumulation of senescent cells in fibrotic kidney repair after AKI. Targeting these chronic senescent cells by senolytics may represent a therapeutic strategy to reverse maladaptive tubular repair and to halt AKI to CKD progression.

Funding: NIDDK Support, Veterans Affairs Support

PO0410 Defects in KIM-1-Mediated Phagocytosis Do Not Predispose to AKI in Humans

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Background: Phagocytosis of dying cells is critical for homeostasis and tissue repair. During renal injury, upregulation of kidney injury molecule-1 (KIM-1) transforms kidney epithelial cells into phagocytes that engulf apoptotic and necrotic cells. A mutation that inactivated KIM-1 phagocytic function (mucin domain deletion) resulted in worse kidney dysfunction after ischemia-reperfusion-injury (IRI) in mice, but this has not been studied in humans.

Methods: We expressed three common mucin domain nonconservative variants (rs12237866, rs45439103, and rs45439070) of the human KIM-1 gene (HAKFR1) in human kidney cells. To test if impaired KIM-1-mediated phagocytosis predisposes to kidney dysfunction after IRI, we genotyped 627 consecutive kidney donors and assessed risk of delayed graft function in recipients.

Results: These cells expressing mutations exhibited markedly reduced phagocytosis of apoptotic and necrotic cells, compared to cells expressing wild-type KIM-1. rs6149307 showed the most severe defects (<5% phagocytosis vs. wild type). Surprisingly, the risk of delayed graft function in recipients of donor kidneys homozygous for rs6149307 was not significantly increased compared to recipients of kidneys with one or two copies (adjusted relative risk 1.0 [0.7-1.3]). Analysis of rs1252248 and rs45439103 yielded similar results.

Conclusions: Contrary to murine models, these results suggest severe defects in KIM-1-mediated phagocytosis do not predispose to acute kidney dysfunction after IRI in humans.

Funding: Government Support - Non-U.S.
Conclusions: DeR2-positive tubules were failed-repair cells in AKI. And DeR2 primes failed-repair of tubular cells through regulating the expression of HMGCS2, then affects the metabolism of β-hydroxybutyrate, suggesting that DeR2 may be a potential intervention target during the progression of AKI.

Funding: Government Support - Non-U.S.

PO0413
Mini-Pulse and Fast-Tapering Corticosteroids in Acute Tubulointerstitial Nephritis Related to Immune Checkpoint Inhibitors: Testing a Treatment Scheme

Raquel B. Rico, Hospital Universitario 12 de Octubre, Madrid, Spain.

Background: Acute tubulointerstitial nephritis (ATIN) is the most common lesion seen on kidney biopsy related to immune check-point inhibitors (ICIs) in oncological patients. Clinical and laboratory features as well as risk factors are well known, albeit non-specific in predicting the underlying renal lesion. Corticosteroid-based therapy has proven to be effective, however, the optimal duration of treatment has not yet been established.

Methods: We conducted a retrospective single-center study to evaluate a treatment scheme with low-dose corticosteroids in patients diagnosed with ATIN between 2017-2021. Extrapolating our treatment scheme for acute interstitial nephritis, we administer pulses of methylprednisolone (2 mg/kg/day for 3 consecutive days) followed by prednisone 1mg/kg/day with rapid-tapering until total withdrawal 2 months after treatment onset. The main outcome was a successful renal response during follow-up.

Results: We included a total of 8 patients (87.5% males) with a median age of 66.5 years and diagnosis of metastatic disease in all cases. Three patients had urtheelial cancer, two had renal cell carcinoma and lung cancer, and one had hepatocellular carcinoma. Moreover, we compared our mini-pulse treatment with PDE-1 and PDE-1 inhibitors that were employed in 62.5 and 37.5% of the cases, respectively. Baseline serum creatinine (SCr) was 1.1 mg/dl(0.82-1.5), three patients had chronic kidney disease and six patients were on treatment with protein pump inhibitors. Acute kidney injury presented 13.5 weeks after starting ICI therapy. The median highest SCr was 3.2 mg/dl(2.5-3.5) and one patient required acute dialysis. Renal biopsies were obtained in all patients (proteinuria in 50%, hematuria in 75%, and sterile pyuria in 87.5%). Complete renal response was observed in all cases, except for one patient who showed a partial response. ICI rechallenge was not applied to any patient and no ATIN recurrences were documented after corticosteroids discontinuation. Two patients died due to oncologic disease progression. Median follow-up was 12.5 months(2.5-27.5).

Conclusions: Our treatment scheme with fast-tapering corticosteroids was effective for inducing renal response in ICIs-related ATIN, without evidence of relapses.

PO0414
Contralateral Nephrectomy Stimulates Proliferation of Renal Epithelial Progenitor Cells After Unilateral Ischemia

Lies Moonen, 1 Elena Lazzeri, 2 Anna J. Peired, 2 Carolina Conte, 2 Paola Romagnani, 3 Patrick D’Haese, 1 Benjamin A. Vervaet, 1 Laboratory of Pathophysiology, 2Université Antwerp Laboratory voor Pathofysiologie, Wilrijk, Belgium; 3Università degli Studi di Firenze Dipartimento di Scienze Biomediche Sperimentali e Cliniche Mario Serio, Firenze, Italy.

Background: Acute kidney injury is a global health concern and important risk factor for the development of chronic kidney disease. Crucial for successful recovery after AKI is the proliferation of surviving tubular epithelial cells. We established a murine model in which functional and histological recovery of a kidney, injured by ischemia, is enhanced by removal of the contralateral kidney, i.e. nephrectomy-induced recovery. The epithelial reparative response in this unique model has not been investigated, yet can provide new insights in the inherent regenerative potential of the renal epithelium.

Methods: AKI was induced in two different mouse strains by left unilateral ischemia/reperfusion (UIR) after which either right nephrectomy (Nx) or no Nx was performed on day 3. In R26Leo-Confetti mice kidney-to-body-weight ratio, renal function (serum creatinine) and fibrosis (Sirius Red histology) were measured at week 6. Additionally, renal tissue of Patients having a high percentage of PAX2+/Confetti mice was processed for clonal analysis by lineage pattern analysis of PAX2+ renal epithelial progenitor cells at day 28.

Results: When no Nx was performed after UIR, a significant decrease in left kidney-to-body weight ratio along with increased fibrosis and functional loss were observed in the injured kidney at week 6 compared to controls. However, when Nx was performed, renal function and mass were preserved. During spontaneous repair after UIR (i.e. without Nx) clonal analysis in PAX2+/Confetti mice revealed a significant increase in clone size frequency from mainly monoclonal PAX2+ progenitor cells in controls to an increased number of multiclonal clones. When Nx was performed after UIR, this clonal expansion was further significantly stimulated. Likewise, the percentage of PAX2+ cells stimulated to divide (i.e. clonogenicity) was significantly higher when Nx was performed after UIR (42%) as compared to when no Nx was performed (28%).

Conclusions: Nx overcomes loss of renal mass and function after UIR. This enhanced recovery is at least established by increased clonogenity and enhanced clonal expansion of renal progenitor cells that surmounts that of spontaneous repair after UIR. Getting insight in the signaling mechanisms by which nephrectomy achieves this response may open new therapeutic research avenues.

Funding: Government Support - Non-U.S.

PO0415
Long Noncoding RNA Neat1 Promotes Tubular Epithelial Cells Apoptosis to Facilitate the Progression of AKI to CKD

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Background: The severity and frequency of acute kidney injury (AKI) determine if the injury leads to chronic kidney disease (CKD). A growing number of research shows that the injury of tubular epithelial cells (TECs) is the driving force during chronic progression of AKI. However, there are limited knowledge about the role of lncRNAs in the progression of AKI.

Methods: To screen out the candidate IncRNA in the progression of AKI to CKD, 8-week old C57BL/6 mice were subjected to mild-AKI (20 min-ischemic reperfusion injury) and severe-AKI (40 min- ischemic reperfusion injury). RNA-sequencing was performed with the isolated tubules from mild- or severe- AKI mouse. The expression of a candidate IncRNA Neat1 was evaluated by FISH, Northern blot and real-time qRT-PCR in HK2 cells and mouse kidney tissues. To study the biological function of Neat1 in vitro, CCRPR-Cas9 was used to knock out Neat1, while Neat1 was ectopic overexpressed by lentivirus. HK2 cells were cultured in anoxic environment as the in vitro model to study the function of Neat1. RNA pull down was performed to screen out the microRNAs that bound to Neat1. Knocking down Neat1 in vivo was performed by injecting Adeno-associated virus serotype 9 (AAV9) particles carrying siRNA targeting Neat1. Flow cytometer was used to calculate the apoptotic cells under each treatment. TUNEL was applied to evaluate the apoptotic TECs in kidney sections.

Results: The expression of Neat1 was upregulated in the tubules from severe AKI mouse, as compared to mild AKI mouse. Knocking out Neat1 inhibited hypoxia-induced HK2 cells apoptosis while overexpression of Neat1 enhanced the apoptosis of HK2 cells in vitro. Furthermore, knockdown of Neat1 in vivo reduced the apoptosis of TECs and improved the kidney functions of IRI mice.

Conclusions: Our results showed that lncRNA neat1 regulated apoptosis of TECs and might be served as a therapeutic target to ameliorate AKI.

Funding: Government Support - Non-U.S.

PO0416
Effects of Proton Pump Inhibitors (PPIs) on Renal Vascular Reactivity in Cirrhotic Rats

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Background: Hepatorenal syndrome is, a lethal complication of cirrhosis, defined as renal hypoperfusion resulting from intense renal vasoconstriction. Vascular dysregulation such as ET-1 and nitric oxide (NO) might be the contributing factor. Proton pump inhibitors (PPIs) are widely used for peptic ulcer. Although generally safe, recent studies reported that PPIs decreased NO production, leading to reduction of arterial relaxation. The prevalence of gastric ulcer in cirrhotic patients is higher than healthy controls. The impact of PPIs on renal vascular responsiveness in cirrhosis is worth to be studied.

Methods: Liver cirrhosis was induced in S-D rats by common bile duct ligation (CBDL). Sham-operated (SHAM) rats were surgical controls. On the 29th day after surgery, in-situ renal perfusion was performed. In acute treatment study, rats were randomly assigned to Krebs solution or Esomeprazole (30 mM) incubation for 1h before renal perfusion. In chronic treatment study, rats were randomly received oral distill water or Esomeprazole (3.6 mg/kg/d) for 28 days.

Results: The were no significant changes in renal vascular reactivity to ET-1 after acute (Fig. A) and chronic (Fig. B) PPIs treatment in CBDL rats. Chronic PPIs treatment had no significant effects on systemic hemodynamics and renal function but decreased hemoglobin in both SHAM and CBDL rats (Table). In conclusion, PPIs showed no renal vascular effects. The mechanisms of lower hemoglobin following PPIs treatment need further analysis.

Table. Hemodynamic and biochemistry data

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<th>Group</th>
<th>Sham (n=8)</th>
<th>CBDL (n=8)</th>
<th>P (*0.05 vs Sham)</th>
<th>CBDL (n=8)</th>
<th>P (*0.05 vs Sham)</th>
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<tr>
<td>Systolic Blood Pressure (mmHg)</td>
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<td>135±6</td>
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<td>Triglycerides (mg/dL)</td>
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</table>

Expressed as mean ± SEM

* P < 0.01 vs Sham group

† P < 0.01 vs corresponding DW-treated group
AKI: Repair and Progression

**PO0417**

**Hospitalized AKI Is Associated with Long-Term Increases in TNFR1 and TNFR2: Findings from the CRIC Study**

Ian McCoy,1 Jesse Y. Hsu,2 Joseph V. Bonventre,1 Chirag R. Parikh,1 Chi-yuan Hsu,1 University of California San Francisco, San Francisco, CA; 1University of Pennsylvania, Philadelphia, PA; 2Brigham and Women’s Hospital, Boston, MA; 3Johns Hopkins University, Baltimore, MD.

**Background:** Evaluation of plasma biomarkers before and after AKI may yield valuable insights into the pathogenesis of progressive CKD after AKI. Markers of endothelial inflammation and injury, Tumor Necrosis Factor Receptors 1 and 2 (TNFR1 and TNFR2), are associated with progressive CKD, but it is unknown whether an episode of hospitalized AKI may cause long-term changes in these biomarkers.

**Methods:** Among participants in the prospective Chronic Renal Insufficient Cohort (CRIC), episodes of hospitalized AKI were identified using acute changes in inpatient serum creatinine values (peak/nadir ≥1.5). For each AKI hospitalization, we found the best matched non-AKI hospitalization (unique patients) using the following factors: diabetes, age, sex, and duration between hospital admission and prior CRIC visit (max 2 years). We measured plasma levels of TNFR1 and TNFR2 using banked plasma samples collected at CRIC study visits before and after the hospitalization. Biomarkers were measured using a customized U-Plex assay on a MesoScale Device.

**Results:** Study participants who did and did not have AKI were well matched (Table). Pre-hospitalization TNFR1 and TNFR2 levels were also similar. AKI was associated with greater increases in TNFR1 (p<0.01) and TNFR2 (p<0.01).

**Conclusions:** Hospitalized AKI was associated with increases in plasma TNFR1 and TNFR2 months after the hospitalization.

**Funding:** NIDDK Support

**PO0418**

**Can Urinary Biomarkers at AKI Predict Progression to CKD?**

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**Background:** Acute kidney injury (AKI) can cause permanent structural changes and progressive chronic kidney disease (CKD). If kidney function normalizes after AKI, it is difficult to distinguish who will progress to CKD. We evaluated urinary biomarkers from mice at the time of AKI and correlated them to a range of structural features derived from histopathology and cationic ferritin enhanced-MRI (CFE-MRI) in the kidney later in life. We investigated whether these biomarkers at AKI could predict future progression to CKD.

**Methods:** Adult male mice were injected with folic acid (AKI) or NaHCO3 (controls), (n=8/gp) and urine was collected after 4 days. Biomarkers were measured using the Cytoscreen Array Q1000 (Ray BioTech). Mice received CF 12 wks after AKI and kidneys were imaged ex vivo using 7T MRI. Structural metrics were derived by CFE-MRI (Vglom, %ATG, and PT content) and histology (proximal tubule (PT) content, atubular glomeruli (ATG), and scarred area).

**Results:** We performed a univariate analysis comparing the AKI and controls. Using hierarchical edge bundling, there were 19 connections between the urinary biomarkers and structural metrics at 12 wks and 7 connections in the control group (Fig 1A). EGF, OPG, TARC and TNF RII (r=0.8, Fig 1B) were correlated to structural metrics in AKI and only IGFBP-6 was correlated to the structural metrics in controls. We developed predictive models using the 13 urinary markers in Fig 1B. The best model predicted mean aVglom (r=0.67), %ATG (r=0.50) and PT content (r=0.47).

**Conclusions:** Urinary biomarkers, alone or in combination, may provide noninvasive predictive markers for progression to CKD after AKI. We identified 13 urinary biomarkers that appear to predict structural changes in the kidney 12 weeks after AKI and may serve as candidate biomarkers to predict outcomes in patients.

**Funding:** NIDDK Support

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**Figure 1.**

- **A.** Concentration-response curves in perfuse kidneys of CBDL rats following (A) acute and (B) chronic PPIs treatment.
- **B.** Findings from the CRIC Study
- **C.** Concentration-response curves in perfuse kidneys of CBDL rats following (A) acute and (B) chronic PPIs treatment.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

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Air Pollution Aggravates Ischemia-Reperfusion-Induced AKI in Mice

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Background: The biggest city in Latin America is Sao Paulo (SP), where disorganized urbanization has had a negative impact on air quality and vehicle emissions are the main source of fine particulate matter (PM2.5). Epidemiological studies have linked PM2.5 exposure to an increased risk of I/R injury. The mechanisms mediates the adverse health effects of PM2.5 include oxidative changes, endotoxic stress and inflammation. The role of PM2.5 in AKI has yet to be described. We hypothesized that PM2.5 exposure would aggravate renal ischemia/reperfusion (IRI) injury in mice.

Methods: In temperature-humidity-controlled chambers within an ambient particle concentrator, animals were exposed to a concentrated PM2.5 stream (PM2.5) or to high-efficiency particulate air-filtered clean air (CA). Mass concentrations of PM2.5 were measured with an airborne particle monitor, and the target dose was 600 µg m⁻³/day (equivalent of the daily exposure in SP). After 12 weeks, some PM2.5 and CA mice underwent bilateral 30-min clamping of the kidney hilus and subsequent reperfusion. All studies were performed 48 h after I/R groups: CA, PM2.5, CA+IR, and PM2.5+IR. Data are mean±SEM.

Results: Renal TLR4 protein expression was higher in CA+IR and PM2.5+IR than in CA and PM2.5 (128.1±2.2 vs. 146.0±2.0, P<0.05) and being much higher in PM2.5+IR than in CA+IR (P<0.05). Manganese superoxide dismutase levels were higher in PM2.5+IR than in CA+IR, AF and PM2.5 (146±12 vs. 99±3.6, 102±3.9 and 96±2.8; P<0.05).

Conclusions: PM2.5 aggravates I/R-induced AKI by decreasing renal Klotho protein, leading to increased renal TLR4 expression and inflammatory cell infiltration. (FAPESP, NWO)

Funding: Government Support - Non-U.S.

Biochemistry and histology

*Immunohistochemical analysis; P<0.05 vs. CA, PM2.5 and CA+IR; P=0.05 vs. CA and PM2.5.

PO0421

Proteogenomic Effects of Environmental and Uremic Toxin Acrolein on Mouse Kidneys

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Background: Acrolein is present in the environment, water, food, and is a uremic toxin endogenously produced through lipolysis peroxidation and polychromat oleic acid. Its mechanism of action involves cellular thiol reactivity and glutathione depletion-induced oxidative stress. However, direct effects of acrolein on kidneys are not known. The current study conducted a protease and proteomic analysis on mouse kidneys exposed to acrolein.

Methods: C57BL/6 mice were subjected to filtered-air (control) or inhaled-acrolein (equivalent of the daily exposure in SP). After 12 weeks, some PM2.5 and CA mice underwent bilateral 30-min clamping of the kidney hilus and subsequent reperfusion. All studies were performed 48 h after I/R groups: CA, PM2.5, CA+IR, and PM2.5+IR. Data are mean±SEM.

Results: Renal TLR4 protein expression was higher in CA+IR and PM2.5+IR than in CA and PM2.5 (128±2.1 146.0±2.0, P<0.05), also being much higher in PM2.5+IR than in CA+IR (P<0.05). Manganese superoxide dismutase levels were higher in PM2.5+IR than in CA+IR, AF and PM2.5 (146±12 vs. 99±3.6, 102±3.9 and 96±2.8; P<0.05).

Conclusions: PM2.5 aggravates I/R-induced AKI by decreasing renal Klotho protein, leading to increased renal TLR4 expression and inflammatory cell infiltration. (FAPESP, NWO)

Funding: Government Support - Non-U.S.

Biochemistry and histology

*Immunohistochemical analysis; P<0.05 vs. CA, PM2.5 and CA+IR; P=0.05 vs. CA and PM2.5.

PO0422

Impaired Renal Hemodynamic Reserve Following Ischemic AKI Is Associated with Inflammation and Capillary Rarefaction and Reversed by Retrograde Hydrodynamic Isotonic Fluid Delivery

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Background: We have previously shown that retrograde hydrodynamic delivery of isotonic fluid (HIFD) improved renal function in established AKI between 24-48 hours following ischemia and reperfusion injury (IRI). This improvement was associated with decreased inflammation and vascular congestion and improved microvascular perfusion. However, it is unknown whether HIFD results in sustained effects on renal hemodynamic reserve and CKD progression.

Methods: Male Sprague Dawley rats underwent left unilateral IRI-35 min with right unilateral nephrectomy to induce AKI. 24 hours later, serum creatinine (SCr) was measured and rats received either HIFD via the renal vein or 0.5ml of isotonic saline (0.9%) as control. SCr was measured and rats received either HIFD via the renal vein or 0.5ml of isotonic saline into anesthetized rats. Kidneys were evaluated for further analysis.

Results: At 5 weeks of recovery from surgery, baseline renal blood flow (RBF) and renal vascular resistance (RVR) were similar in the experimental groups (sham-, HIFD-, and VC-treated rats). Following 40 minutes of arginine infusion RBF increased similarly in both the sham group and the I/R HIFD group (22.6% and 19.8%) compared to their corresponding baseline value (P<0.001). However, I/R-VC treated rats showed an impaired response to arginine infusion relative to the sham group (P<0.001). As expected, RVR to blood flow was decreased significantly by 14% and 17% in sham-operated and HIFD treated rats compared to their corresponding baseline respectively. In the kidney, HIFD treatment attenuated recruitment of inflammatory CD4+IL17+ cells (77±65 vs. 41±609, P<0.05), as assessed by flow cytometry compared to the VC-treated rats. Peritubular capillary density in medulla, measured by cebelin inflammation, was significantly reduced by (41%) in VC-treated rats compared to sham group. HIFD treatment significantly improved capillary density after 35 days of IRI.

Conclusions: HIFD treatment showed improved impaired renal blood flow response to arginine infusion following 35 days IRI. This is associated with improved capillary density and attenuated infiltration of CD4+IL17+ cells. This data shows that HIFD treatment has long-term protective effects following IRI injury.

Funding: NIDDK Support, Veterans Affairs Support

PO0423

Evidence for a Critical Role of ARNT Homodimerization in Renal Regeneration and Attenuation of Fibrosis

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Background: Based on the organ-spanning effectiveness of ischemic preconditioning we hypothesized that underlying mechanisms could be utilized to aid the kidney in regenerative processes and to prevent and cure renal fibrosis. Previous studies implied that ARNT, also known as HIF alpha, plays an important role independent of HIF1alpha in ischemic preconditioning. Here we aimed to explore the mechanisms underlying the renoprotective activity of ARNT and to exploit these mechanistic insights for novel therapeutic strategies.

Methods: ARNT homodimerization in vivo and in vitro was studied by mass spectrometry, immunoprecipitation, proximity ligation assays, native gel analysis and the use of mutant ARNT variants. Control of ARNT expression was studied by use of qRT PCR, immunoblot and promoter assays. To study impact of ARNT homodimerization in vivo we utilized more models of UU and CC44-induced liver fibrosis.

Results: We provide evidence that transcriptional induction of ARNT by administration of FK506 or Tacrolimus enhances renal regeneration and attenuates fibrosis in vivo. This effect is not realized when ARNT is targeted by administration of in vivo morpholinos. We demonstrate that the protective effect of ARNT is only realized when fibromed. ARNT homodimers acts as transcription factor on ALK3 and the protective effect of ARNT homodimers is not realized when ALK3 is lacking. We identify that ARNT dimerization decision to form homodimers is controlled by phosphorylation of a critical serine 77 amino acid. ARNT Ser77 phosphorylation is controlled by PP2A. The PP2A inhibitor LB100 enhances Ser77 phosphorylation, ARNT homodimer formation and attenuates fibrosis in the kidney. Combination of GPI0146 (to induce ARNT transcription) and LB100 (to enhance ARNT homodimers) has additive effect to protect against fibrosis in kidney and liver.

Conclusions: Increased intracellular ARNT levels through enhanced transcription and augmented homodimerization through phosphorylation of ARNT Ser77 are prerequisites to realize the renoprotective activity of ARNT. Utilization of this dual mechanism through combination therapy has potential to protect the kidney.
PO0424
TGF-β1-Mediated Tubular Injury and Cell Death Requires Recruitment of Inflammatory Cells via CCL5
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Background: Activation of the TGFβ signaling pathway plays an important role in both AKI and CKD pathogenesis. We have previously shown that ligand-independent activation of TGFβ in proximal tubules results in rapid epithelial cell injury and death, as well as immune cell infiltration. This study aims to determine the drivers and mechanism of epithelial cell injury.

Methods: In vivo studies were performed in transgenic Pax8Tgβr1 mice with proximal tubular activation of TGFβ1 signaling by +/- doxycycline (Dox) chow. Immortalized proximal tubular epithelial cells (PTECs) from Pax8Tgβr1 mice were treated with Dox and with activated spleen derived leukocytes. Cell death was determined by TUNEL or AnnexinV/PI staining, lipid-derived free radicals by electron paramagnetic resonance (EPR) spin resonance spectroscopy and in vivo spin trapping, and mitochondrial superoxide was determined by mitoSOX. Gene and protein expression were determined by RT-PCR, western blotting and immunofluorescence.

Results: Canonical TGFβ signaling induced by Dox was confirmed in Pax8Tgβr1 mice and in isolated PTECs cells by increased Tgfb1 gene expression and phospho-
SMAD2 or nuclear translocation of SMAD2/3. Markers of tubular cell injury and inflammation were prominent in kidney sections from Pax8Tgβr1 mice after 5 days of Dox. There was also increased oxidative stress and cell death after 5 days. TGFβ1 signaling activation in cultured Pax8Tgβr1 PTECs did not induce cell death, but showed an increase in CCL5/RANTES expression, a chemokine involved in recruitment of several immune cell types, among them monocytes and T-cells. PTECs co-cultured with leukocytes isolated from spleens resulted in spleen-mediated oxidative stress and cell death of PTECs. Cell death and mitochondrial oxidative stress was ameliorated by a β of Dox. There was also increased oxidative stress and cell death after 5 days. TGF
R1 inflammation were prominent in kidney sections from Pax8Tgfbr1 mice after 5 days by RT-PCR, western blotting and immunofluorescence.

Conclusions: Our studies show that induction TGFβ1 signaling in tubular epithelial cells triggers recruitment of inflammatory cells which mediate mitochondrial stress and cell death.

Funding: Other NIH Support - NIH grant R01DK097253

PO0425
Kidney-Draining Lymph Node Fibrosis Following Unilateral Ureteral Obstruction
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Background: Although the primary organ has been the subject of intense investigation in the field of organ fibrosis over the past several decades, the presence of lymph node fibrosis due to persistent activation of the immune response in its partner organ remains largely unknown. Previously, we demonstrated that activation of the immune response following ischemia-reperfusion injury and crescentic glomerulonephritis in the kidney was associated with extracellular matrix (ECM) production by fibroblastic reticular cells (FRCs) of the kidney-draining lymph node (KLN). Here, we sought to determine whether FRCs in the KLN become similarly fibrogenic following unilateral ureteral obstruction (UUO) of the kidney.

Methods: We subjected 6–8-week-old C57BL/6J mice to UUO for 2, 7, and 14 days. We examined the microarchitecture of the kidney and KLN by immunofluorescence staining at each timepoint, and we quantified immune cell populations in the KLN by staining at each timepoint, and we quantified immune cell populations in the KLN by flow cytometry. The contralateral kidney unaffected by UUO and its partner KLN were studied as controls.

Results: We found through immunofluorescence staining that FRCs increased peroxidation (PIR*TxT =0.02) and ER stress (PIR*TxT =0.05), prevented IR-induced tubular cell death (P IR*TxT=0.04), and improved renal function (P IR*TxT=0.001; BUN: PIR*TxT =0.0067; BUN: PIR*TxT =0.001; P sex* IR=0.2). At 7 days post-IR, Pcr and BUN remained elevated in male SHR but returned to baseline in female SHR (P sex* IR=0.04; BUN: P sex* IR=0.001) in male and female SHR compared to respective sham controls at 24 hrs (Psex*IR=0.0001; Psex*IR=0.002). At 7 days post-IR, Pcr and BUN remained elevated in male SHR but returned to baseline in female SHR (P sex* IR=0.001; P sex* IR=0.001) in male and female SHR. Delayed recovery of renal function in male SHR was associated with activation of 12/15-LOX (P<0.05; P<0.005) and ER stress (P<0.005; P<0.001) in male and female SHR compared to sham-boards. Pre-treatment of male SHR with ML355 reduced IR-induced lipid peroxidation (P=0.02) and ER stress (P=0.05), prevented IR-induced tubular damage (P<0.02) and tubular cell death (P<0.04), and improved renal function (P<0.002) compared to vehicle-treated IR male rats 7 days post-IR.

Conclusions: In conclusion, our data demonstrate that enhanced activation of 12/15-LOX contributes to impaired renal recovery post-IR via ER stress and cell death in male SHR.

Funding: Other NIH Support - AHA and NHLBI, Private Foundation Support

PO0428
The Immunomodulatory Effect of LMW5F5A on Infiltrating Immune Cells Supports Its Clinical Use for AKI
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Background: Infiltrating immune cells are critical to acute kidney injury (AKI) pathogenesis. They are activated to clear cellular debris, secrete pro-inflammatory mediators and drive leukocyte infiltration. We sought to identify factors that mediate anti-inflammatory mediators that promote tissue repair. However, dysregulated, continuous, or excessive immune activation can result in further tissue damage. The <5KD low molecular weight fraction of human serum albumin (LMW5F5A) has anti-inflammatory/ pro-regenerative effects. This study sought to evaluate the ability of LMW5F5A to treat AKI by examining its effects on immune cells relevant to AKI.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: Peripheral blood mononuclear cells (PBMC) were treated with vehicle control, LMWF5A and activated with lipopolysaccharide (LPS). LPS + interferon (IFN) γ, or interleukin (IL)-14 + IL-13. Media and total RNA were collected at 24h. Secreted molecules were analyzed using multiplex cytokine arrays or prostaglandin E2 (PGE2) ELISA, and differential gene expression was determined by mRNAseq. Data were then subjected to in silico interrogation of known AKI signaling pathways and comparison to public datasets featuring human AKI samples.

Results: Cytokine release by PBMC was significantly modulated by LMWF5A treatment. While cytokine profiles differed depending on stimulant, the most highly downregulated cytokines included C-X-C chemokine ligand 10, IFNγ, IL-10, IL-12, IL-17, monocyte chemotactrant protein (MCP)-1, and MCP-3 (n=5; p<0.05), which have been implicated in AKI. In addition, the release of PGE2, which has been shown to be beneficial to kidney injury, was potentiated with LMWF5A treatment. In silico secretome and transcriptome analysis of LMWF5A-treated PBMC displayed predicted inhibition of pathways known to drive AKI, notably IFN and IL-17 signaling. Further, comparison to public human AKI biopsy data revealed that pathways activated by AKI were predicted to be significantly inhibited in LMWF5A-treated PBMC.

Conclusions: These data reflect the ability of LMWF5A to reduce inflammatory cytokines and shift the immune response towards resolution. Moreover, global regulation of pathways activated by AKI in kidney tissue are predicted to be inhibited by LMWF5A. This preliminary study suggests a potential role for LMWF5A as an effective AKI therapeutic.

Funding: Commercial Support - Ampio Pharmaceuticals

PO0429
Mutation of Regulatory Phosphorylation Sites in PFKFB2 Does Not Affect Metformin’s Protective Effects Against Renal Fibrosis
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Background: Metformin has been shown to have protective effects in mouse models of renal fibrosis via its effects on fatty acid oxidation but the contribution of glycolysis to this effect is unclear. 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase (PFKFB) is a key regulator of glycolysis in the kidney and is not believed to have an effect on fatty acid oxidation. We aimed to determine if modification of glycolysis has a critical role in metformin’s protective effects against renal fibrosis.

Methods: Mice with inactivating mutations of the phosphorylation sites in PFKFB2 (PFKFB2 KI mice) were generated, which is predicted to reduce the ability to increase the rate of glycolysis following stimulation. These were compared with wild-type controls. Mice were administered metformin via drinking water and a unilateral ureteric obstruction (UUO) model was used. The degree of fibrosis was assessed by Western blot and RT-PCR.

Results: In the PFKFB2 KI mice treated with metformin, there was decreased fibrosis following UUO as assessed by Western blot for fibronectin (p<0.05) and RT-PCR for alpha-SMA, collagen-3 and F4. There was no significant difference between WT and PFKFB2 KI mice treated with metformin in regards to the degree of fibrosis following UUO in any of the Western blot or RT-PCR parameters that were measured.

Conclusions: These data show that inhibition of the regulation of glycolysis by PFKFB2 does not prevent metformin from having protective effects against renal fibrosis in a UUO model.

Funding: Government Support - Non-U.S.

PO0430
Scaffold Protein Na+/H+ Exchanger Regulatory Factor 1 (NHERF1) Protects Tenofovir-Induced Nephrotoxicity by Regulating Na+/Pi Cotransporter (Npt) and Intracellular Phosphorus Balance
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Background: Tenofovir disoproxil fumarate (TDF) could cause proximal tubular (PT) dysfunctions and eGFR decline with mitochondria damages. PDZK1, MAP17, and NHERF1 are scaffold proteins that influence the localization and function of membrane proteins. We tried to investigate the changes of both membrane-associated proteins and proximal tubular transporters in TDF-induced nephrotoxic model.

Methods: C57/B6 mice (n = 8) were gavaged daily with 10mg/kg/d, 50mg/kg/d of TDF for 8 weeks. The human renal tubular epithelial cells (HK-2) were grown and received 24 to 72 h exposure to 0–128 μM TDF or vehicle. NHERF1 was overexpressed in HK-2.

Results: Chronic TDF administration to mice resulted in swollen and exfoliated tubular epithelial cells, brush border cilia lodging and dissolving, and serum creatinine elevation (p<0.05, mean 10.23±2.68 μmol/L vs. 27.18±18.41 μmol/L) compared to the control group. The protein expressions of scaffold protein NHERF1, Na–Pi co-transporter (Npt), and sodium-glucose cotransporter type 2 (SGLT-2), but not PDZK1 and MAP17 were decreased in the kidneys of TDF-treated mice and cells. The intracellular phosphorus concentrations decreased dose-dependent with TDF concentration and the exposing time, compared with down-regulated Npt expressions. ATP levels reflected mitochondrial functions were also decreased with a time and dose-dependent exposure of TDF. NHERF1 overexpressing cells are well resistant to transporter damage and mitochondrial damage caused by TDF.

Conclusions: NHERF1 protects the TDF-induced AKI by Npt, intracellular phosphorus, and mitochondria dysfunction pathway.

Funding: Ahrend-1,2 Vanderbilt University Medical Center, Nashville, TN

PO0431
Renal Papillary Function and Repair After Reversible Ureteral Obstruction
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Background: Models of reversible UUO (R-UUO) have provided insight into the mechanisms of repair in the renal cortex, but little is known about the mechanisms or extent of renal papillary repair after reversal of obstruction. Here we characterize long-term functional and structural papillary repair in a new mouse model of R-UUO.

Methods: Vascular clamps are placed on the L ureter, removed on day 7, and a R nephrectomy (Nx) performed on day 17. We evaluated serial BUN; transdermal GFR (iGFR); urinary osmolality (OSM) after water restriction; histology and fibrosis; tubules, paracellular gaps, and capillaries; and mRNAs for markers of repair, and lineage analysis with Six2-CRE+; R26R-Td Tomato reporter mice to assess repair of nephronic epithelium.

Results: At clamp removal (day 0) all mice had hydropnephrosis. 60-80% survived 48hrs after Nx, and day 14 BUN in Nx vs. R-UUO+Nx was 18.5 (0.9) vs. 42.6 (8.5) mg/dl, p<0.001, indicating reversal and consistent injury. iGFR was reduced at day 28 (991.0 (46.6) vs. 569.8 (82.6) ml/min/100gm, p<0.001), reversed by day 84, with decreased urinary OSM up to day 84 (3525 (106.9) vs. 1718 (175.7) mOsm/L, p<0.0001). There was cortical fibrosis from 0-84 days. Fibrosis increased day 0-28 in the papilla but was absent by day 84. There was papillary necrosis days 0-3; repopulation of tubular structures starting day 7 with disorganized tubulointerstitial repair by day 28 but normal histology by day 84. There was loss of AQP1 (descending thin limb, DTL) and AQP2 but not LTL staining (total collecting duct, CD) days 3-28. AQP1 and 2 were restored by day 84, but there was a reduction in capillary density by CD31 staining days 14-84. Lineage analysis showed persistent Six2 lineage in the papilla at day 28, indicating effective repair of nephronic epithelium.

Results: At clamp removal (day 0) all mice had hydropnephrosis. 60-80% survived 48hrs after Nx, and day 14 BUN in Nx vs. R-UUO+Nx was 18.5 (0.9) vs. 42.6 (8.5) mg/dl, p<0.001, indicating reversal and consistent injury. iGFR was reduced at day 28 (991.0 (46.6) vs. 569.8 (82.6) ml/min/100gm, p<0.001), reversed by day 84, with decreased urinary OSM up to day 84 (3525 (106.9) vs. 1718 (175.7) mOsm/L, p<0.0001). There was cortical fibrosis from 0-84 days. Fibrosis increased day 0-28 in the papilla but was absent by day 84. There was papillary necrosis days 0-3; repopulation of tubular structures starting day 7 with disorganized tubulointerstitial repair by day 28 but normal histology by day 84. There was loss of AQP1 (descending thin limb, DTL) and AQP2 but not LTL staining (total collecting duct, CD) days 3-28. AQP1 and 2 were restored by day 84, but there was a reduction in capillary density by CD31 staining days 14-84. Lineage analysis showed persistent Six2 lineage in the papilla at day 28, indicating effective repair of AQP1+ DTL. There was a marked increase in Ki67+Six2 lineage and LTL+ CD cells days 3-7 after reversal, but no expression of the de-differentiation marker, Sox8, in the papilla.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.

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Conclusions: There is robust, Socs9-independent repair of tubules in the papilla that is inhibited by albumin but ultimately restores tubular organization after R-UU. Despite this, a persistent defect in urinary concentrating capacity associated with decreased papillary capillary density, suggests that despite robust tubular repair, disorganized vascular integrity results in long-term papillary dysfunction after R-UU.

Funding: NIDDK Support, Other NIH Support - DOD

PO0432

The Susceptibility Mechanism of AKI in Cirrhosis Through Regulation of rs4746720 Polymorphism

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Background: Previous study has confirmed that SIRT1/PGC-1α signaling pathway might be involved in the pathogenesis of acute kidney injury (AKI) in cirrhosis. This study aimed to analyze the association between SIRT1 single nucleotide polymorphism (SNP) and the risk of AKI in cirrhosis in a Chinese Han population, and to further explore the molecular mechanism of SIRT1 SNP in vitro.

Methods: A total of 29 patients in AKI group and 87 patients in control group were selected from a Chinese Han population. Genotypes of SIRT1 rs4746720 and rs2275773 were detected by SnaPshot technology. Bioinformatics softwares predicted that miR-599 might bind to the rs4746720 loci within SIRT1 3′UTR. The dual luciferase reporter vectors pmir-GLO-SIRT1-3′UTR-T/C were constructed and respectively co-transfected with miR-599 mimic or NC into HK-2 cells, and the overexpression recombinant plasmids pcDNA3.1-SIRT1-T/C were further constructed and respectively co-transfected with miR-599 mimic, miR-599 inhibitor or NC into HK-2 cells, and the expression of miR-599 and SIRT1 and SIRT1/PGC-1α were respectively measured by qRT-PCR and Western blot.

Results: There was no significant association between SIRT1 SNP and the risk of AKI in cirrhosis (P>0.05). But stratified analysis based on risk factors showed that in the subgroup of hepatic encephalopathy, SIRT1 rs4746720 polymorphism was significantly associated with the risk of AKI in cirrhosis (OR=6.00, 95%CI: 1.22-29.48, P=0.027). Analysis of liver and kidney function showed that Scr and BUN of TT genotype of rs4746720 was significantly higher than that of CC+CT genotype in the AKI group, and eGFR was significantly lower than that of CC+CT genotype (P<0.05). Dual luciferase reporter vectors showed that rs4746720 T allele of SIRT1 could increase the binding of miR-599, which resulted in significantly reduced luciferase activity (P<0.001). Overexpression recombinant plasmids showed that rs4746720 T allele of SIRT1 could mediate the binding of miR-599, which resulted in significantly reduced expression of SIRT1 and its downstream pathway (P<0.05).

Conclusions: The rs4746720 polymorphism in SIRT1 3′ UTR may be associated with the risk of AKI in patients with cirrhosis. The rs4746720 T allele of SIRT1 may mediate the binding of miR-599, affect the expression of SIRT1 and its downstream pathway.

Funding: NIDDK Support

PO0433

RAP Inhibits Proximal Tubule Endocytosis and Protects Against Gentamicin-Induced Nephrotoxicity

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Background: The proximal tubule (PT) reabsorbs and concentrates filtered nutrients by clathrin mediated (CME) and fluid phase mediated (FPE) endocytosis, leading to PT injury and AKI. The molecular chaperone RAP (Alpha-2-macroglobulin receptor-associated protein) a 39kd protein inhibits LDL receptor family members like megalin, binding including, megalin. Our hypothesis was that RAP would inhibit megalin endocytosis, but not FPE, and reduce gentamicin nephrotoxicity.

Methods: We utilized daily injections of gentamicin (100mg/Kg) in a uninephrectomy CKD model in Munich Wistar Fromter rats with a baseline serum creatinine (sCr) of 0.80 ± 0.23. Gentamicin was given with or without RAP (40mg/Kg, IP) daily injections of gentamicin (100mg/Kg, IP) in a uninephrectomy CKD model in Munich Wistar Fromter rats with a baseline serum creatinine (sCr) of 0.80 ± 0.23. Gentamicin was given with or without RAP (40mg/Kg, IP) to evaluate RAP’s impact on function, sCr, 24 hr urinary creatinine clearance and proteinuria, and endocytosis, 2-photon microscopy to determine FPE i.e. 10 KDa Cascade Blue dextran, and Megalin mediated CRE, i.e. albumin, endocytosis.

Results: RAP injections markedly reduced PT cell albumin uptake over 80% (80%), dextran (67%) and gentamicin (62%) in normal rats in a rapid and fully reversible fashion. In rats treated with or without RAP, daily gentamicin treatment resulted in elevated serum Cr by day 5 (1.4 ± 0.2 vs 3.1 ± 0.4mg/dl, p<0.001) and day 6 (1.5 ± 0.5 vs 5.4 ± 0.8mg/dl, p=0.01). CCl decreased on day 6 to 0.49 ± 0.16 ml/min vs 0.09 ± 0.07 ml/min and urine protein increased to 488 mg/ml/100 gm wt vs 2,512 mg/ml/100 gm wt in RAP treated and untreated rats, respectively.

Conclusions: These results indicate RAP treatment induced reductions of both CME and FPE PT endocytosis suggesting a link between megalin and FPE. Clinically, RAP inhibits proximal tubule endocytosis and protects against gentamicin-induced nephrotoxicity. Other NIH Support - DK 091623 and 079312

PO0434

Role of Protease-Activated Receptor 1 (PAR1) in Glomerular Filtration Barrier Integrity

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Background: Protease-activated receptors (PARs) play a significant role in the regulation of angiogenesis and fibrosis. Their role in the regulation of glomerular filtration barrier (GBF) function is incompletely elucidated. We had demonstrated that PAR1 inhibition with SCH79779 results in glomerular hemorrhage and acute kidney injury in the 5/6 nephrectomy rats (5/6NE), effects similar to those of a direct thrombin inhibitor (dabigatran) and mimic features of anticoagulant-related nephropathy in humans. The aim of the current study was to investigate potential synergistic effects of dabigatran with PAR1 inhibition or agonism in 5/6NE.

Methods: Three weeks after surgery 5/6NE rats were treated with dabigatran (150 mg/kg/day) alone or with PAR1 inhibitor SCH79779 (1.0 mg/kg/day and 3.0 mg/kg/day) or PAR1 activation peptide, TFFLR-NH2 10.25 mcml/kg/day and 0.5 mcml/kg/day. Serum creatinine (SCr), activated partial thromboplastin time (aPTT), and hematocrit were measured daily; kidney morphology was evaluated at the end of the study.

Results: As expected, treatment with PAR1 modulators did not alter the anticoagulant effects of dabigatran and did not prolong aPTT when used alone. Both SCH79779 and TFFLR-NH2 aggravated increased SCr levels induced by dabigatran in a dose-dependent manner in the 5/6NE. Interestingly, both PAR1 activation peptide and PAR1 inhibition significantly lowered SCr in the 5/6NE when used alone (P<0.05). Neither SCH79779 nor TFFLR-NH2 significantly affected dabigatran-induced hematuria in 5/6NE. Morphologically, 5/6NE treated with dabigatran, SCH79779 and TFFLR-NH2 alone or in combination, had red blood cell casts in the tubules and acute tubular epithelial cell injury.

Conclusions: PAR1 homotypic aggregation is necessary to maintain GBF integrity in 5/6NE. Pharmacological activation or inhibition of PAR1 results in glomerular hematuria and acute kidney injury in 5/6NE. These effects are similar to those of dabigatran-mediated thrombin inhibition in 5/6NE, suggesting that the thrombin-PAR1 signaling axis is important to GBF function.

Funding: NIDDK Support

PO0435

Renal GPNMB Is Highly Upregulated in Rodent Models of AKI and Is Further Elevated with Pharmacological AMPK Activation


Background: Glycoprotein nonmetastatic melanoma B (GPNMB) is highly expressed in macrophages. GPNMB is an AMP-activated protein kinase (AMPK) up-regulated gene in whole blood. GPNMB deficient mice fail to undergo repair and injury resolution following kidney ischemia reperfusion injury (IRI). Here we investigated GPNMB expression in the rat IRI and mouse cisplatin AKI models with or without an AMPK activator treatment. We also characterized GPNMB expression in human proximal epithelial cells, M1 and M2 macrophages.

Methods: RPECT and HK2 cells were exposed to hypoxia for 24 h. GMCSF- or MCF5-primed human M1 or M2 macrophages were isolated from human LeukoPaks. Male SD rats were subjected to 40 min of bilateral renal ischemia. Kidneys were harvested 2 days after IRI. Male C57B mice were administered with a single injection of cisplatin. Kidneys were harvested 72 h after cisplatin injection.

Results: In human proximal epithelial HK2 and RPECT cells, an AMPK activator treatment resulted in a dose-dependent increase of GPNMB mRNA. Significant increase of GPNMB mRNA was observed in HK2 and RPECT cells cultured in hypoxic versus normoxic conditions. We also demonstrated that AMPK activation increased IFNγ and LPS-induced GPNMB secretion in human M2 but not M1 macrophages. After a single oral administration of an AMPK activator in normal mice or rats, a robust induction of GPNMB mRNA in the whole blood was seen starting 3 h and lasting up to 22 h. We found that GPNMB mRNA was expressed at low levels in the kidneys of normal mice or rats. GPNMB mRNA was markedly up-regulated following IRI in the kidneys at 48 h.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.

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In a mouse cisplatin-induced AKI model, a dramatic increase of GPMB mRNA was observed in the kidneys. Pharmacological activation of AMPK in both AKI models resulted in further increase of renal GPMB.

**Conclusion:** GPMB mRNA is highly up-regulated in the kidneys of rat IRI and mouse cisplatin AKI models and is further elevated after an AMPK activator treatment. GPMB is a marker for AMPK activation in tubular epithelial cells, M2 macrophages, and whole blood. Our results support that GPMB could modulate macrophages polarization which may be involved in inflammation and immune response, contributing to injury and repair post AKI.

**Funding:** Commercial Support - Janssen Pharmaceutical Research & Development of Johnson & Johnson

**PO0436**

**Loss of Stimulator of Interferon Genes (STING) Pathway Does Not Protect the Kidney Against Acute Injury or Inflammatory and Fibrotic Pathways Induced by Folic Acid**


**Background:** Acute kidney injury (AKI) greatly increases the risk for developing chronic kidney disease (CKD), but it is currently not well understood how this progression from injury to inflammation and fibrosis takes place. Recently it was discovered that with injury, damaged mitochondria in the kidney can leak mitochondrial DNA into the cytosol, where it activates the cyclic GMP-AMP synthase (cGAS) stimulator of interferon genes (STING) pathway causing inflammation and fibrosis. To explore the significance of this pathway in the setting of AKI and CKD transition we induced folic acid nephropathy in mice with no detectable STING activity and evaluated them for kidney function and inflammation/fibrosis comparison 7 days after administration.

**Methods:** 23-month Goldenticket (GT) mice (no detectable STING protein due to a missense mutation) and age matched wild type (WT) littermate controls were injected with 250 mg/kg of folic acid. Seven days later plasma, urine, and kidneys were collected for analysis of plasma biochemistry, blood urea nitrogen (BUN) and arterial blood creatine ratio (UCR). 8 mice were used for both WT and GT group animals and 11 mice were used for WT and GT groups treated with folic acid.

**Results:** In WT control mice folic acid treatment significantly elevated plasma creatinine (0.47±0.06 to 0.62±0.33mg/dl, BUN levels from 25±1.3 to 66.8±2.1mg/dl, and UACR more than doubled from 21±13.4 to 53.5±64.3mg/ng. This effect was not statistically different from what was observed in GT mice (plasma creatinine increasing from 0.25±0.04 to 0.55±0.20mg/dl, BUN increasing from 20.9±1.9 to 54.7±2.1mg/dl, and UACR increasing from 15.9±3.8 to 140.2±313.5mg/ng with folic acid, respectively). Kidney gene expression for genes involved in fibrosis (Tgf-β, Col1a1), inflammation (Tnfa, Il6, Il1b), and apoptosis (Bax, Tnfr3) were all elevated with folic acid treatment. Only Il6 which is a direct effector gene of STING, was significantly decreased in the folic acid treated GT mice as compared to the folic acid treated WT controls.

**Conclusions:** Ablation of STING did not protect kidney function, nor did it impact fibrotic or inflammatory gene expression. Our data suggest that the cGAS/STING pathway is not involved in the development of AKI and in the transition to CKD in the folic acid nephropathy model.

**Funding:** Commercial Support - Janssen Research & Development LLC

**PO0437**

**Extracellular Matrix Protein 1 Organized Microenvironment Keys to Kidney Repair After AKI**

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**Background:** In AKI, the kidney tubule is well-known as the epicenter of damages, yet little attention has been paid to changes in the microenvironment and associated repair processes. Amid this process, the extracellular matrix (ECM) is the principal organizing component for microenvironment construction and tubule repair, serving as a scaffold for remodeling. How ECM interacts with its surrounding materials to dictate the prognosis of AKI remains unclear in the field.

**Methods:** Kidney ischemia-reperfusion injury was employed to induce AKI in mice. In vivo, vitro, and ex vivo translational experiments and quantitative proteomic analyses were performed.

**Results:** Quantitative proteomics revealed that extracellular matrix protein 1 (ECM-1) was the earliest activated matrix protein in ischemic AKI kidneys. Immunostaining revealed that ECM-1 was predominantly expressed in the activated kidney fibroblasts. In cultured fibroblasts, knockdown ECM-1 markedly reduced cell migration and proliferation, as assessed by the decreased expression of α-SMA, vimentin, PDGFR-β, and PCNA. Ex vivo, knockdown ECM-1 in the decellularized AKI kidney scaffold directly reduced its capacities in promoting the proliferation of the seeded tubular cells. In vivo, loss of ECM-1 caused elevated serum creatinine levels, more severe morphologic changes, and reduced inductions of α-SMA, vimentin, and PDGFR-β than the controls after AKI. By using affinity-purification mass spectrometry, we identified a vital mechanism that ECM-1 could bind to an essential tubule-derived growth factor protecting against AKI, namely hedgehog (Shh). In conclusion, we confirmed that recombination ECM-1 promoted tubular cell proliferation and Shh expression.

**Conclusions:** Our finding implied that ECM1 created a favorable microenvironment by interacting with Shh to promote AKI recovery.

**Funding:** NIDDK Support

**PO0438**

**TNF Drives AKI-to-CKD Transition Downstream of Proximal Tubule EGFR**

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**Background:** Inflammation is a key driver of fibrosis and progression of human chronic kidney disease (CKD), often caused or worsened by acute kidney injury (AKI-to-CKD transition). Sustained epithelial-growth-factor-receptor (EGFR) activation in injured proximal-tubule-cells (PTC) is strongly pro-inflammatory and has emerged as a key paradigm in AKI-to-CKD transition and CKD progression. Whether the key Type 1 inflammatory cytokine tumor-necrosis-factor (TNF) has a role in PDK progression and how TNF relates to the PTC transition is unknown.

**Methods:** We compared mice treated with control, TNF-inhibition (etanercept, TNF-scavenger), EGFR-inhibition (erlotinib, EGFR-kinase-inhibitor) or their combination in an AKI-to-CKD bilateral renal-ischemia-reperfusion model.

**Results:** WT, TNF- or EGFR-inhibition did not affect initial kidney injury, but significantly ameliorated in reducing kidney injury-upregulated cytokines and equally strongly reduced kidney fibrosis, while combination treatment had no additive effect, suggesting EGFR and TNF act in the same fibrosis pathway. TNF exerted its profibrotic effects downstream of PTC-EGFR, as TNF-inhibition did not affect tubular EGFR activation in vivo. Consistent with this, TNF-PTC-KO did not reduce inflammation or fibrosis, suggesting that PTC-derived TNF does not contribute to profibrotic PTC-EGFR activation. Kidney single-cell-previous analysis identified macrophages, dendritic cells and T cells, but not PTC, as dominant TNF sources after AKI. Only EGFR-inhibition, but not TNF-inhibition significantly blocked injury-induced kidney ingress of macrophages, however, macrophage numbers where equal one month after AKI independent of treatment. Thus EGFR-inhibition reduces ingress and accumulation of TNF-producing proinflammatory and proinflammatory immune cells whereas TNF-inhibition mechanistically largely acts by neutralizing their proinflammatory and profibrotic activities.

**Conclusions:** Our work provides mechanistic background to motivate examination of TNF pathway inhibition in human AKI or CKD.

**Funding:** NIDDK Support, Private Foundation Support

**PO0439**

**Antioxidant Prevents Detrimental Heart-Kidney Cross-Talk in a Novel Experimental Model of Cardiorenal Syndrome Due to Isolated Right Heart Failure**

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**Background:** Since recognition of CRS, most studies have investigated left heart failure models due to isolated RVF is under recognized. However, renal dysfunction is an independent predicator of death and hospitalization in RVF. To examine experimental models of CRS improve our understanding of the pathophysiology of RV-Kidney interaction and enable us to explore new therapeutic modalities.

**Methods:** In a alkaloid (ALK) injection induced CRS in rats we investigated whether antioxidant prevents detrimental interactions of RV-Kidney in CRS. Rats were treated with an antioxidant, 1 wk pre & post-ALK injection. At 3 and 4 wks post-ALK injection, serial echocardiography was performed to monitor cardiac function. RV systolic pressure (RVSVP), RV hypertrophy (Rvh), RV function, RV levels of superoxide dismutase (SOD), catalase, glutathione peroxidase (GSHPx) and lipid peroxidation (LPX) were measured. After sacrificing animals, hearts and kidneys were removed for histopathology.

**Results:** At 4 weeks, ALK-induced CRS resulted in increased mortality, RVSVP, Rvh, and LPX in RV myocardium accompanying RVF as well as the kidney. Antioxidant enzymes activities including SOD and GSHPx were decreased in RV and the kidney. Kidney histopathology with Periodic acid-Schiff (PAS) staining demonstrated tubular epithelial denudation, a marker of ATN that was not seen at 3 weeks post-ALK injection. This excludes renal toxicity of the alkaloid. Antioxidant treatment prevents not only ALK-induced CRS and decreased oxidative stress but also increased the SOD and GSHPx levels in the RV myocardium and the kidney.

**Conclusions:** A reduction in oxidative stress by antioxidant may explain the prevention of ALK-induced CRS. Thus, targeting oxidative stress may lead to the development of novel therapies for CRS and antioxidants as an adjuvant therapy may be beneficial.

**PO0440**

**Inability to Increase Fatty Acid Oxidation Worsens AKI and Impacts the Benefit of Metformin**

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**Background:** Energy metabolism is critical to the pathogenesis of ischemic acute kidney injury (AKI) - its role in nephrotoxic AKI is less understood. Fatty acid oxidation (FAO), the kidney’s most important energy source, is regulated by acetyl-CoA carboxylase (ACC). Metformin increases Kashem’s ACC to enhance phospho-ACC induced ACC phosphorylation of ACC. We aimed to determine whether regulation of FAO affects the outcome of nephrotoxic AKI.

**Methods:** Cisplatin AKI was induced in ACC knockin (KI) mice, which have mutations of ACC-phospho sites that disrupt FAO regulation, and compared to wild-type (WT) controls. A primary tubular epithelial cell (TEC) culture model of cisplatin toxicity was used to further study the findings.

**Results:**
Results: ACC KI mice demonstrated more severe cisplatin-AKI versus WT as assessed by day 2 serum urea (ACC KI 40.5±11.6 mg/dL vs WT 27.2±7.6 mg/dL, p <0.005) and creatinine (ACC KI 0.09±0.03 mg/dL vs WT 0.06±0.03 mg/dL, p <0.05). Western blot for neutrophil gelatinase associated lipocalin (NGAL) was increased 9.3±2.1 fold in ACC KI compared to 3.3±3.4 fold in WT (p<0.0001 for ACC KI vs WT). WT and ACC KI TEC cultures exposed to cisplatin revealed increased apoptosis in ACC KI, as assessed by increased cleaved caspase-3 (cCasp3) (p<0.0001). In TECs, metformin was protective against cisplatin mediated apoptosis, however this was diminished in ACC KI cells (cCasp3 reduced 49.5%) versus WT cells (cCasp3 reduced 72%) (p<0.03 for ACC KI vs WT).

Conclusions: Severity of nephrotoxic AKI is dependent on maintenance regulation of FAO. Metformin reduces cisplatin-AKI severity by its ability to increase FAO.

Funding: Government Support - Non-U.S.

PO0442
The MLL1/WDR5 Complex Contributes to Cisplatin-Induced Renal Epithelial Death by Promoting p53-mediated E-Cadherin Repression
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Background: The mixed-lineage leukemia 1 (MLL1)/WD-40 repeat protein 5 (WDR5) complex is a methyltransferase deemed a positive regulator of histone H3 lysine 4 trimethylation (H3K4me3) and functions as an oncogenic factor in many cancer types. The role of the MLL1/WDR5 complex in acute kidney injury (AKI) and renal epithelial cell death is still unclear. In this study, we investigated the role and mechanism of this complex in the apoptosis of renal epithelial cells following cisplatin exposure.

Methods: Cultured mouse kidney proximal tubular (TKP) cells were exposed to cisplatin in the presence or absence of MM102, a MLL1/WDR5 protein–protein interaction inhibitor or small interfering RNAs (siRNA) specific targeting MLL1 or WDR5.

Results: Expression of MLL1, WDR5 and H3K4me3 as well as phospho-p53 and cleaved caspase 3 were increased whereas that of E-cadherin was decreased in cultured TKP cells exposed to cisplatin in a time dependent manner. Inhibition of the MLL1/WDR5 complex with MM102 or siRNA-mediated silencing MLL1 or WDR5 attenuated cisplatin induced cleavage of caspase 3 and cell death, which was coincident with downregulation of p-p53 and preservation of E-cadherin expression. Inhibition of p53 by pifithrin-α also alleviated cisplatin-induced cell death and restored E-cadherin expression in TKP cells with or without MM102 treatment. In contrast, activation of p53 by Nutlin promoted TKP cell death and E-cadherin repression. Moreover, siRNA mediated silencing of E-cadherin attenuated the protective effect of MM102 following cisplatin treatment while expression of p-p53 was not affected. Finally, we found that pharmacological inhibition of MLL1/WDR5 reduced cisplatin-induced phosphorylation of ataxia-telangiectasia mutated protein, ataxia telangiectasia and Rad3-related protein, checkpoint kinase 1 (Chk1), checkpoint kinase 2 (Chk2) and γ-H2AX, which are activated in response to DNA damage and associated with p53 transcriptional activation.

Conclusions: These data suggest that the MLL1/WDR5 complex may contribute to cisplatin-induced apoptosis of renal tubular epithelial cells by promoting p53-mediated E-cadherin repression following DNA damage. Targeting the MLL1/WDR5 complex may have a therapeutic potential for the treatment of cisplatin-induced AKI.

Funding: NIDDK Support

PO0443
Comparison of Inflammatory Responses in Sepsis-Induced AKI Mouse Models and Response to Dexamethasone
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Background: AKI occurs in the majority of patients with severe sepsis and contributes to high morbidity and mortality. Despite the frequency of AKI, the underlying reasons for the injury are not fully understood, and effective therapies to prevent or reverse this condition. Systemic and local inflammatory responses play a large role in the development of sepsis induced acute kidney injury (S-AKI).

Methods: To develop novel treatments for patients with S-AKI, animal models of polymicrobial sepsis are used, the most widely reported models being cecal ligation puncture (CLP) and cecal slurry (CS). We compared the acute (24h) renal function and inflammatory response of these two models, as well as the ability of dexamethasone (dexa) to prevent the development of S-AKI.

Results: CLP significantly reduced renal function, with increased plasma creatinine (0.18±0.11 mg/dL), blood urea nitrogen (BUN, 81.1±12.8 mg/dL), and increased inflammatory markers IL-6 (127±33 ng/mL), TNF-α (176±33 pg/mL), and IL-1β (164±141 pg/mL) compared to sham animals. Dexa (8 mg/kg) significantly decreased BUN but did not significantly decrease plasma creatinine or the inflammatory markers. Dexa (2.5 mg/kg) had no significant effects on renal functional markers or circulating cytokines. CS significantly increased plasma creatinine (0.7±0.1 mg/dL), BUN (103±20 mg/dL), cystatin C (244±94 ng/mL), IL-6 (124±63 ng/mL), TNF-α (134±39 ng/mL) compared to basal levels. Dexa treatment (2.5 mg/kg) significantly decreased creatinine, cystatin C, IL-6, TNF-α, and IL-1β. In this study, we have shown the CS model elicits a more robust increase in AKI and inflammatory measurements than the CLP model, with reduced variability. It also responds to a greater extent to the same dose of dexa. Our results suggest that the CS model may be a provide a better window with less variability compared to the CLP model, to test novel treatments for S-AKI.

Conclusions: We have shown the CS model elicits a more robust increase in AKI and inflammatory measurements than the CLP model, with reduced variability. It also responds to a greater extent to the same dose of dexa. Our results suggest that the CS model may be a provide a better window with less variability compared to the CLP model, to test novel treatments for S-AKI.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Prohibitin Ligand FL3 Protects Renal Proximal Tubular Cells Against ATP-Depletion-Induced Injury
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Background: FL3 is a synthesized ligand of prohibitins, a family of proteins located on and important for mitochondrial inner membrane. FL3 has been reported to protect neonatal cardiomyocytes by regulating mitochondrial function. Whether FL3 can protect kidney cells against cell stress remains unknown. This study aims to evaluate the effect of FL3 on ATP-depletion-induced cell death in renal proximal tubular cells (RPTC).

Methods: RPTCs were pre-treated with 50µM FL3 for 3 hours and incubated with 10mM azide in glucose-free Krebs-Ringer bicarbonate solution for 3 hours to induce ATP depletion. The cells were then returned to a normal cultured medium for recovery. Cells were also exposed to the same concentration of FL3 throughout the ATP depletion and recovery phases to monitor changes including mitochondrial fragmentation, Basolateral translocation, cytochrome C release, prohibitin complex breakdown, OPA1 and OMA1 protein expression were examined immediately after azide treatment; whereas apoptosis events including apoptosis and caspase activation were examined after 2 hours of recovery.

Results: RPTCs with azide-induced ATP depletion developed apoptotic morphology, caspase 3 activation and PARP cleavage, which were suppressed by FL3. Mitochondrial fragmentation and membrane leakage of cytochrome C were increased in RPTCs during ATP depletion. FL3 suppressed mitochondrial fragmentation and inhibited mitochondrial injury. Under cell stress, the large prohibitin ring complex was disrupted to medium and small complexes, releasing OMA1 to the cleaver inner membrane fusion protein OPA1. FL3 treatment decreased both the small prohibitin complex and the activation of OMA1. FL3 also partially prevented the degradation of the long isoforms of OPA1 during ATP depletion.

Conclusions: FL3 can protect against ATP-depletion-induced injury in renal tubular cells, likely through the regulation of mitochondrial dynamics.

Funding: NIDDK Support, Veterans Affairs Support

Mechanisms of Aristolochic Acid I (AAI)-Induced Proximal Tubule Cell Injury
Rohit Upadhyay, Vecchi Batuman. Tulane University School of Medicine, New Orleans, LA.

Background: Aristolochic acids (AAs) are naturally occurring polyaromatic nitrogen compounds extracted from certain plants that were used to treat various diseases for centuries until their nephrotoxicity and carcinogenicity began to be recognized. Aristolochic acid I (AAI) is potentially one of the main pathogenic compounds and has been demonstrated to have nephrotoxic, carcinogenic, and mutagenic effects. Previous studies have indicated that AAI acts mainly on proximal renal tubular epithelial cells; however investigation into the mechanisms of AAI-induced proximal tubule cell damage is still warranted.

Methods: Human kidney proximal tubule cells (PTCs; HK2 cell line) were exposed to 10 and 20µM AAI at different time conditions in vitro. Cell proliferation, ROS generation, NO production, m-RNA/protein expressions and mitochondrial dysfunction was checked in HK2 cells after treatment with AAI. AA1 exposure increased ROS generation and inhibited mitochondrial activity was measured to reflect apoptotic cell death. TNF-α was used to induce injury. AMPK activation was confirmed by measurement of pACC. Data were analyzed using 1-way ANOVA.

Results: At 10, 30, and 100 ng/ml TNF-α significantly induced HUVEC monolayer permeability after 24 hr treatment, with 11.2-, 8.1-, and 8.1-fold increases, respectively. Direct alloseric AMPK activator (CpdA) protected against permeability induced by 24 hr of 100 ng/ml TNF-α treatment, with a maximum reduction of 57.6% permeability at 20µM CpdA (P=0.03550), down to 30.2% at 62.5%. 100 ng/ml TNF-α treatment for 24 hr increased apoptosis by 2.8-fold. CpdA treatment significantly protected cells from apoptosis in a dose dependent manner. TNF-α treatment for 6 hr increased HUVEC permeability (~ 6.4-fold), which was reduced (40.6% reduction) by CpdA treatment. Cells incubated with CpdA maintained their shape and cell-cell contacts and showed less intercellular gaps when compared to those treated with DMSO vehicle control.

Conclusions: AMPK activation alleviated endothelial leakage, potentially via decreasing apoptosis and maintaining cell-cell contacts. Our data supports AMPK activation as a novel therapeutic approach for AKI.

Funding: Commercial Support - Johnson & Johnson

Establishment and Evaluation of a Primary Human Renal Tubular 3D Spheroid Model for AKI and CKD
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Background: Acute kidney injury (AKI) is defined by a rapid decline in the kidney function, occurs in approximately 5-20% hospitalized patients and is associated with high mortality. Renal ischemia-reperfusion (IR) injury is a leading cause of AKI. Despite intensive research and progress in understanding the pathophysiological mechanisms, IR-AKI remains an critical problem without any effective treatment available. Dagapilofin is a novel antidiabetic drug from the class of sodium-glucose cotransporter 2 (SGLT2) inhibitors that reduce glucose reabsorption in renal proximal tubules. SGLT2 inhibitors have been recently suggested to cause protection even in renal injury conditions beyond diabetes, such as AKI. In our work, we aimed to test the effectivity of dagapilofin in decreasing kidney injury in a mouse model of severe IR-AKI.

Methods: We developed a mouse model of severe IR-AKI. C57BL/6j males underwent 35 minutes of renal ischemia by bilateral clamping of renal pedicles followed by 24h of reperfusion. The levels of 8-hour nitric oxide (NO) and plasma creatinine at 24h after reperfusion were high but all mice undergoing IR surgery survived. Histological analysis showed severe tubular injury in the outer stripe of outer medulla. Mice undergoing IR surgery were divided into groups and received either no treatment, 1 mg/kg dagapilofin, 10 mg/kg dagapilofin or vehicle only administered by oral gavage 24h and 1h before the onset of ischemia. BUN and other parameters of kidney function were assessed 24h after reperfusion.

Results: In our preliminary data oral administration of dagapilofin did not prevent kidney function decline in the model of severe IR-AKI. The BUN levels in plasma at 24h after reperfusion were not significantly different in groups of mice undergoing IR surgery. This is in contrast to previously published study1 where, however, less severe model of IR-AKI with 27 minutes of renal ischemia was used.

Conclusions: Dagapilofin did not improve severe IR-AKI. We hypothesize that dagapilofin may be effective in improving less severe kidney injury, however, lacks efficacy in more severe cases of AKI. In our future studies, we would like to test the ability of dagapilofin to prevent kidney injury at different stages of IR-AKI. Chang et al. PLoS ONE. 2016;11(7):e0159233.

Funding: Other U.S. Government Support

AMPK Activation Alleviates TNF-ω Induced Human Umbilical Vein Endothelial Cell Monolayer Permeability Increase

Background: The proximal tubule of the nephron is a prime site for tubular injury due to its high energy requirements and its dependence on oxidative metabolism to meet its energy needs. Our understanding of the central role of mitochondrial abnormalities and alterations in metabolism in both acute and chronic kidney injury has steadily improved with potential targets to improve mitochondrial dysfunction that occurs in AKI and in AKI to CKD transition. Two-dimensional (2D) monolayer cultures and rodent animal models are unable to fully recapitulate clinical drug response, hence 3D models are being developed to provide a physiologically relevant context for the perm, and rep, of a rep.

Methods: Here, we developed a primary human renal tubular 3D spheroid culture and established a cisplatin-injury model for therapeutic target evaluation. Human primary renal tubular cells (RPTEC) seeded in ULA plates showed aggregation after 4 hours and formed initial spheroids after 4 days and the primary cells can be cultured over 5 weeks without major physiological changes. In addition, CpdA treatment significantly protected cells from apoptosis in a dose dependent manner. TNF-α treatment for 6 hr increased HUVEC permeability (~6.4-fold), which was reduced (40.6% reduction) by CpdA treatment. Cells incubated with CpdA maintained their shape and cell-cell contacts and showed less intercellular gaps when compared to those treated with DMSO vehicle control.

Results: In 3D setting, gene expression of tubular markers was significantly induced/restored close to the human tissue level compared to 2D culture (AQP1, OAT, LRP2, PEP2, SLC12A1). This study provides a more physiologically relevant condition. As NAD+ levels increase in the mitochondrial to decrease, NADH/NAD+ ratio is determined in 3D culture and the levels of SLC7A9, SLC2A2 and SLC13A2 are increased in CpdA treatment.

Conclusions: Our 3D spheroids model offer a physiologically relevant condition that may be used to further understand the role of each drug in the improvement of mitochondrial dysfunction in tubular cells, we evaluated gene expression in de novo NAD synthesis pathway and observed increased
expression in 3D- vs. 2D culture (AFMID, KAO, KYUV, HAASO, ACHMS, NMATs, etc.). Moreover, once resistance is activated in AKI and is involved in AKI to CKD transition, we confirmed that TGF-β treatment repressed de novo NAD pathway gene expression, suggesting a possible link to the decrease of de novo NAD+ in the cells producing TGF-β. Lastly, in our cisplatin-induced tubular cell injury model in 3D spherical, cisplatin induces the dose-dependent increase of cell apoptosis associated with dose-dependent reduction of total cellular NAD+ and GSH.

Conclusions: Taken together, our 3D primary human spheroid model restored key marker gene expression and recapitulated in vivo response to the TGF-β treatment and cisplatin-induced injury, which provide a physiological and pathophysiologically relevant tool and translational model to enable the quick screening and evaluation of therapeutic targets for AKI and CKD.

PO0449
Succinylation of Metabolic Enzymes Protects Against AKI
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Background: Acute Kidney Injury (AKI) is an increasingly prevalent outcome of hospitalizations, affecting up to 50% of ICU patients in America. Kidney function depends on the metabolic activity of Renal Proximal Tubule Epithelial Cells (RPTECs). To understand AKI pathology, we focused on a class of proteins that affect posttranslational modifications of major proteins, and especially the deacylase Sir2um 5 which is highly expressed in RPTECs. Our previous studies indicate that knockout of this protein has a protective role in RPTECs post AKI which presents the exciting possibility of clinical translation in preventing or ameliorating any long-term damage from AKI.

Methods: Through independent pathway analysis and mass spectrometry we attributed the major protective effect of Sir5 knockout to be succinylation of key mitochondrial and peroxisomal proteins, leading to a metabolic shift from mitochondrial Fatty Acid Oxidation (FAO) to peroxisomal-dependent FAO. To test this hypothesis in a less invasive manner than genetic knockdown, we used the mitochondrial FAO inhibitor Etomoxir and the peroxisomal stimulant Benzilic acid. In both cases we found a significant reduction in the kidney injury marker NGAL after ischemia-like injury.

Results: We postulate that the switch to more peroxisomal-mediated fatty acid oxidation is protective. We found a decrease in the Reactive Oxygen Species. To promote this shift, we investigated the effects of supplementing the mouse diet with medium-chain fatty acids (10% dodecanedioic acid) pre or post ischemia-reperfusion-injury (IRI). Mass spectrometry of the succinylation signature of murine kidneys after diet treatment was analyzed. We found that mice sirtuin a target of succinylation and knockdown of this gene has a functional phenotype. We have preliminary evidence that there is less oxidative stress when the dodecanedioic acid diet was administered pre- or post-injury and there is less overall damage to the proximal tubule epithelium.

Conclusions: The data from these experiments suggest a simple but effective diet treatment could reduce the burden of AKI cases.

Funding: NIDDK Support

PO0450
Efficacy and Safety of Roxadustat in Patients with Anemia of Non-Dialysis-Dependent CKD (NDD-CKD) Treated Continuously for ≥2 Years
Chuan-Ming Hao,1 Neera K. Duhl,2 Stefan Tham,3 Marcelo Orías,2 Roberto Pecocis-Filho,4 Huashan Hospital Fudan University, Shanghai, China; 2Yale University School of Medicine, New Haven, CT; 3Clinical Research, AstraZeneca, Gothenburg, Sweden; 4Arbor Research Collaborative for Health, Ann Arbor, MI.

Background: Roxadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, is in development in the US for chronic treatment of anemia of CKD. This pooled post hoc analysis explored outcomes in NDD-CKD patients (pts) treated with roxadustat for >a3 years (y). Methods: Pts were randomized to open-label roxadustat (<943) or epoetin alfa (EPO; n=1947) for up to 4y in 3 Phase 3 DDD-CKD trials (ROCKIES, SIERRAS, AMENDS). Intravenous iron was given per local care for EPO and limited to need for roxadustat. Data were analyzed in pts treated continuously for ≥2y, regardless of rescue therapy use. P values are exploratory. Adverse events (AEs) were assessed.

Results: Overall, 789 roxadustat and 392 PBO pts were treated for ≥2y; of these, 87% (688/789) completed treatment. Baseline (BL) values for roxadustat vs PBO were not balanced due to more discontinuation in PBO prior to 2y: mean hemoglobin (Hb) 9.2 vs 9.3 g/dL, 59% vs 78% of pts had hypertension, 56% vs 60% of pts had diabetes, mean eGFR 21 vs 24 mL/min/1.73 m2. Change from BL Hb was greater with roxadustat vs PBO over Weeks (wk) 28–52 (+2.0 vs +0.5 g/dL, P=0.001), with differences seen from wk 4, and proportion of pts with Hb ≥10 g/dL over wk 28–52 was higher (95% vs 32%). Roxadustat maintained Hb ≥11 g/dL to wk 100 (Figure). Mean roxadustat weekly dose was increased by 11% from wk 25–28 to wk 97–100. Rescue therapy need (22% vs 34% pts), including red blood cell (RBC) transfusion (13% vs 18% pts), was less with roxadustat vs PBO; IV iron use was 9% for both. Serious AEs rates with roxadustat vs PBO were 20 vs 17 per 100 pt-exposure years, respectively.

Conclusions: In NDD-CKD pts who remained on treatment for ≥2y, roxadustat maintained Hb ≥11 g/dL with minimal dose change and less need for rescue therapy, including RBC transfusion, than PBO.

Funding: Commercial Support - AstraZeneca; AstraZeneca, Astellas, and Fibrogen

PO0451
Efficacy and Safety of Roxadustat in Patients with Anemia of Non-Dialysis-Dependent CKD (NDD-CKD) Treated Continuously for ≥2 Years
Roberto Pecocis-Filho,1 Neera K. Duhl,2 Stefan Tham,3 Marcelo Orías,2 Chuan-Ming Hao.1 Arbor Research Collaborative for Health, Ann Arbor, MI; 2Yale University School of Medicine, New Haven, CT; 3Clinical Research, AstraZeneca, Gothenburg, Sweden; 4Huashan Hospital Fudan University, Shanghai, China.

Background: Roxadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, is in development in the US for chronic treatment of anemia of CKD. This pooled post hoc analysis explored outcomes in NDD-CKD patients (pts) treated with roxadustat for ≥2 years (y).

Methods: Pts were randomized to double-blind roxadustat (n=2391) or placebo (PBO; n=1886) for up to 4y in 3 Phase 3 NDD-CKD trials (OLYMPSUS, ALPS, ANDES). Oral iron was administered without restriction; intravenous (IV) iron was limited to rescue therapy. Data were analyzed in pts treated for ≥2y, regardless of rescue therapy use. P values are exploratory. Adverse events (AEs) were assessed.

Results: Overall, 789 roxadustat and 392 PBO pts were treated for ≥2y; of these, 87% (688/789) completed treatment. Baseline (BL) values for roxadustat vs PBO were not balanced due to more discontinuation in PBO prior to 2y: mean hemoglobin (Hb) 9.2 vs 9.3 g/dL, 59% vs 78% of pts had hypertension, 56% vs 60% of pts had diabetes, mean eGFR 21 vs 24 mL/min/1.73 m2. Change from BL Hb was greater with roxadustat vs PBO over Weeks (wk) 28–52 (+2.0 vs +0.5 g/dL, P=0.001), with differences seen from wk 4, and proportion of pts with Hb ≥10 g/dL over wk 28–52 was higher (95% vs 32%). Roxadustat maintained Hb ≥11 g/dL to wk 100 (Figure). Mean roxadustat weekly dose was increased by 11% from wk 25–28 to wk 97–100. Rescue therapy need (22% vs 34% pts), including red blood cell (RBC) transfusion (13% vs 18% pts), was less with roxadustat vs PBO; IV iron use was 9% for both. Serious AEs rates with roxadustat vs PBO were 20 vs 17 per 100 pt-exposure years, respectively.

Conclusions: In NDD-CKD pts who remained on treatment for ≥2y, roxadustat maintained Hb ≥11 g/dL with minimal dose change and less need for rescue therapy, including RBC transfusion, than PBO.

Funding: Commercial Support - AstraZeneca; AstraZeneca, Astellas, and Fibrogen

PO0452
Number Needed to Treat with Roxadustat to Avoid One Transfusion or Intravenous Iron Administration in Anemia of Non-Dialysis-Dependent CKD
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Background: Red blood cell (RBC) transfusion is the most common anemia treatment for non-dialysis-dependent chronic kidney disease (NDD CKD), but risks alloimmunization, which may delay or preclude kidney transplantation, and is associated with adverse events. Intravenous (IV) iron is recommended for poor response to oral iron, but requires travel to clinics. Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor for anemia. It stimulates a coordinated erythropoietic response, increasing plasma endogenous erythropoietin levels and reducing hepcidin.

Methods: Data were pooled from 3 pivotal, randomized, phase 3 studies of roxadustat vs placebo NDD CKD populations. A phase 3 study of roxadustat vs darbepoetin alfa in NDD CKD was also analyzed. The number of patients needed to treat (NNT) with roxadustat for 1 year to avoid 1 RBC transfusion was calculated by taking the reciprocal
PO0453

Effects of Roxadustat in Patients with Dialysis-Dependent CKD (DD-CKD) Across All Baseline (BL) Hemoglobin (Hb) Values

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Background: Roxadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, increases Hb by stimulating endogenous erythropoietin synthesis and improving iron bioavailability. This pooled post hoc analysis evaluated the efficacy and safety of roxadustat in patients (pts) with DD-CKD across all available BL Hb values.

Methods: Pts were randomized to open-label roxadustat (n=1943) or epoetin alfa (EPO; n=1947) in 3 Phase 3 DD-CKD trials (ROCKIES, SIERRAS, HIMALAYAS). Across trials, Hb eligibility criteria were ≤10 g/dL at final screening, study drug dose was titrated to Hb 11±1 g/dL. Oral iron was administered without restriction; intravenous (IV) iron was limited to rescue therapy (IV iron, red blood cell [RBC] transfusion or ESA). Pooled post hoc subgroup analyses were performed by selected Hb values (g/dL: <8.0, ≥8.0–<9.0, ≥9.0–<10, ≥10.0) at BL (mean of up to 4 pre-randomization values) regardless of study rescue therapy use. Adverse events (AEs) were assessed.

Results: Pt study discontinuation rates were similar across all BL Hb ranges. Pts with lower BL Hb had less time on dialysis (Table), suggesting pts incident to dialysis. At BL, pts with Hb ≥9 g/dL had the lowest weekly ESA doses, but by Weeks (wk) 49–52 their weekly ESA doses were highest (Table). Pts with BL Hb ≤8 g/dL received on average ~1 mg/kg/wk more roxadustat dose at wk 49–52 than pts with BL Hb ≥10 g/dL (Table). Rates of serious AEs (SAEs) and treatment-emergent SAEs per pt-exposure year were comparable for roxadustat vs EPO and appeared more common in pts with higher BL Hb (Table). Pts with lower BL Hb had higher study discontinuation rates and lower Pt study discontinuation rates and lower BL Hb (Table).

Conclusions: DD-CKD pts with more severe anemia at BL required more IV iron during the study. Roxadustat was effective and had comparable tolerability to EPO across all BL Hb studied.

Funding: Commercial Support - AstraZeneca, Astellas, and Fibrogen
PO0455

Roxadustat in Elderly Patients with Anemia of CKD

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Background: Elderly patients with anemia of chronic kidney disease (CKD) typically have several comorbidities requiring polypharmacy, but slower drug metabolism than younger patients. Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor that promotes coordinated erythropoiesis and increased iron availability. We explored roxadustat treatment in elderly (≥65 years) vs younger (<65 years) patients in dialysis-dependent (DD) and non-dialysis-dependent (NDD) CKD populations.

Methods: Data were pooled from pivotal phase 3 studies of roxadustat vs placebo (stage 3-5 NDD-CKD) and vs epoetin alfa (DD-CKD). Data were analyzed for patients <65 and ≥65 years old. The primary endpoint in the overall trials was mean change from baseline in hemoglobin (HB) weeks 28-52, regardless of rescue therapy. Least square mean difference (LSMD) was determined between treatments. Secondary endpoints were transfusion rate per 100 patient-exposure years (NDD and DD) and change in mean IV iron use (DD). Adverse events were monitored during treatment >28 days post treatment (NDD and DD).

Results: In NDD (N=4277) and DD (N=3590) populations, the majority were female (NDD) or male (DD) (Table). Baseline HB levels were higher in elderly vs younger patients (Table). Age did not affect improvements in HB, but mean CF was greater in elderly vs younger DD and NDD patients (Table). Transferon rates were lower in younger vs elderly DD patients and in elderly vs younger NDD patients (Table). Trends in mean IV iron use were lower with roxadustat vs epoetin alfa and similar among age groups (Table). Roxadustat was well tolerated, regardless of age (Table).

Conclusions: Roxadustat was effective and well tolerated, regardless of age, in patients with anemia of CKD.

Funding: Commercial Support - FibroGen, Inc. and AstraZeneca

Table: Baseline characteristics and efficacy and safety endpoints

<table>
<thead>
<tr>
<th>Age Category</th>
<th>N (n%)</th>
<th>Mean Baseline Hemoglobin (g/dL)</th>
<th>Mean Baseline Ferritin (µg/L)</th>
<th>Mean Baseline IV Iron (µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Elderly</td>
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PO0456

Roxadustat Effectively Treats Anemia in Dialysis-Dependent CKD (DD-CKD) Patients with Ferritin ≥200 ng/mL

Pablo E. Pergola,1 Steven Fishbane,2 Chaim Charytan,3 Stefan Tham,4 Simon D. Roger,5 Elizabeta Nemeth,6 Renal Associates, San Antonio, TX; 1Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Great Neck, NY; 2NewYork-Presbyterian/Queens, Flushing, NY; 3Clinical Research, AstraZeneca, Gothenburg, Sweden; 4Renal Research, Gosford, NSW, Australia; 5University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA.

Background: Roxadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor being investigated for treatment of anemia due to chronic kidney disease (CKD), is an oral agent that promotes coordinated erythropoiesis and increased iron availability. This pooled post hoc analysis evaluated roxadustat vs ESA in DD-CKD patients (pts) with ferritin (pts) with high ferritin.

Methods:Pts were randomized to roxadustat (n=1943) or epoetin alfa (EPO; n=1947) in 3 Phase 3 DD-CKD trials (ROCKIES, SIERRAS, HIMALAYAS). Ferritin was ≥100 ng/mL at entry. EPO and intravenous (IV) iron were given per usual care for rouadustat vs ESA in DD-CKD patients (Table). Age did not affect improvements in HB, but mean CFT was greater in elderly vs younger DD and NDD patients (Table). Transferon rates were lower in younger vs elderly DD patients and in elderly vs younger NDD patients (Table). Trends in mean IV iron use were lower with rouadustat vs epoetin alfa and similar among age groups (Table). Rouadustat was well tolerated, regardless of age (Table).

Conclusions: Rouadustat was effective and well tolerated, regardless of age, in patients with anemia of CKD.

Funding: Commercial Support - FibroGen, Inc. and AstraZeneca

Table: Changes From Baseline in Iron-Related Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EPO (n=1943)</th>
<th>Rouadustat (n=1947)</th>
<th>Primary Efficacy Period (wk 26-52)</th>
<th>Secondary Efficacy Period (wk 52-102)</th>
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<tbody>
<tr>
<td>Hemoglobin</td>
<td>-0.97</td>
<td>-1.01</td>
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<td>-0.97</td>
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<tr>
<td>Ferritin</td>
<td>61.5</td>
<td>62.0</td>
<td>0.054</td>
<td>61.5</td>
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<tr>
<td>IV iron</td>
<td>150</td>
<td>150</td>
<td>1.000</td>
<td>150</td>
</tr>
</tbody>
</table>

PO0457

Iron-Related Outcomes in Patients with Dialysis-Dependent CKD Randomized to Vaddustat vs. Darbepoetin Alfa

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Background: Vaddustat (VADA) is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor being investigated for treatment of anemia due to chronic kidney disease (CKD). We conducted 2 global phase 3, randomized, open-label, active-controlled, noninferiority trials (INNO-VATE) comparing once-daily oral dosing of VADA with the erythropoiesis-stimulating agent darbepoetin alfa (DA) in patients with anemia and incident (N=369) or prevalent (N=3554) dialysis-dependent (DD) CKD. Inclusion criteria: serum ferritin ≥100 ng/mL and transferrin saturation (TSAT) ≥20%. Safety and efficacy results of the INNO-VATE trials were previously reported. Here we report iron-related outcomes, including the changes in mean serum hepcidin, ferritin, total iron-binding capacity (TIBC), iron, and TSAT from baseline to the primary (wk 24-36) and secondary (wk 40-52) evaluation periods.

Results: A total of 1958 patients received VADA and 1965 received DA. VADA treatment was associated with greater decreases in mean hepcidin and ferritin, and increases in TIBC from baseline to the primary and secondary evaluation periods (Table). Mean serum iron decreased more in the DA than the VADA group from baseline to wk 24-36 and 40-52. Oral and intravenous iron use was similar in the 2 treatment groups throughout both studies. Similar results were seen in the non-DD-CKD populations (PROTECT studies).

Conclusions: The observed relative decreases in hepcidin and ferritin and the increase in TIBC are consistent with a VADA-induced facilitation of iron mobilization from intracellular stores that support erythropoiesis.

Funding: Commercial Support - Akebia Therapeutics, Inc., and Otsuka Pharmaceuticals Development and Commercialization, Inc.
PO0458

Associations Between Hepcidin and Laboratory Measures of Iron and Inflammation in Patients with Anemia and CKD Not on Dialysis in the Roxadustat Global Phase 3 Program

Methods: This study analysis used data from 3 similarly designed pivotal phase 3 studies (OLYMPUS, ANDES, and ALPS) of roxadustat vs. placebo in anemic patients with stage 3-5 NDD-CKD. Quintiles of baseline (BL) hepcidin levels and changes from baseline (CFB) in hepcidin were evaluated for associations with select labs at BL and changes at weeks 20-28. Multivariate regression to hepcidin was performed at BL and after treatment using full analysis set.

Results: 2717 patients were assessed (1630 roxadustat, 1087 placebo). BL hepcidin (range 0.75 to 808.2 µg/L) was analyzed by quintile regardless of treatment group. Patients with higher BL hepcidin were observed to have a lower hemoglobin (HB), lower eGFR, higher C-reactive protein (CRP), higher serum iron, higher ferritin, lower total iron binding capacity (TIBC), and higher transferrin saturation (TSAT) compared to lower hepcidin groups (Table 1). Further analysis of these relationships using multivariate regression models with minimalized AIC score model selection criteria showed that hepcidin (log-transformed) was significantly associated with the following BL parameters (log-transformed) in the descending order of importance (+/- indicated the direction): ferritin(+), TIBC(-), eGFR(+), albumin(+), Hb(-). The mean (SD) CFB to week 24 in hepcidin was -34.84 (141.6) µg/L in the descending order of importance (+/- indicated the direction): ferritin(+), TIBC(-), eGFR(+), albumin(+), Hb(-). The most frequent serious AEs (SAEs) in the V ADA and DA groups occurred in the SOCs for infections and infestations (23.4%, 24.0%) and renal and urinary disorders (18.6%, 18.1%). TEAEs leading to death in the V ADA and DA groups were cardiac arrest (1.7% in each group), end-stage kidney disease (1.3%, 1.0%), and cardio-respiratory arrest (0.9%, 1.0%). AESIs (+10%) in the V ADA and DA groups were hypertension (18.0%, 21.0%), congestive heart failure (10.3%, 11.5%), and hyperkalemia (9.9%, 11.9%), all of which were more frequent with DA.

Background: V ADA (VAD) is an oral hypoxia- inducible factor prolyl hydroxylase inhibitor being investigated for treatment of anemia due to chronic kidney disease (CKD).

Methods: We pooled safety data from 4 global phase 3, randomized, open-label studies evaluating VADA vs darboepoetin alfa (DA) in patients from 2 dialysis- and 2 non-dialysis-dependent CKD trials (INNO-VATE and PROTECT, respectively) who received 1 dose of study drug. We summarized treatment-emergent adverse events (TEAEs) by MedDRA system organ class (SOC) and preferred term. We retrieved AEs of special interest (AESIs) using Standardized MedDRA Queries and analyzed as groups of PTs (medical topics).

Results: A summary of TEAEs by treatment group is provided (Table). The most common in the VADA and DA groups by SOC were infections and infestations (50.8%, 50.7%), gastrointestinal disorders (40.2%, 35.2%), metabolic and nutrition disorders (34.6%, 36.2%), and injury, poisoning and procedural complications (29.5%, 30.7%). The most common drug-related TEAEs in the VADA group were the PFTs of diarrhea (2.2%) and nausea (1.2%), leading to study drug discontinuation in 0.4% and 0.2% of patients, respectively. The most frequent serious AEs (SAEs) in the VADA and DA groups occurred in the SOCs for infections and infestations (23.4%, 24.0%) and renal and urinary disorders (18.6%, 18.1%). TEAEs leading to death in the VADA and DA groups were cardiac arrest (1.7% in each group), end-stage kidney disease (1.8%, 1.3%), and cardio-respiratory arrest (0.9%, 1.0%). AESIs (+10%) in the VADA and DA groups were hypertension (18.0%, 21.0%), congestive heart failure (10.3%, 11.5%), and hyperkalemia (9.9%, 11.9%), all of which were more frequent with DA.

Conclusions: VADA exhibited a TEAE safety profile generally comparable to DA. Further analyses to determine the risk of malignancy in patients with chronic kidney disease (CKD) with V ADA vs darboepoetin alfa in the VADA and DA groups are warranted.
cell carcinoma of the skin, cutaneously resected squamous cell carcinoma of the skin, or cervical carcinoma in situ. Malignancies are reported here as events per 100 patient-years (PY).

**Results:** In total, 3686 patients were exposed to VADA and 3687 to DA for a median of 56.7 wk (25%, 75th percentile range 31.9–91.7 wk) and 70.0 wk (39.9–102.1 wk); 54% of patients were exposed for ≥100 wk and 18.9% and 24.1% for 100–148 wk, respectively. Malignancies in the VADA and DA treatment groups were 2.1 events/100 PY and 2.7 events/100 PY, respectively (relative risk [RR], 0.81; 95% confidence interval [CI], 0.64–1.03). Specifically, malignancies in patients with NDD-CKD were 2.7 events/100 PY (RR, 0.85; 95% CI, 0.65–1.21), and in patients with DD-CKD, 1.5 vs 2.4 events/100 PY (RR, 0.72; 95% CI, 0.50–1.03), for VADA vs DA, respectively. In both studies, no pattern was observed for any specific type of malignancy, including renal cell carcinoma in patients with DD or NDD CKD.

**Conclusions:** Vadadustat VADA was associated with an increased risk of neoplasms compared with DA in patients with anemia and CKD.

**Funding:** Commercial Support - Akbeia Therapeutics, Inc., and Otsuka Pharmaceuticals Development and Commercialization, Inc.
Suboptimal Treatment of Anemia in CKD Non-Dialysis Patients: What Role Will HIF-PH Inhibitors Play?  

Background: The purpose of this study was to understand the real-world patient presentation and treatment priorities for CKD non-dialysis patients, focusing on the treatment of anemia of CKD.

Methods: Using a HIPAA-compliant, online chart audit tool, nephrologists (n=183) submitted de-identified clinical and non-clinical demographic information for 1,030 non-dialysis patients with CKD (eGFR<60) in Fall 2020. This independent, retrospective patient chart audit collected data beginning at the time of patient referral and concluded with details from the most recent visit.

Results: As CKD progresses so too does the prevalence of anemia, with nearly six-in-ten CKD Stage 5 patients identified by their physicians as having anemia. However, while anemia is a common comorbidity in CKD, non-dialysis patients, physicians tend to deprioritize the disease when consulting with these patients in their offices. When asked about topics discussed during their most recent patient visit, anemia falls behind other topics such as hypertension, weight and diet, and quality of life. Although anemia is less of a priority, more than 60% of patients did have a hematoglobin test ordered at their most recent visit, indicating that physicians are monitoring hemoglobin levels somewhat regularly to help keep track of potential anemia. More than one-half of CKD non-dialysis patients treated with ESAs have a hemoglobin level below 10.0 g/dL; however, the most common reason for non-treatment in patients below 9.0 and 9.9 g/dL is that the hemoglobin is “not low enough”, indicating physicians are waiting until hemoglobin is substantially low before starting treatment with ESAs. HIF-PH inhibitors are a novel class of anemia treatment, with details from the most recent visit.

Conclusions: Enhanced communication with non-dialysis patients about anemia, as well as earlier detection and intervention with novel HIF-PH inhibitors, could lead to substantial improvement in the treatment of anemia of CKD.

Renal Injury Biomarkers Are Elevated in Acute Hepatic Porphyria  
Simina Ticau, Kristina Yucius, Alexandre Kararra, Eliane Sard, Laurent Gouya, Amy Simon, Anna Borodovsky, Alyna Pharmaceuticals Inc, Cambridge, MA; 1Department of Nephrology, Hôpital Européen Georges Pompidou, APHP, Paris, France; 2Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden; 3CRMR Porphyries, Hôpital Louis Mourier, APHP, Paris, France; 4CRMR Porphyries, Hôpital Louis Mourier, APHP, Paris, France; 5Beam Therapeutics, Cambridge, MA

Background: Acute hepatic porphyria (AHP) is a group of rare genetic diseases caused by defects in enzymes in the heme biosynthesis pathway. Acute intermittent porphyria (AIP) is the most common subtype. In patients with AHP, accumulation of heme pathway intermediates, delta-aminolevulinic acid (ALA) and porphobilinogen (PBG), lead to acute attacks and long-term complications including hypertension and chronic kidney disease which is present in 30-60% of patients with biochemically active AIP. Chronic high excreters (CHE) are a group of patients that carry a genetic mutation and have elevated levels of ALA and PBG but are not experiencing acute attacks.

Methods: Proteomic analysis (Olink® platform) was used to measure 1196 proteins and additional kidney injury biomarkers (neutrophil gelatinase-associated lipocalin, cystatin C (CST3) and chitinase-3-like protein 1) showed significant elevations in patients with acute AHP compared to controls. Rates of AHP were similar (75/6% Dapro vs 72% Darbe).

Conclusions: In a high-risk incident dialysis population, Dapro was non-inferior to Darbe in maintaining Hb in the target range. Dapro was well tolerated and appears to be a safe alternative to Darbe.

Anemia Care of Hemodialysis Patients: A National Study from Qatar  

Background: Achieving anemia targets in dialysis patients is hard. Challenges like cost, compliance and erythropoietin stimulation agents (ESA) resistance can hamper anemia management. We established a new national anemia nurse manager model to improve care of anemia in dialysis patients in the State of Qatar. Key drivers of the model are summarized in Figure below. We studied the effects of this program in improving anemia care in hemodialysis patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
PO0071
Contemporary Anemia Treatment in Prevalent Patients Undergoing Hemodialysis
Eric D. Weinhandl,1,2 William Eggert,1 Jeffrey Peterson,1 Yunji Hwang,3 David T. Gilbertson.1 Hennepin Healthcare Research Institute, Minneapolis, MN; 3Amgen Inc, Thousand Oaks, CA.

Background: Anemia treatment remains a major area of focus in the management of maintenance dialysis patients. We assessed hemoglobin (Hb) and erythropoiesis-stimulating agent (ESA) dosing among hemodialysis (HD) patients with records in CROWNWeb, a national reporting system that captures data from all prevalent patients undergoing maintenance dialysis, regardless of whether patients carry Medicare coverage.

Methods: We analyzed United States Renal Data System Standard Analysis Files. For each calendar month from January 2015 to September 2019, we identified adult patients who received HD during the entire month and whose CROWNWeb records included a valid measurement of single-pool Kt/V. In each prevalent patient, we identified Hb and ESA treatment (agent [epoetin alfa, darbepoetin alfa, or pegylated epoetin beta]) and monthly cumulative dose. Subsequently, we tabulated the distribution of Hb in each month, incidence of 3-month and 6-month series with Hb <10.0 g/dL; utilization of ESAs, overall and by agent; and mean weekly ESA dose, by agent.

Results: Among 878,883 patients in the study period, 7.2% of patient-months had Hb <9.0 g/dL, 15.2% had Hb 9.0-9.9 g/dL, 35.3% had Hb 10.0-10.9 g/dL, 28.5% had Hb 11.0-11.9 g/dL, and 13.9% had Hb ≥12.0 g/dL. The prevalence of Hb <9.0 g/dL was relatively higher with age 18-44 years, Black race, and female sex. Among all 6-month series of Hb measurements, 5.8% had Hb <10.0 g/dL for 3 consecutive months and only 2.0% had Hb <10.0 g/dL for 6 consecutive months. Approximately 76% of patients received an ESA in each month. In 2019, 34% used epoetin alfa, 9% used darbepoetin alfa, and 33% used pegylated epoetin beta. Mean (median) weekly doses were 10,562 (7727) IU for epoetin alfa, 35.9 (23.0) mcg for darbepoetin alfa, and 33.6 (23.0) mcg for pegylated epoetin beta.

Conclusions: Between 2015 and 2019, despite substantial flux in the mix of ESAs used, distributions of hemoglobin and ESA doses among patients undergoing HD were stable, with only a small percentage of patients experiencing persistently low hemoglobin.

Funding: Commercial Support - Amgen Inc.
The Effect of a Patient Blood Management Program on Renal Outcome in Patients with CKD

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Background: Transfusion burden is high in CKD patients to treat anemia. However, transfusions have risks including volume overload, alloimmunization, blood stream infections and thromboembolism. We evaluated the effect of a monitoring program to identify appropriate transfusions in CKD patients.

Methods: Based on the guidelines of the Korean Society of Blood Transfusion, Korea University Anam Medical Center developed a verification program to assess the adequacy of transfusion (patient blood management(PBM)) in August 2018. We analyzed 1,192 CKD patients admitted to the department of nephrology from August 2016 to July 2020. Patients were divided into two groups: patients who admitted before the implementation of PBM (pre-PBM(n=592)) and after the implementation of PBM (post-PBM(n=600)).

Results: The amount of blood transfused was 628 units in pre-PBM group and 443 units in post-PBM group. The patients who received more than 2 units was significantly lower in post-PBM group (20.1% vs. 13.5%, p=0.002). There were no differences in the administered doses of erythropoietin and iron between the groups. Although hemoglobin(Hb) (10.5±2.0 vs. 10.3±2.2) were not different between the two groups at admission, Hb levels were significantly lower in post-PBM group at discharge (10.4±1.8 vs. 10.1±2.0, p=0.010) and 6 months after admission (11.5±1.9 vs. 11.1±2.0, p=0.007). Kaplan-Meier analysis showed a survival benefit of CKD progression (p=0.001) and percutaneous coronary intervention (p=0.030) in the post-PBM group. The incidence of end stage kidney disease or mortality was not different between groups. In multivariate analysis, PBM was associated with lower risk for CKD progression (HR of 0.387; 95% CI 0.416-0.830).

Conclusions: Patient blood management program may reduce inappropriate RBC transfusion. Implementation of PBM was associated with lower risk of CKD progression in hospitalized CKD patients.

Ferric Pyrophosphate Citrate (Triferic® AVNU): Alternate Intravenous Dosing Strategies Compared to Continuous Infusion over 3 Hours

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Background: Ferric pyrophosphate citrate injection (FPC-IV) is an iron replacement product to maintain hemoglobin by intravenous infusion over 3 to 4 hours. The aim of this study was to investigate FPC-IV pharmacokinetics and confirm safety of alternate dosing strategies.

Methods: An open-label, randomized, multiple period single dose study was conducted in 23 CKD-3HD patients to establish the equivalence of doses between FPC-IV as a 3-hour infusion using the on-machine syringe pump and 5 alternate dosing strategies. The treatments were A) Baseline FPC-IV 6.75 mg Fe/3 hours (approved rate); B) FPC-IV 3.38 mg Fe bolus injections at t=0 and t=3 hours; C) FPC-IV 6.75 mg Fe bolus injection at t=0 hours over 0.5 - 5 min. and D) FPC-IV 2.25 mg Fe bolus injections at t=0, t=1.5 and t=3 hours and E) FPC-IV 6.75 mg Fe by infusion using a spring-driven syringe pump with flow restrictive tubing to deliver 2 mL/hr. Blood samples were obtained to assess total iron (Fe₉), transferrin bound iron (TBI), transferrin saturation (TSAT) and iron binding capacity (TIBC).

Results: The results for TSAT (Fig.1) track the administration group. FPC-IV was generally well tolerated in all treatments. There was transient flushing and abdominal discomfort of mild to moderate severity associated with treatment C (bolus injection of FPC over 0.5-5 min.) experienced by 15 of 16 patients. All symptoms spontaneously resolved over 2 to 5 minutes and no adverse events or intolerance was reported with any other treatment.

Conclusions: The results of this study demonstrate that FPC-IV can be safely administered as a continuous infusion using a spring-driven pump (FP) over 71 to 195 minutes. The mean increment in sFe pre- to post infusion was 202 ± 42.7 µg/dL. The pump set up, including loading the syringe, took an average of 47 ± 251 sec. The incremental sFe in this study is compared to the dialysate and IV FPC infusions over 3 hours in Figure 1. The sFe was rapidly cleared with no increase in pre-dialysis sFe. FPC-IV was well tolerated with no reported adverse events.

Conclusions: The results of this study demonstrate that FPC-IV can be safely administered as a continuous infusion using a spring-driven pump (FP) over 71 to 195 minutes. The increment in sFe is slightly greater than the 3 or 4-hour FPC infusions due to the shorter administration time. A spring-driven infusion pump to administer FPC IV is well-tolerated and a suitable alternative to use of the Hemodialysis machine syringe pump.

Funding: Commercial Support - Rockwell Medical Inc.

Figure 1. Comparison of pre- and post-dialysis sFe across FPC studies.
PO0476
Association Between Serum Indices of Iron Metabolism and Cardiovascular Morbidity in Patients with Pre-Dialysis CKD
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Background: The optimal ranges of serum iron markers are uncertain in predialysis chronic kidney disease (CKD) patients. Therefore, we aimed to investigate the association between serum indices of iron metabolism and the incidence of CVD events in patients with predialysis CKD using the CKD-Japan Cohort (CKD-JAC) data.

Methods: We prospectively followed 1,550 CKD patients aged 20-75 years with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m2 for a mean of 4.21 years. We set serum transferrin saturation (TSAT) and ferritin levels as the main exposures to be tested. Our main outcome measures were any of the CVD events including congestive heart failure (CHF) identified at each facility and adjudicated by the independent cardiac function evaluation committee. Multivariable Cox proportional hazards regression models were employed to examine the association between serum TSAT or ferritin levels with time to events. All models were stratified by facilities and adjusted for potential confounders. We also applied the multivariable fractional polynomial interaction (MFPi) approach to investigate whether serum TSAT or ferritin levels are the effect modifier of the association between iron supplementation and the outcomes.

Results: In the overall cohort, 268 (13.4%) patients developed CVD events (including 97 CHF) during the follow-up period (26.6 events/1000 person-year). The incidence rate of CVD events was the highest in the TSAT < 20% category (33.0 events/1000 person-year). Compared to patients in the TSAT > 40% category, those in the TSAT < 20% category demonstrated an increased risk of CVD events (adjusted hazard ratio [AHR]: 1.64, 95% confidence interval [CI]: 1.06-2.56) and CHF events (AHR: 2.82, 95% CI: 1.15-6.89), respectively. There was no association between serum ferritin levels and the risk of CVD or CHF events. MFPi analyses showed a reduced risk of CVD in patients receiving iron supplementation only in patients with TSAT < 20% (p for interaction<0.02).

Conclusions: Maintaining TSAT > 20% could be effective to reduce the risk of developing CVD events (especially CHF) in patients with predialysis CKD. Our analyses also suggest that iron-deficient patients with predialysis CKD may benefit from iron supplementation for reduced risk of CVD events.

PO0477
Serum Erythroferrone and Serum Hepcidin 25 Are Associated with CKD
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Background: Erythroferrone is a recently discovered hepcidin suppressor expressed in erythroblasts in response to erythropoietin (EPO) with the downstream effect of increased iron availability. In light of the central role of hepcidin-25 in the pathogenesis of anemia, we determined serum erythroferrone, serum hepcidin-25, the hepcidin/ferritin ratio, and the ESA hyporesponsivess index (ERI) in different stages of chronic kidney disease (CKD).

Methods: Erythroferrone was determined by ELISA in 602 CKD patients (97 CKD 3-4, 220 CKD 5 non-dialysis patients, 76 prevalent peritoneal dialysis (PD) patients, and 209 prevalent hemodialysis (HD) patients). The ERI was calculated as follows: ESA dose (international units) per kg/hemoglobin level (g/L) per week. Differences in levels of erythroferrone (ng/ml), hepcidin-25 (nmol/L), the hepcidin ferritin ratio, and ERI between stages of CKD were assessed by non-parametric ANOVA.

Results: Serum erythroferrone and serum hepcidin-25 increased with increasing CKD stage and was higher in patients with CKD 5, in PD patients, and in HD patients as compared to patients with CKD 3-4 (Figure A, B). When levels of hepcidin-25 were corrected for serum ferritin levels (hepcidin/ferritin ratio), only patients in CKD 5 had higher levels as compared to patients in CKD 3-4 (Figure C). Estimated ERI was higher in CKD 5 and HD patients as compared to CKD 3-4 patients (Figure D). The high tertile of erythroferrone in CKD 5 was associated with worse clinical outcome. No significant association with clinical outcome was observed in other cohorts.

Conclusions: Serum erythroferrone, serum hepcidin and ERI were linearly associated with deteriorating renal function. We found significant association of erythroferrone to all-cause mortality in CKD 5 patients.

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PO0479

Hypersensitivity Reaction to Epoetin-Alfa: A Therapeutic Challenge

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Introduction: Use of erythropoiesis stimulating agents (ESA) prevent the need for recurrent blood transfusions in patients with advanced kidney disease. Rarely, patients can have allergic reactions to the ESA components which can range from pruritic rash to fatal angioedema. We report a case of delayed-type hypersensitivity reaction (DTH) due to epoetin-alfa (EPO). Cross-reactivity between molecular structures of various agents raises a therapeutic challenge.

Case Description: A 78 year old man with anemia in the setting of chronic kidney disease stage 4 secondary to diabetes mellitus was initiated on EPO 10,000 units per month. He developed an urticarial rash in the back and chest after the first dose, which gradually worsened after receiving the second dose. Review of recent history was negative for any other new medication or chemical exposure. He underwent skin biopsy which showed dermatitis with eosinophils supporting a drug reaction. EPO was discontinued with resolution of the rash. Given known risk of cross-reactivity between various ESA molecules, he was subsequently referred to an allergist for desensitization protocol, followed by successful re-introduction of ESA therapy.

Discussion: Currently, ESA remains the treatment of choice for anemia of kidney disease, in order to limit need for blood transfusions. ESA-related DTH reactions can be due to excipients such as polysorbate, as well as the structural subunits of erythropoietin. Cross-reactivity has been reported between different ESA structures, which raises a therapeutic challenge in the care of such patients. Clinicians should consider desensitization, which can lead to successful re-introduction of ESA therapy.

PO0480

An Unusual Cause of Anemia: Duodenal Compression by Polycystic Kidneys


Introduction: We report a rare case of gastrointestinal bleeding due to extrinsic compression and shearing of bowel in a patient with autosomal dominant polycystic kidney disease (ADPKD).

Case Description: A 52-year-old male presented with progressive dyspnoea and melaena over one week. He was noted to have an eGFR of 9 ml/min/1.73 m², giant polycystic kidneys and a family history of ADPKD. A diagnosis of ADPKD was made and he was commenced on peritoneal dialysis. He was noted to have mital regurgitation and hypertension. His haemoglobin at presentation was 39 g/L and his blood film revealed ovalocytes, without evidence of haemolysis. Haematocrits were suggestive of iron deficiency. While uraemic at presentation, he had no other notable risk factors for bleeding. Upper GI endoscopy and colonoscopy were both unremarkable. He was treated with red cell transfusion, intravenous iron and commenced on an erythropoiesis-stimulating agent. He presented on four subsequent occasions over an 8 month period with recurrence of severe anaemia and melaena. A capsule endoscopy suggested bleeding at the duodenal-jejunal flexure, however no source was visualised. The cause of the bleeding was revealed by double balloon enteroscopy which demonstrated extrinsic compression of the scope at D3. Review of imaging confirmed this was due to a large right renal cyst. Ongoing tranexamic acid and lanreotide treatment has reduced the frequency of bleeds. While a nephrectomy would potentially provide a definitive solution to the underlying cause, this carries substantial risk and would need to be carefully coordinated with his mitral valve repair.

Discussion: While peptic ulcer disease is slightly increased in ADPKD, this is the first description of mechanical trauma to bowel by polycystic kidneys resulting in severe recurrent GI bleeding. Teaching points: 1. Giant polycystic kidneys can rarely compress small bowel and cause GI bleeding 2. Correlation of advanced endoscopy such as double balloon enteroscopy with radiology may be required to make the diagnosis 3. Tranexamic acid and lanreotide may reduce bleeding.

PO0481

Targeted Literature Review (TLR) Exploring Adherence to Treatments, with Potential to Extrapolate to Patients with Anemia of CKD

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Background: Adherence to long-term treatment for chronic diseases, e.g. anemia of CKD, is problematic. Adherence to a patient’s preferred treatment is critical to successful CKD management. We explored: availability of published best practice guidance for long-term disease; how analog scenarios from healthcare teams and patients provide learning about treatment adherence and persistence; patient preferences; and how to measure adherence-related outcomes.

Methods: We conducted a TLR of analog scenarios where an oral therapy was introduced in a setting with injectable/subcutaneous therapy as standard of care. Embase and Cochrane searches included administration route, dosing frequency and titration, from 2016–2020. Searches were limited to literature reviews and clinical guidelines for adults with chronic disease from 10 countries.

Results: Of 1421 papers identified, 85 were relevant. Inspection of these papers revealed that non-adherence may be intentional or non-intentional, and can be linked to numerous factors, e.g. polypharmacy, treatment regimen complexity, number of daily tablets, lengthy treatment duration, and patient beliefs about treatment. Intentional non-adherence may link to patients’ motivations/beliefs, and non-intentional non-adherence may link to patients’ skill/ability to take a medicine. Regimen complexity can be influenced by drug dosage form, product characteristics, dosage schemes, specific additional instructions (e.g. fixed-time daily dosing), patient characteristics and administration errors. Discrete choice experiments and conjoint analyses provide robust means of measuring patient preferences, but evidence is conflicting of preference for injectable vs oral treatments, which is relevant to anemia of CKD management. Accurately documenting evidence of medication ingestion/administration is difficult. While several methods exist for assessing treatment adherence and persistence, no gold standard was identified.

Conclusions: In a competitive treatment setting, there remains significant opportunity to support patients in their treatment choice. Identifying best practice models of treatment adherence, persistence and measuring patient outcomes may prove important for differentiating between treatments.

Funding: Commercial Support - Astellas Pharma Inc.

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PO0482

Iron-Related Outcomes in Patients with Non-Dialysis-Dependent CKD Randomized to Vadadustat vs. Darbepoetin Alfa

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Background: Vadadustat (VADA) is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor being investigated for treatment of anemia due to chronic kidney disease (CKD).

Methods: We conducted 2 global phase 3, randomized, open-label, sponsor-blind, active-controlled, noninferiority trials (PROTECT, TECT) comparing once-daily oral dosing VADA with the erythropoiesis-stimulating agent (ESA) darbepoetin alfa (DA) in 1751 patients with non-dialysis-dependent CKD (NDD-CKD) not previously ESA treated and in 1725 NDD-CKD patients previously ESA treated. Inclusion criteria included serum ferritin ≥100 mg/mL and transferrin saturation (TSAT) ≥20%. Safety and efficacy results were previously reported. Here we report iron-related outcomes, including the changes in mean serum hepcidin, ferritin, total iron-binding capacity (TIBC), iron, and TSAT from baseline to the primary (wk 24–36) and secondary (wk 40–52) evaluation periods (PEP and SEP).

Results: A total of 1741 patients received VADA and 1735 received DA. VADA treatment was associated with greater decreases in mean hepcidin, ferritin, and TSAT, and increases in TIBC from baseline to PEP and SEP (Table). A small increase in serum iron was seen in the VADA group as was a decrease in the DA group from baseline to PEP and SEP. Oral and IV iron use was similar in the 2 treatment groups throughout both studies.

Conclusions: Treatment with VADA resulted in relative decreases in hepcidin and ferritin and increases in TIBC and serum iron. Decreases in TSAT should be interpreted in the light of a greater increase in TIBC than that of serum iron. These changes are consistent with a VADA-induced increase in iron mobilization from extracellular stores that support erythropoiesis.

Funding: Commercial Support - Akebia Therapeutics, Inc, and Otsuka Pharmaceuticals Development and Commercialization, Inc.

PO0484

IL-6 Inhibitor Ziltivekimab Increases Serum Hemoglobin and Iron Biomarkers in Patients with CKD Stage 3–5: A RESCUE Trial Analysis

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Background: Interleukin-6 (IL-6)-mediated inflammation causes functional iron deficiency and anemia in patients (pts) with chronic kidney disease (CKD). IL-6 inhibitor, ziltivekimab, reduced inflammation markers (RESCUE trial; NCT03926117) and improved anemia and serum albumin in hemodialysis pts (NCT02868229). We examined the effect of ziltivekimab on serum hemoglobin (Hb) and iron homeostasis in pts with CKD stage 3–5 in the RESCUE trial.

Methods: Changes in anemia markers from baseline (BL) to Week 12 were assessed in pts (CKD stage 3–5, high-sensitivity C-reactive protein ≥2 mg/L) treated with ziltivekimab 7.5, 15 or 30 mg vs placebo (PBO). The intention-to-treat population was analyzed using a mixed model for repeated measurements (no adjustment for multiplicity). Analysis by BL Hb level (<11 or ≥11 g/dL) was conducted.

Results: In the RESCUE trial overall, mean age was 66 years, median Hb 12.5 g/dL at BL, (N=198, ziltivekimab; N=66, PBO). Ziltivekimab increased Hb from BL to Week 12 vs PBO (p<0.001 for each dose; Figure/Table), with numerically greater increases with ziltivekimab vs PBO in pts with BL Hb <11 g/dL than pts with BL Hb ≥11 g/dL (Table). Ziltivekimab increased serum iron levels (p<0.0001), total iron-binding capacity and transferrin saturation (both p<0.01) vs PBO. No major safety concerns were reported.

Conclusions: Ziltivekimab improved levels of Hb, serum iron and other iron biomarkers vs PBO in pts with CKD stage 3–5. By reducing inflammation and improving functional iron deficiency, ziltivekimab may improve anemia in pts with CKD.

Funding: Commercial Support - Novo Nordisk.

PO0483

Elevation in Red Cell Distribution Width (RDW) Is a Risk Factor for Future Hyponatremia and Hypokalemia

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Background: Elevation in red cell distribution width (RDW), a marker of size variance in red blood cells, recently has been reported to predict mortality, future cardiovascular events, and faster CKD progression. Putative mechanisms in RDW elevation include factors such as inflammation, aging, oxidative stress or malnutrition. It has not been clearly reported whether elevation in RDW has any significant impact on future electrolyte metabolism.

Methods: A hospital-wide study with all the laboratory data for a period of 4 years and 2 months was conducted. First, for each patient, hemoglobin (Hb) measurements of 1565 days were retrieved and the maximum RDW was obtained. Then the latest measurements of serum sodium (Na) and potassium (K), at least 365 days apart from the initial Hb and RDW measurement, were obtained. Prevalence and odds ratio (OR) of hyponatremia and hypokalemia were calculated for each quartile of RDW. Statistical analysis was performed with R 3.6.0 on Ubuntu and with Microsoft Excel.

Results: A total of 5,537 patients were included in the study. Hb ranged from 7.7 to 20.2 (median 13.4) g/dL, MCV 55.7-124.5 (93.1) fl, and RDW 10.1-34.6 (12.7)%.

Conclusions: Elevation in RDW is a risk factor for future development of hyponatremia and hypokalemia.

PO0485

Sodium-Glucose Cotransporter 2 Inhibitors and Anemia Among Diabetic Patients in Real Clinical Practice

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Background: Sodium-glucose cotransporter 2 inhibitors (SGLT2i) were reported to increase hemoglobin levels in short-term clinical trials. Whether it is also true in real clinical practice is unknown.

Methods: This is a retrospective cohort study. Inclusion criterion was diabetics who visited our outpatient clinic from January 2019 to August 2020. Exposure of interest was the use of SGLT2i. Outcomes were hemoglobin levels. For the cross-sectional analyses, nonlinear regression models were fitted with restricted cubic splines to investigate the association between hemoglobin levels and estimated glomerular filtration rate (eGFR) for users and non-users of SGLT2i. For the case-control study, cases (anemia defined as hemoglobin <12 g/dL for men, <11 g/dL for women or the use of erythropoiesis stimulating agents) and controls were matched by age, sex, and eGFR.

Results: Among 2063 diabetics, 723 were on SGLT2i. In the cross-sectional analyses, hemoglobin levels were higher among SGLT2i users compared with non-users at eGFR >15 mL/min/1.73m2. For the case-control study, 197 cases and controls were matched by age, sex, and eGFR.

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matched. Conditional logistic regression showed that the use of SGLT2i was associated with significantly lower prevalence of anemia (OR: 0.35 [0.21-0.58]). Adjusted mean differences (95% CIs) in hemoglobin levels between users and propensity score-matched non-users of SGLT2i were 0.7 (0.3-1.0) g/dL at 6 months. Among SGLT2i users, odds of increase in 6-month hemoglobin were similar across eGFR categories except for eGFR <15 mL/min/1.73m².

Conclusions: The use of SGLT2i was associated with higher hemoglobin levels and lower prevalence of anemia in real clinical practice.

PO0487

ASCEND-TD: A Randomized, Double-Blind, Active-Controlled Study of Daprodustat Administered Three Times Weekly in Hemodialysis Patients

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Background: Daprodustat (dapros) is a hypoxia-inducible factor prolyl hydroxylase inhibitor being investigated for the treatment of anemia of chronic kidney disease (CKD). This study evaluated the efficacy and safety of dapros administered three-times-weekly (TIW) vs recombinant human erythropoietin (rEPO) for in-center prevalent hemodialysis (HD) patients.

Methods: This double-blind study (NCT03400033) randomized (2:1) HD patients with a baseline hemoglobin (Hb) of 8–11.5 g/dL already on rEPO to dapros TIW (n=270) or rEPO (n=137) for 52 weeks. A dosing algorithm aimed to maintain Hb between 10–11 g/dL. The primary endpoint was a mean change in Hb in the evaluation period (EP; Weeks 52-55). The principal secondary endpoints were median IV iron dose. Other secondary endpoints included blood pressure (BP) and Hb variability.

Results: Baseline characteristics in 407 randomized patients were balanced between the dapros and rEPO groups. Dapros TIW was non inferior to rEPO for mean change in Hb (model-adjusted mean treatment difference [dapros-rEPO] -0.05; 95% CI: -0.21, 0.10). In the EP, mean (SD) Hb was 10.45 (0.549) g/dL and 10.51 (0.849) g/dL for dapros and rEPO groups, respectively. However, 80.0% in the dapros group were responders (mean Hb during EP in the analysis range [10–11.5 g/dL]) vs 63.6% in the rEPO group, with a difference of 15.6% (one-sided nominal p=0.0007 after adjustment for region). Mean monthly IV iron dose was not statistically significantly lower with dapros vs rEPO. While fewer BP elevations occurred with dapros vs rEPO (one-sided nominal p=0.0093), the overall effect of dapros on BP was similar to rEPO. In general, safety findings were comparable between treatment groups, with the incidence of treatment-emergent adverse events similar between dapros (75%) and rEPO (79%).

Conclusions: Dapros was non inferior to rEPO in Hb response and was well tolerated. Dapros administered TIW using the protocol employed in this study is a viable alternative to rEPO in prevalent HD patients with anemia of CKD.

Funding: Commercial Support - GlaxoSmithKline

PO0488

Stabilization of Hypoxia-Inducible Factors Leads to Profound Epigenetic Changes in Primary Human Tubular Cells

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Background: Pharmacological stabilization of hypoxia-inducible factors (HIFs) to induce erythropoietin expression presents a novel therapeutic approach to treat patients with renal anemia. Whereas the transcriptional activity of HIFs on chromatin composition are well studied, insights in HIF-mediated alterations at the epigenetic level remain limited. The epigenetic landscape determines cellular identity and may be shaped by environmental factors such as hypoxia via HIF. In this study, we aim at generating a genome-wide atlas of the tubule-specific chromatin landscape while investigating the epigenetic plasticity of regulatory DNA elements provoked by HIF stabilization.

Methods: Primary tubular cells (PTC) were isolated from tumor nephrectomy specimens. We performed unbiased analyses of chromatin structure and HIF DNA-interactions using the Assay for Transposase Accessible Chromatin followed by sequencing (ATAC-Seq) and Chromatin Immunoprecipitation DNA-Sequencing (ChIP-seq), respectively. These epigenetic data sets were complemented with transcriptome information gained by RNA sequencing.

Results: ATAC-seq data generated in PTC obtained from four different individuals were combined to create a genome-wide landscape of chromatin accessibility comprising approx. 110,000 consensus regions. We validated cellular identity by benchmarking these sites against publicly available epigenomic data sets provided by ENCODE. Further characterization of chromatin activity was achieved by integration of ChIP-seq data for the histone marks H3K27ac. Pharmacological stabilization of HIF resulted in a remarkable change of chromatin accessibility yielding several hundred differentially open regions. Alterations of the chromatin coincided with HIF-binding events and HIF-mediated changes in mRNA expression suggesting a functional role for HIF in shaping chromatin accessibility in renal tubular cells.

Conclusions: Our genome-wide atlas of chromatin accessibility and activity in primary tubular cells represents a valuable reference data set for the investigation of tubule-specific features. Furthermore, our comprehensive approach allows for in-depth analyses of favourable as well as adverse epigenetic effects of HIF stabilizers in human tubular cells.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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PO0490

Triferic (Ferric Pyrophosphate Citrate, FPC) Maintains Hemoglobin and Reduces Total IV Iron Requirement: Results from a Mid-Sized Dialysis Organization (MDO) Pilot Observational Analysis

Samuel L. Shull, Marc L. Hoffman. Rockwell Medical Inc, Wixom, MI.

Background: Triferic is approved as an iron (Fe) replacement product to maintain hemoglobin (Hb) in adults (pts) receiving chronic hemodialysis (HD). Randomized clinical trial data have demonstrated that FPC maintains Fe stores and Hb while reducing IV Fe usage with a safety profile similar to placebo. We now report the first 8 mos of an independent MDO’s experience using FPC for all HD patients (pts) during a pilot implementation at 14 clinics.

Methods: FPC was added to centrally delivered liquid bicarb to provide 110 µg Fe/L dialysate. All patients received FPC at each HD. Anonymized prospective data were provided between Sep 2020—Apr 2021. Clinics added FPC into their anaemia mgmt. practices per existing protocols and standards of care (SoC). Supplemental IV Fe, up to a max of 1000 mg Fe/mth, was administered according to a protocol based on serum ferritin and TSAT values. At baseline, the av. utilization of IV Fe was 197 mg/pt/mo. During the first 3 mos of FPC, clinics saw a modest 23% reduction of IV Fe (151 mg/pt/mo). A new Fe mgmt. protocol was released specifically designed to guide IV Fe use in conjunction with FPC; this was adopted by 9 clinics while 5 clinics chose to maintain their SoC.

Results: Within 3 mos of initiation of the new protocol, Fe utilization in this group decreased by 81%, conversely Fe utilization increased by 19% in the SoC group. During this period, Hb remained stable in both groups (~0.2 g/dL from baseline). Concurrent with these changes Mircera® (epoetin beta) dose remained stable in the SoC group but was reduced 37% (from post-adoption baseline) in the new group.

Conclusions: Additional clinics continued to adopt the new protocol over time. Taking into account the staggered adoption of the protocol, after 8 mos, the aggregate Fe utilization across all 14 clinics was reduced by 51% and trending lower. Mircera dose was stable (decreased 5%) and Hb remains stable. This observational study demonstrates that FPC is a well tolerated replacement for IV Fe when administered to all patients in a HD unit. The findings of this real-world observational study align with pivotal clinical trials and previously reported real-world evidence in terms of reduction of IV Fe use and maintenance of Hb.

Funding: Commercial Support - Rockwell Medical

PO0491

Automated Tubular Morphometric Analysis in Kidney Biopsies

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Background: Tubular atrophy is prevalent in kidney disease. We automated tubular morphometric analysis and applied it to diabetic nephropathy (DN) and transplant biopsies.

Methods: Tubules (n = 302696) were segmented with a convolutional panoptic network (Fig. 1) from 57 native DN and 30 transplant surveillance renal biopsies. Distributions of digitally quantitated tubular diameter and basement membrane (TBM) were evaluated with respect to chronic kidney disease (CKD) stage and interstitial fibrosis and tubular atrophy (IFTA) severity.

Results: The trends in Fig. 2 show that generally, as CKD and IFTA increase, tubular diameter decreases and TBM average width increases, with the DN trend being more prominent. However, significant distribution heterogeneity is observed.

Conclusions: High-throughput computation can be leveraged to automate morphometric analysis of tubules. Further data mining using a similar approach may reveal novel features that may have diagnostic or prognostic benefit.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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Conclusions: We have shown the potential of our pipeline for image curation, and segmentation and sub-characterization of renal histologic primitives.

Funding: NIDDK Support

Results: At a total pump flow rate of 45.3 μL/min, 17.7 μL/min (± 5.08 μL/min) existed for the CMP, and 27.6 μL/min (± 7.3 μL/min) recirculated in the bloodstream. In the MPS, average daily filtrate output was 0.016 mL/min, filtration of FITC-HSA in the MPS was over 90%, and glucose output in the filtrate supported PCT reabsorption. Confocal images displayed cell type-specific protein expression.

Conclusions: Filtering of HSA, glucose reabsorption, and marker expression in the MPS indicates a physiological representation of renal filtration and reabsorption in a human glomerulus and PCT. Our glomerulus and PCT MPS is a relevant preclinical tool for testing drug candidates for kidney toxicity.

PO0494

Renal Proximal Tubule Chip (RPTC) for Disease Modeling and Drug Toxicity Testing

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Background: Tissue chips are an emerging technology in disease modeling and screening therapeutics to address discrepancies between animal models and human clinical trials. They utilize tissue engineering, fluid mechanics, and biomaterials to replicate in vivo architectures and functions of complex organs and tissues. For the renal proximal tubule (PT), there are currently limited options in terms of human cell types, scalable platforms for evaluation of drug toxicity, and tissue engineered solutions where the complexity of the PT is accurately modeled.

Methods: We developed both 2D and 3D versions of the RPTC which incorporates immortalized human renal PT epithelial cells (hRPTEC-TERT1) under static and perfused conditions (i.e. physiological pressure, shear stress, and stretch). Additionally, we have begun generating peritubular vascular networks using a co-culture of human umbilical vascular endothelial cells (HUVECs) and human dermal fibroblasts (hDFs) in gelatin methacryloyl (GelMA). These models were then used to investigate the effect of pressure and flow on nephrotoxicity by introducing drugs with known levels of toxicity. Our initial evaluations have been limited to non-invasive measurements such as transepithelial electrical resistance (TEER) and pro-inflammatory soluble factors, and ICC.

Results: Compared to static controls, hRPTEC-TERT1 subjected to fluid shear demonstrate that culture under physiologically relevant forces results in cytoskeletal reorganization, establishment of barrier function (adherens and tight junctions) and increased expression of transporters like aquaporin 1 and mechanosensors like α-tubulin. Additionally, noninvasive readouts such as TEER indicate the greater integrity of the renal proximal epithelium. Lastly, after 7 days, we can form dense microvascular networks to mimic the surrounding peritubular capillary networks which can actively reabsorb solutes from the glomerular filtrate. This network will enable us to test drugs in an environment where both reabsorption and secretion functions of the tubule are replicated.

Conclusions: These results provide preliminary evidence of our ability to subject hRPTEC-TERT1 to in vivo like flow conditions and demonstrate that replication of biomechanical cues from fluid shear significantly enhance the formation of an in vivo–like phenotype which enhances the relevance of our in vitro models.

Funding: NIDDK Support

PO0495

Modeling Ischemia-Reperfusion in a High-Throughput Tubular/ Microvascular Co-Culture-on-a-Chip

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Background: Ischemia-reperfusion (IR) is a major cause of acute kidney injury (AKI). IR involves a period of inadequate perfusion that deprives highly metabolic kidney epithelia of nutrient and waste exchange impacting tissue structural integrity.

Methods: We demonstrate the potential of the PREDICT96 (P96) platform as a tool for examining tubule cell responses to IR. The oxygen-impermeable construction and robust pumping capabilities of P96 enable comparison of simulated IR and control conditions on a single culture plate. Here, primary human renal proximal tubule epithelial cells and human microvascular endothelial cells were cultured in adjacent microfluidic channels for 5 days under physiological fluid shear (0.07 Pa) to establish confluent layers. Subsequently, a portion of the tissue replicates underwent simulated IR consisting of 3 days of static conditions followed by 2 days of physiological flow. Transepithelial electrical resistance (TEER) was measured daily, and all tissues were fixed after 10 days in culture for structural characterization via immunofluorescence confocal microscopy.

Results: TEER measurements highlighted a transient increase in barrier function (concurrent control tissues) in response to the onset of ischemia, followed by a reduction in integrity over subsequent days that persisted through reperfusion. IR tissues exhibited primary cilia that were on average less abundant but roughly double the length of those exhibited by control tissues. This is consistent with previous observations of cilia lengthening among IR-injured kidney epithelia in vivo. IR tissues also displayed nuclear staining for β-catenin suggestive of a proliferative response to injury.

Conclusions: The described model has significant potential to clarify mechanisms of IR injury in the kidney.

Funding: Other U.S. Government Support

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Underline represents presenting author.
Niacin Supplementation Increases In Vitro Apicobasal Volume Transport and Oxygen Consumption by Proximal Tubule Cells

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Background: Renal tubule cells are energetically demanding as they consume ATP to transport salt and water within the kidney. In vitro, renal tubule cells have an attenuated glycolytic phenotype described as cell culture stress. We hypothesized that Krebs cycle intermediates might be rate-limiting for tubule cell function. The significant increase in oxygen consumption with addition of supplemental niacin supports the hypothesis that Krebs cycle intermediates might be rate-limiting for ATP-dependent transport. We tested the influence of supplemental niacin as a source for NAD+/NADH on mitochondrial oxygen consumption.

Methods: Primary human renal tubule epithelial cells (HREC) were seeded on polystyrene tissue culture plates and cultured with normal (2 mg/L) or high niacin (4 mg/L). After two weeks of treatment, cell oxygen consumption (OCR) and extracellular acidification rates (ECAR) were assessed using a Seahorse XF96 analyzer. Respiratory inhibitors oligomycin (2 µM), CCCP (5 µM), rotenone (0.5 µM), antimycin A (0.5 µM) and 2-deoxyglucose (2-DG, 50 mM), and glucose (10 mM) were used to probe mitochondrial and non-mitochondrial respiration. Statistical differences between control and experimental groups were estimated by two-tailed Student’s t-test. Results are considered significant at p<0.05. Cells from the same lot were seeded on permeable supports and cultured with an inhibitor of TGF-b receptor 1 and low or high niacin concentrations. Apicobasal volume transport was measured gravimetrically.

Results: High-dose niacin was associated with increased oxygen consumption compared with normal dose niacin (225 vs 157 µmol/min, p < 0.01), and with increased transport (187 +/- 83 vs 87 +/- 2.8 µL/cm²/day; p < 0.0004).

Conclusions: Our observation that mitochondrial oxygen consumption increased with addition of supplemental niacin supports the hypothesis that Krebs cycle intermediates may be rate-limiting in tubule cell function. The significant increase in apicobasal transport with added niacin suggest that some of the dysfunctional phenotype induced by cell culture stress may be mitigated by nutritional supplementation.

Funding: Private Foundation Support

Microenvironmental Influences on 3D Embedded and Bioprinted Induced Renal Tubular Epithelial Cells (iRECs)

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Background: Conventional cellular models of renal tubular origin only partially maintain their functional properties. Recent advances in 3D culture techniques and bioprinting technology promise to improve physiological conditions by reconstituting the tissue architecture in vitro. We previously described that direct reprogramming with a defined lentiviral cocktail of four transcription factors (Hnf1b, Hnf4a, Pax8, Emx2) can convert fibroblasts to induced renal tubular epithelial cells (iRECs). We analyzed how the microenvironment influences behavior, expression profile and the cellular function of iRECs to determine their utility for bioprinting applications.

Methods: iRECs were subjected to manual pipetting and inkjet bioprinting methods, embedded in three ECM-like microenvironments (Matrigel, Fibrin and Collagen I), and two culture media (DMEM and REGM). Morphology and viability of multicellular structures were assessed at several time points after seeding. Moreover, RNA-Seq was carried out to describe differentially regulated genes, and their protein products analyzed via immunofluorescence.

Results: iRECs showed high viability and biocompatibility with dispensing methods and biomixes. However, the morphology of multicellular aggregates was dramatically influenced by the microenvironment (e.g. they formed smaller spherical aggregates in Matrigel, but elongated tubule-like structures in Collagen I). Transcriptomic analysis revealed differentially expressed signature genes in each of the used biomaterials. For example, expression of apical endocytic machinery components was elevated in Matrigel embedded cells. In contrast, transcripts of ECM components showed strongest expression in the Fibrin condition. In addition, the tubule segment identity of iRECs was altered by the microenvironment. Microdispensing (drop on demand) bioprinting achieved perfusible tubule-like structures.

Conclusions: The design of specific tubule microenvironments for reprogrammed kidney tubule cells can be tailored to better reflect physiological conditions and to the desired purpose of in vitro applications. This will facilitate the use of appropriate biomaterials to optimize the construction of mimetic kidney tubule models at scale.

Funding: Government Support - Non-U.S.
Tunable Stiffness Hydrogels for Renal Cell Tissue Culture

Background: Tunable stiffness polyacrylamide (PA) based hydrogels have been utilized for tissue engineering studies. PA gels require functionalization for cell attachment. Reagents such as sulfo-SANPAH or acrylic acid NHS ester are often used to attach protein to the gel surface. However, these methods do not provide adequate binding to maintain cell attachment for studies involving fluid shear stress or long-term culture. In order to produce PA gels with uniform surfaces and robust cell attachment, we tested gels incorporating N-(3-Aminopropyl) methacrylamide (APMA) to create a positively charged polyelectrolyte-like biocompatible surface.

Methods: APMA was substituted in varying amounts in PA mixes previously reported to produce gels with expected stiffnesses of 2.6 kPa or 40 kPa. Gels were produced by free radical polymerization under nitrogen, using TEMED (1:300) and 10% ammonium persulfate (1:100). Gels were cast on glass coverslips soaked overnight in 2M NaOH, dried and treated with a 5% solution of 3-aminopropyltrimethoxysilane in isopropanol, then 1% glutaraldehyde. Gels were sterilized with 70% ethanol for 30 minutes, and then placed in sterile PBS. Different amounts of APMA were tested using primary human renal tubule cells (Lonza). The elastic modulus of the modified gels was measured using an Electroforce 3100 mechanical analyzer.

Results: Cells attached rapidly to gels in standard medium with 10-20% APMA substitution at both stiffness levels, and maintained excellent attachment for at least 6 weeks, under both static and shaking conditions. Cells proliferated on gels until confluent. Higher APMA amounts were less effective with softer gels. Cells initially attached to 5% APMA gels, but detached after 2-3 days. The addition of APMA decreased the stiffness of the softer gels by ~25%, while it increased by ~25% for the harder gels.

Conclusions: Primary human renal tubule cells were found to attach rapidly and remain attached to polyacrylamide hydrogels containing 10-20% APMA. Cells proliferated well on APMA based gels, and remained attached for at least 6 weeks, even under fluid shear stress (~2 dyn/cm2). We conclude that the addition of APMA to PA gels provides a very simple and reproducible method of functionalizing PA gels for renal cell attachment, and allows for the testing of soft, tissue-like substrates under physiological fluid flow conditions.

Funding: Private Foundation Support

PO0499
Tunable Stiffness Amino Functionalized Polyacrylamide-Based Hydrogels for Renal Cell Tissue Culture

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Background: Tunable stiffness polyacrylamide (PA) based hydrogels have been utilized for tissue engineering studies. PA gels require functionalization for cell attachment. Reagents such as sulfo-SANPAH or acrylic acid NHS ester are often used to attach protein to the gel surface. However, these methods do not provide adequate binding to maintain cell attachment for studies involving fluid shear stress or long-term culture. In order to produce PA gels with uniform surfaces and robust cell attachment, we tested gels incorporating N-(3-Aminopropyl) methacrylamide (APMA) to create a positively charged polyelectrolyte-like biocompatible surface.

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Funding: Private Foundation Support

PO0500
Canonical TGF-β Signaling Mediates Renal Tubule Epithelial Cell Differentiation In Vitro

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Background: Transforming growth factor-β (TGFβ) initiates multiple signaling pathways involved in the regulation of epithelial cell fate and cell plasticity. Here we identify canonical TGFβ signaling as a critical regulator of renal tubule epithelial cell membrane transporter expression in vitro.

Methods: Primary human renal tubule epithelial cells (HREC) were cultured on permeable supports on an orbital shaker. After two weeks in culture, cells were supplemented with TGFβ receptor I (TβRI) inhibitors SB431542 or A8301, Smad3 inhibitor SIS3, PI3K inhibitor LY294002, Rapamycin, p38 MAPK inhibitor SB203580, TAK1 inhibitor (2nM), Trametinib. After four weeks, apicobasal fluid transport and gene expression by RT-PCR was measured. Statistical differences were estimated by two-tailed Student’s t-test in MatLab.

Results: Canonical TGFβ inhibitors SB431542 and A8301 increase apicobasal fluid transport, while Smad3 inhibitor SIS3 does not. Non-canonical TGFβ inhibitors LY294002, Rapamycin, SB203580, TAK1 inhibitor (2nM), Trametinib do not increase apicobasal fluid transport. SB431542 and A8301 suppress Snail1 transcription, while SIS3 does not. SB431542 and A8301 increase AQ2P2 transcription, while SIS3 does not, and have a greater effect on NHE3 transcription.

Conclusions: Increased inhibitable transport by renal tubule cells in vitro appears to be mediated by canonical TGFβ signaling. The lack of response to SIS3 suggests that Smad2, rather than Smad3, is responsible.

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PO0501
TGF-β Mediates In Vitro Renal Tubule Cell Fatty Acid Oxidation
Kuniko Hunter, 1 Rachel C. Evans, 2 Harold D. Love, 3 H. David Humes, 4 Shuvo Roy, 5 William H. Fissell, 6 The Kidney Project 7Vanderbilt University, Nashville, TN; 8Vanderbilt University Medical Center, Nashville, TN; 9University of California San Francisco, San Francisco, CA; 10University of Michigan, Ann Arbor, MI.

Background: Renal tubule cells (HREC) are energetically demanding due to their role in transporting solutes, but undergo a shift toward glycolysis and away from oxidative phosphorylation of fatty acids in vitro. We identified Transforming Growth Factor-β (TGFβ) as a critical modulator of HREC differentiation. Here, we find that TGFβ inhibition increases HREC fatty acid oxidation.

Methods: Primary HREC were seeded on polycarbonate Transwells or polystyrene Seahorse XFe96 tissue culture plates. Cells were supplemented with AMPK activator metformin, TGFβ receptor I inhibitor SB431542, or a combination of both. After four weeks, cell oxygen consumption (OCR) and extracellular acidification rates (ECAR) were assessed using a Seahorse XFe96. Glutamine oxidation inhibitor BPTES, fatty acid oxidation inhibitor etomoxir, and glucose oxidation inhibitor UK5099 were used to probe HREC substrate utilization. Gene expression was measured using RT-PCR. Statistical differences were estimated by two-tailed Student’s t-test. Results are considered significant at p<0.05.

Results: MET and SB43 increase transcriptome of electron transport chain Complexes I, II, IV, and V. Control and MET OCR did not respond to inhibitors. MET changes have diminished basal OCR and decreased ECAR in response to BPTES. SB43 increases basal OCR and cellular responses to UK5099 and etomoxir, implying increased glucose and fatty acid oxidation. SB43 increases transcription of fatty acid transporter CD36 and fatty acid oxidation genes FABP1, CPT1, and CPT2.

Conclusions: Inhibition of TGFβ increases in vitro transcription of mitochondrial genes and oxidative phosphorylation of fatty acids by HREC.

Funding: Private Foundation Support

PO0502
Investigating the Use of Smartwatch-Based Self-Assessments to Monitor Fluid Consumption of Hemodialysis Patients
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Background: Fluid intake control is a bedrock component of treatment for End Stage Kidney (ESKD) Patients, but continues to be a major challenge for patients, healthcare providers, and organizations. The ramifications of poor fluid control include increased mortality and morbidity, frequent hospitalizations and increased total cost of care. The goal of this work is to investigate the feasibility of leveraging self-assessments based on smartwatches to monitor fluid consumption of ESKD patients.

Methods: ESKD patients on hemodialysis (n=11) were given an Android smartwatch with an in-house developed app pre-installed (Fuisense, available on Android play store). Patients were asked to log their fluid intake through the app by choosing from a list of predefined volumes each time they consume any liquid. The app computed and displayed the self-reported daily volume intake to help patients monitor their own fluid consumption (Figure 1-A). Patients received text messages twice a day (9am and 8pm) to remind them to use the watch. We also recorded patients’ weights before and after each of the three weekly dialysis sessions. The sum of self-reported interdialytic fluid intake was computed and compared against the interdialytic weight gain recorded in the clinic.

Metformin and SB431542 modulate substrate oxidation A-D. RNA expression of NDUF8, mt-Cyb, mt-CO2, and mt-ATP6. Data are mean ± SEM (n=4). E-G. OCR and H-J. ECAR of substrate inhibition assays. Data are mean ± SD (n=5). K-N. RNA expression of CD36, FABP1, CPT1/2. *p<0.05, **p<0.01, ***p<0.001.

Results: Patients recorded fluids in 214 days out of 259 total days (i.e., 83% compliance rate). The average self-reported interdialytic fluid consumption is 51 oz +/- 64, and the average interdialytic weight gain is 2.67 kg +/- 1.56. We found a moderate but significant correlation between the self-reported fluid volumes and the interdialytic weight gain (r=0.363, P<0.001, r2=0.06).

Conclusions: Leveraging smartwatches for the self-assessment of fluid intake is a promising solution for fluid monitoring of ESKD patients. This can be related to the ease of utilization of this technology and the ecological validity of its measurements given they are collected close to when they happen, reducing recall biases. In the future, we will leverage low-burden sensor data to monitor patients’ fluid intake continuously and unobtrusively.

PO0503
Heterogeneous Local Hemodynamics in Rat Arteriovenous Fistula with Sildenafil Treatment
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Background: Arteriovenous fistula (AVF) maturation failure is an unmet clinical need. Aberrant blood flow is thought to impair AVF remodeling, but previous literature has largely focused on hemodynamics averaged over the entire AVF. We hypothesize that hemodynamics is not uniform and thus any treatment’s effect size is not uniform in AVF. We used the PDE5A inhibitor sildenafil and performed MRI-based computational fluid dynamics (CFD) to test our hypotheses.

Methods: Femoral AVFs were created in young male Sprague-Dawley rats. Sildenafil was given daily starting at 14 days before AVF creation and continuing for 21 days, at which time rats underwent MRI. MRI scans were used for measuring cross-sectional lumen area (CSA), and for CFD to derived flow rate, wall shear stress (WSS), oscillatory shear index (OSI), and vorticity. Results were split into 4 zones: 0-5, 5-10, 10-15, and 15-20mm away from the anastomosis.

Results: Sildenafil treated rats had significantly larger CSA, flow rate, WSS, OSI and vorticity than control rats in all zones (p<0.05)(Fig. 1). In both groups: (1) While flow rate remains constant in all zones, CSA increased from 0-5 to 15-20 zone. (2) Velocity, WSS and vorticity were the highest in the 0-5 zone, and each parameter drops significantly thereafter. (3) OSI increases at the 5-10 zone and then decreases gradually.

Conclusions: Sildenafil increased CSA and hemodynamics parameters in AVF. The magnitudes of increases are heterogeneous along the AVF. Thus, the effect size of sildenafil on AVF remodeling and the association between hemodynamics and AVF remodeling depends on location. Increased knowledge of local hemodynamics and effect size may lead to treatments to improve AVF maturation.

Funding: NIDDK Support, Other NIH Support - NHLBI, Veterans Affairs Support
PO0504

Effects of Smoothing Methods on Hemodynamic Assessment of a Human Arteriovenous Graft
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Background: Aberrant hemodynamics contribute to the formation of neointimal hyperplasia in arteriovenous grafts (AVG) for hemodialysis, but the detailed hemodynamic environment in an AVG is unclear. Computational fluid dynamics (CFD), while a useful tool for hemodynamic analysis, is influenced by lumen geometry. 3D vascular lumens reconstructed from medical images must be smoothed to remove surface deformities and improve their uniformity before being used in CFD. We investigated whether different smoothing methods may cause different hemodynamic analysis results.

Methods: MRI scans were performed on a dialysis patient’s AVG and then used to reconstruct a 3D AVG lumen, on which four smoothing methods were applied that vary in their uses of interpolation, unconstrained smoothing, and additional surface smoothing (Fig 1A, B). The four smoothed lumens were used in the same CFD protocol to calculate velocity, wall shear stress (WSS), and oscillatory shear index (OSI). Results from different methods were compared using standard deviation (SD) and relative standard deviation (RSD = SD/mean x 100%) (Fig 1C).

Results: All methods give similar AVG lumen areas (RSD<3%). Although velocity has RSDs of 6-9%, their SDs are <0.1 m/s, and thus the differences are not considered biologically significant. Along the same line, all methods do not give biologically significant differences in OSI, as the SDs are <0.01. However, different smoothing methods give very different WSS, with RSD >12% and large SDs.

Conclusions: A variety of smoothing methods can be used to create AVG lumen reconstructions for CFD and hemodynamic analysis. These different methods can lead to significantly different WSS values. Therefore, researchers should consider the smoothing techniques used to characterize the hemodynamic environment in a AVG.

Funding: NIDDK Support, Other NIH Support - NHLBI, Veterans Affairs Support

PO0505

Transdermal Glomerular Filtration Rate Measurement in Conscious Pigs Using the Novel Fluorescent Tracer Agent Relmapirazin
Sabine Neudecker,1 Daniel Schock-Kusch,1 Jochen Friedemann,1 Marlene Jostock,1 Yury Shulhevich,1 Dzmitry Stepanou,1 Jesse Ross-Jones,1 James R. Johnson,2 Thomas E. Rogers,2 Ivan R. Riley,2 Jeng-Jong Shieh,2 Jim M. Hart,2 Richard B. Dorshow,2 1MediBeacon GmbH, Mannheim, Germany; 2MediBeacon Inc., St. Louis, MO; 3milD Diagnostics, Wendelsheim, Germany.

Background: Transdermal measurement of glomerular filtration rate (GFR) using a miniaturized fluorescence detector (“TGFR Mini Monitors”) in combination with a fluorescent exogenous GFR tracer agent is a common technique to measure kidney function in the preclinical setting, most commonly employed with rodents. However, larger animals are used in translational research on the way to human applications. The employ of an exogenous tracer agent in the preclinical setting which will also be amenable for seamless transition to human use would enhance the applicability of the preclinical data to clinical data.

Methods: The renal function of three healthy pigs (35-40 kg) was measured for 5 consecutive days. The novel fluorescent exogenous tracer agent Lumitrace™ (relmapirazin) was used in combination with two TGFR Mini Monitors per animal (MediBeacon, Germany). Excretion kinetics were measured transdermally, as well as in plasma, over the course of 4 hours. After attachment of the devices on the animal’s skin, relmapirazin was administered intravenously. Seventeen blood samples were collected to measure plasma pharmacokinetics.

Results: The slopes of the single-exponential decay of the plasma kinetics and the transdermal kinetics of relmapirazin are in agreement (Slope 0.97; R²=0.57). No statistical differences were detected using a paired t-test.

Conclusions: The collected data supports the suitability of the TGFR Mini Monitor to measure relmapirazin excretion kinetics in pigs, thus providing an important tool for translational research of GFR in larger animals.
and melanocyte markers in TSC2 against human nuclear antigen (HNA) or the human isoform of Lamin A/C (hLamin

molecular fidelity. This model can be used to study tumor mechanisms and to test new ablation.
delivery of the mTOR inhibitor rapamycin using nanocarriers, on xenograft growth and

Renal Organoid Xenografts

Angiomyolipomas In Vivo with Induced Pluripotent Stem Cell-Derived Renal Organoid Xenografts

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Background: Currently there are no animal models of renal angiomyolipoma (AML) for the study of tumor mechanisms in vivo. This is partly due to the fact that biallelic inactivation of TSC1 or TSC2 during development causes embryonic lethality, while previous attempts to ablute TSC1 or TSC2 by means of tissue-specific Cre-mediated recombination have not succeeded in recapitulating the lesions.

Methods: We induced hepatic differentiation of isogenic TSC2−/−, TSC2+/−, and TSC2−/+ human IPSCs derived from a TSC patient, under three-dimensional tissue culture conditions for 21 days. Next we transplanted the resulting renal organoids under the kidney capsule of immunodeficient RNU Nude rats. We next tested the a novel formulation for delivery of the mTOR inhibitor rapamycin using nanocarriers, on xenograft growth and ablation.

Results: Orthotopically transplanted TSC2−/− AML organografts displayed significantly higher growth rate compared to TSC2−/− or TSC2−/+ kidney organoids, at Day 14 post-transplantation. Histological analysis of organoid xenograft tissues using antibodies against human nuclear antigen (HNA) or the human isoform of Lamin A/C (hLamin A/C), revealed prominent presence of human AML-like cells expressing smooth muscle and melanocyte markers in TSC2−/− but not in TSC2−/+ or TSC2−/+ organoid xenografts, indicating that the myomelanocytic phenotype of TSC2−/− AML organografts was maintained in vivo. mTOR activation was observed in ACTA2+ PMEL+ cells of TSC2−/− AML organoid graft cells, but not in the adjacent normal rat tissue or in TSC2−/+ or TSC2−/+ organoid xenografts, indicating that metabolic activation in the absence of TSC2 was consistent with xenograft growth. The rat kidney critically provided vascularization, supporting the growth of TSC2−/− organografts, and promoting the proliferation of AML cells. In our drug testing experiments, 0.70kg rapamycin delivered orally significantly slowed TSC2−/− AML organoid xenograft growth, while local injections of low-dose rapamycin-loaded nanoparticles resulted in organoid AML cell apoptosis and xenograft abrogation after 7 days, without affecting the rat kidney.

Conclusions: These preliminary results are consistent with a maturational increase in growth/stretch-sensitive Ca2+ channels, including Piezo1, and/or associated signaling pathways, in tubules of organoid xenografts in vivo.

Funding: NIDDK Support, Other NIH Support - R56 DK122380, U2C DK126023

PO0507

Functional Maturation of Kidney Organoid Tubules: Mechanosensitive Ca2+ Signaling

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Background: When grown under static conditions, kidney organoids derived from human pluripotent stem cells exhibit glomerular- and tubular-like structures. However, development is limited (Homan et al., 2019; Takasato et al., 2015). As the technology for culturing organoids advances, siming to promote terminal differentiation, the need to better characterize their physiological function has become a priority. To begin to functionally phenotype static organoids, we focused on characterizing mechanoo-induced changes in intracellular Ca2+ concentration ([Ca2+]i) and signaling pathways in tubules isolated from maturing static organoids.

Methods: Tubular structures, microdissected from organoids between 21-57 d of culture, were microperfused in vitro or affixed to the base of a specimen chamber, and loaded with Fura-2 AM (20 µM) to measure [Ca2+]i. Digital ratio imaging was performed in individually identified cells by epifluorescence microscopy using commercial software.

Results: The average baseline [Ca2+]i in microperfused tubules was 180±13 nM (n=6). A rapid increase in [Ca2+]i was observed when tubules were subject to luminal filling, sufficient to cause circumferential stretch and turbulent flow, reaching values of 100±30 nM and 71±8 nM in organoids at 40 and 57 d of culture, respectively (n=3, p<0.002 vs. baseline). Luminal flow-induced increases in [Ca2+]i were not detected in tubules isolated from organoids <40 d in culture (n=3). Mechanosensitive Piezo1 channels contribute to the flow-induced [Ca2+]i response in the fully differentiated distal tubule (Carrizosa-Gaytan et al., EB 2019). Nonperfused organoid tubules exposed to basolateral Piezo1 activator Yoda (20 nM) exhibited increases in [Ca2+]i from 110±36 to 272±114 nM (24-31 d in culture; n=4, p<0.0001) and from 130±36 to 504±197 nM (43-67 d in culture; n=4, p=0.002).

Conclusions: These preliminary results are consistent with a maturational increase in flow/stretch-sensitive Ca2+ channels, including Piezo1, and/or associated signaling pathways, in tubules of organoid xenografts in vivo.

Funding: NIDDK Support, Other NIH Support - R56 DK122380, U2C DK126023

PO0508

Human Primary Renal Tubuloids as Tools for Pathophysiology and Nephrotoxicity Assessment

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Background: Kidney organoids derived from human induced pluripotent stem cells can be used to study pathophysiology and nephrotoxicity using human kidney tissue. We have developed an efficient alternative way to generate homogeneous epithelial-like structures from kidney tissue derived from patients.

Methods: Human primary renal tubular epithelial cell (hRTEC) cultures were generated using non-tumor cells from partially resected human kidneys for renal cancer. Primary cells were cultured on ultra-low attachment plates for several days. The cells were then transferred into media containing matrigel, hepatocyte growth factor, fibroblast growth factor-2 and 5% fetal bovine serum. Tubuloids were treated with multiple nephrotoxants. Morphological changes and KIM-1 expression were evaluated. Functional assays to characterize permeability and selective cellular absorption by tubuloids were conducted using fluorescent inulin and albumin. Co-culture experiments of tubuloids with bEnd.3 endothelial cells were performed.

Results: hRTEC tubuloids were generated based on the method above. We have generated a library of hRTECs derived from 25 patients. Tubuloids had polarized expression of cell surface markers, LTL, KIM-1 (apical) and Na-K-ATPase (basolateral). It took only a week to establish hRTEC cultures from patient kidneys and 2-4 weeks to form tubuloids from hRTECs. Cisplatin and palmitate-bound albumin altered the 3D structure of tubuloids. Treatment with aristolochic acid increased KIM-1 expression in a dose-dependent manner. Functional assays revealed that tubuloids reabsorb albumin from the apical side and release it into basolateral side, while being impermeable to inulin. Coulture of tubuloids and bEnd.3 cells resulted in formation of 3D capillary-like structure of bEnd.3 cells around tubuloids.

Conclusions: This strategy can recapitulate pathophysiology, enable nephrotoxicity screening of human kidney tissue and offers an additional approach to personalized kidney medicine.

Funding: NIDDK Support, Other NIH Support - NCATS

PO0509

Nephrotoxicity Assessment with Human Kidney Tubuloids Using Spherical Nucleic Acid-Based mRNA Nanoflares

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Background: Drug-induced nephrotoxicity represents an important cause of acute kidney injury with associated patient morbidity and mortality and is often responsible for termination of drug development, after extensive resource allocation. Current platforms for testing nephrotoxicity are limited and require disruptive end-point molecular assays. We have paired a 3D human kidney tubuloid system which phenocopies kidney proximal tubule with spherical nanoflares (NF) mRNA nanosensors to achieve facile, real-time assessment of drug nephrotoxicity.

Methods: Primary human tubuloids were generated from tubule cells isolated from patients’ kidney tissue and cultured in 3D matrigel settings using serum-free media. NF nanosensors targeting kidney mRNA, VEGF mRNA and GAPDH mRNA were assembled and used to label tubuloids through overnight incubation. KIM-1 NF signals on tubuloids were monitored over time following drug exposure through fluorescence microscopy imaging. Quantitated NF signals were compared with quantitative polymerase chain reaction (qPCR) to verify the accuracy of NF signals.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
PO0510

Physiological Replication of the Glomerulus Using a Triple Culture

Microphysiological System

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Background: The glomerulus is a complex structure highly adapted for its function. A true representation of the in vivo cell-cell/ECM interactions, which provide the semi-permeable filtration barrier, is essential to interrogate physiological and pathophysiological processes and for understanding the impact of novel therapies.

Methods: We have developed a human microphysiological system with high fidelity to glomerular physiology and structure. For the first time the three resident cell types (glomerular epithelial cells (GECs), induced pluripotent stem cell (iPSC)-derived podocytes and mesangial cells (MCs)) reside in a relevant 3D structure under flow conditions. Analysis was performed on the individual cell types using both transcriptomics (NGS) and high content imaging to shed light on the impact of each cell type on its neighbors. Insulin and albumin permeability assays (fluorescent) were performed to evaluate the integrity of the glomerular barrier.

Results: Transcriptomic analyses demonstrated crosstalk between cells in our microfluidic tri-culture system. An influence of MCs was observed on both podocytes and GECs. For GECs, MCs increased tight junction proteins (CLDN7) and for podocytes there was a reduction of cell cycle control (WDHD1). The differentiation of podocytes in the chip was able to regulate matrix and cell adhesion in MC (COLA63, ITGA2) and influence angiogenic signals in GEC (KDR, THBS1). Analysis of pathways expressed in cells in the less complex co-culture showed that they displayed transcriptomic signals akin to human disease phenotypes (comparison with signatures found in Nephrospec). Imaging showed increases in maturation markers such as synaptopodin in podocytes in triculture. Permeability assays revealed that as cell maturity increased barrier function improved and the passage of molecules was selectively hindered.

Conclusions: Our tri-culture model provides a highly physiologically relevant tool to study healthy glomerular function. This will enable improved understanding of the mechanisms underlying glomerulopathies and improved qualification of new therapies.

Funding: Commercial Support - AstraZeneca

PO0511

Biomimetic Platform for Quantitative Drug Screening of Podocyte Cytoskeletal Dynamics and Morphology

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Background: Foot process effacement is driven by dysregulation of cytoskeletal dynamics. Currently, there are no drugs that primarily target the podocyte cytoskeleton due to dearth of in vitro model systems. To address this limitation, we designed a 3D drug discovery platform with a morpho-mimetic milieu that allows high-throughput quantitative measurements of drug-induced cytoskeletal changes in podocytes.

Methods: Immortalized human podocytes were differentiated on micropatterned surfaces fabricated via photolithography. High-resolution microscopy including confocal, TIRF, SEM and atomic force microscopy (AFM) were used to characterize morphometric and biochemical properties. Protein expression was quantified using automated immunofluorescence, cell proliferation via EdU, and basal motility via fluorescent live-cell imaging. High-throughput analytical capabilities of the system were tested with cytoskeletal dose response to puromycin aminonucleoside (PAN).

Results: Cells cultured in 3D micropatterns for up to 14 days show a significant reduction in morphometric variability compared to unpatterned controls. During differentiation, micropatterned podocytes achieve cell cycle arrest faster and more robustly with reduced motility. Furthermore, the increased speed and the extent of cell cycle arrest is also observed in low serum, suggesting that the effects of morpho-mimetic culture are independent from biochemical stimuli. AFM elastography shows primarily a peripheral distribution of stiff actin fibers in micropatterned podocytes, mimicking

in situ conditions. A cohesive cytoskeletal dose response was observed against PAN in the micropatterned cells only.

Conclusions: 3D micropatterns increase the speed and efficiency of podocyte differentiation while reducing cell-to-cell variability by up to 5-fold. Through its increased reproducibility, our automated system allows for quantitative in vitro study of podocyte morphology, cytoskeleton and biomechanics in response to drugs and pathogens with high fidelity and reproducibility.

Funding: NIDDK Support, Other U.S. Government Support

PO0512

Monitoring Mitochondrial Dynamics Within a Kidney-on-Chip Platform for Investigating Disease Progression and Potential Therapeutics

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Background: The kidneys rely on an abundant number of mitochondria to produce energy to drive key functions, such as fluid/electrolyte balance. Mitochondrial dysfunction has been linked to the progression of renal diseases including acute kidney injury and diabetic nephropathy. Thus, the mitochondria are a key target for therapeutic development. Kidney-on-chip platforms provide a dynamic in vitro-like tissue culture environment to investigate renal pathophysiology. Yet, it is difficult or impossible to investigate mitochondrial dynamics due to lack of real-time measurements. Here, we present a sensor integrated kidney-on-chip platform with real-time cell oxygen consumption rate (OCR) readouts for monitoring the dynamics of mitochondrial function.

Methods: Human primary renal proximal tubule epithelial cells (hRPTEC) were cultured in PREDICT96 (P96), a high-throughput organ-on-chip platform. Integrated optical-based oxygen sensors enabled measurement of dissolved oxygen. Flow was turned off to measure decreases in oxygen and compute OCR. hRPTEC were treated with mitochondrial inhibitors Oligomycin and Antimycin A and un-coupler FCCP. OCR was measured prior to and following the drug treatments.

Results: hRPTEC basal OCR was monitored under flow at 70 µL/min over a 10 day culture period. OCR decreased by 58% and 39% following treatment with Antimycin A and Oligomycin, respectively, and increased 64% following treatment with FCCP (Fig.1). Conclusions: We demonstrated real-time and label-free monitoring of drug-induced shifts in mitochondrial respiration within a high-throughput kidney-on-chip platform. Our work enables new investigations into mitochondrial dynamics in response to nephrotic agents or disease progression, as well as potential therapeutics that target the mitochondria.

Funding: Other U.S. Government Support
PO0513
Demonstrating Preclinical Proof of Concept of an Implantable Bioartificial Kidney (iBAK)
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Background: An implantable bioartificial kidney (iBAK) would provide continuous and convenient treatment while overcoming the challenges of dialysis and renal transplant. We previously demonstrated small-scale experimental versions of an immunoprotective renal tubule cell-containing bioreactor and a pumpless hemofilter utilizing biomimetic silicon nanofiber membranes (SNM). Here we report the successful integration of bioreactor and hemofilter components into an iBAK prototype that demonstrated operational feasibility in swine.

Methods: Designs of the bioreactor and hemofilter were optimized using computational fluid dynamics. Porcine renal (LL-CPK1) cells were cultured on collagen-coated Transwell® (Corning) membranes and inserted into the bioreactor. A hemofilter containing SNM with ~10 nm-wide pores was connected to the bioreactor in series through the hemofilter blood outlet and bioreactor blood inlet. The iBAK was implanted into a healthy Yucatan mini-pig, with anastomoses from the hemofilter blood inlet and bioreactor blood outlet to the iliac artery and vein, respectively, and the bioreactor ultrafilter outlet connected to the bladder. The pig did not receive systemic anticoagulation or immunosuppression. After 3 days, patency was assessed via angiogram and the device was explanted for further analysis. Cell viability was assessed using a LIVE/DEAD™ Cell Viability Assay (Invitrogen).

Results: The iBAK was successfully assembled and implanted with no procedural complications. Post-operatively the pig did not demonstrate signs of sepsis/renal failure, thromboembolism, infection, or other adverse reactions. 3 days after implantation, the device was patent. Ultrafiltrate was noted at both implant and explant, with a flow rate of 0.28 L/min measured at explant. Cells demonstrated ~80% viablility, relative to in vitro controls. No gross thrombi or protein films were observed on the SNM.

Conclusions: We successfully integrated hemofilter and bioreactor components to create a small-scale iBAK. The hemofilter generated ultrafiltrate from blood while the bioreactor sustained renal cells and delivered ultrafiltrate (“urine”) to the bladder. This feasibility study will guide future development of a clinical-scale iBAK.

Funding: Other NIH Support - NIBIB Quantum Grant, Private Foundation Support

PO0514
A 20-lb Portable Continuous Renal Replacement Therapy (PCRRT) Machine Battery Operated Using 300 mL Fluid: CRRT Anywhere, Anytime
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Background: CRRT is challenging due to needing large amounts of sterile fluids excessive labor and cost. Prescribed treatment is frequently interrupted when patients are transported out of the ICU, or during ambulance or helicopter transportation. This machine, weighs 20 pounds, is battery powered and uses 300 ml of sterile fluid. The size and weight, and sterile fluid requirements allow uninterrupted use in ICU, on a stretcher, during ambulance or aircraft transportation.

Methods: The machine connects to a central venous catheter and blood is heparinized during ambulance or aircraft transportation. 300 ml of sterile 0.45 N is circulated into the dialysate compartment of the dialyzer, and blood is circulated through sorbents that regenerate the dialysate allowing for the use of only 300 ml of fluid instead of 30 liters, or more, of sterile fluid. Spent dialysate coming out of dialyzers is recirculated through sorbents that regenerate the dialysate allowing for the use of only 300 ml of fluid instead of 30 liters, or more, of sterile fluid. Spent dialysate coming out of dialyzers during treatment of renal failure patients and with added urea, creatinine and lactacid were circulated through the sorbent canisters. Lactate, urea, creatinine, and electrolytes were measured in the dialysate after recirculating through the sorbents.

Conclusions: Less sterile fluid and less nursing labor, make it cost-effective. Current machines weigh more than 100 pounds, and have a large footprint, making it impossible to use them outside the ICU, or during ambulance or helicopter transportation. This machine, weighs 20 pounds, is battery powered and uses 300 ml of sterile fluid. The size and weight, and sterile fluid requirements allow uninterrupted use in ICU, on a stretcher, during ambulance or aircraft transportation.

Funding: Other U.S. Government Support, Commercial Support - Wearable Artificial Organs Inc

PO0515
High Sodium Reduced the Expression of PTH1R and Klotho by Inhibiting 1,25(OH)2D3 Synthesis
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Background: The proximal tubule is not only the sensing site of sodium and phosphorus, but also the main place for the synthesis and metabolism of 1,25(OH)2D3. Sodium may share the sensing mechanism with phosphate in proximal tubule epithelial cells, whether sodium cooperates with phosphate, or it plays an independent role in the regulation of phosphorus homeostasis remains unknown. In this in vitro study, we were to investigate the effects of high sodium on the synthesis and function of active vitamin D and local phosphorus regulation in proximal tubular epithelial cells.

Methods: Human proximal tubule epithelial (HK-2) cells were treated with different concentrations of sodium/phosphorus. The expressions of 1α-OHase (Cyp27b1) and 24-OHase (Cyp24a1) were determined by RT-PCR and Western Blot respectively. LC/MS and ELISA was used to detect the levels of 1,25(OH)2D3. Intracellular Ca2+ ((Ca2+)) was detected with the Ca2+ indicator dye Fura-4. Chromatin samples were immunoprecipitated with antibodies against PTH1R and Klotho.

Results: High sodium decreased the expression of 1,25(OH)2D3 by reducing 1α-OHase and 24-OHase in HK-2 cells. Sodium phosphorus transporter inhibitor (PFA) and sodium hydrogen transporter inhibitor (Caliporide) increased the expression of 1α-OHase and 24-OHase, while ouabain decreased their expressions. High sodium intervention increased intracellular calcium concentration, and chelating extracellular calcium reversed high sodium induced 1α-OHase and 24-OHase expression. High sodium reduced the expression of PTH1R and klotho, combined use of PFA and Caliporide significantly increased the gene and protein expressions of PTH1R and klotho, while ouabain intervention further decreased their levels. Vitamin D receptor agonists significantly increased the recruitment of VDR to the VDRE of PTH1R and klotho promoter, thus increased the expression of PTH1R and klotho.

Conclusions: High extracellular sodium can not only lead to a decrease in the synthesis of active vitamin D in the proximal tubules, but also affect the gene regulation of 1,25(OH)2D3. Sodium phosphate interaction increased 24-OHase expression and decreased PTH1R expression, which may explain the disturbance of phosphorus metabolism and vitamin D metabolism in kidney.

PO0516
Enhancement of In Vitro hPTH1-84 Bioactivity by hPTH38-84 and hPTH45-84
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Background: Recent research using high resolution mass spectrometry demonstrates that serum concentrations of full-length parathyroid hormone (hPTH1-84) and its fragments (hPTH28-84, 34-77, 34-84, 37-37, 37-84, 37-38, 38-38, and 45-84) are increased significantly in CKD patients with an eGFR of ≤17-23 mL/min/1.73m2 (Krintemtapak et al. Clin Chem. 2021 Mar 6;67(3):10.1093/clinchem/hva013). Online ahead of print.PMID: 33693557). Information about the bioactivity of these newly discovered hPTH fragments is lacking.

Methods: Recombinant hPTH1-84 was synthesized in Escherichia coli and purified by immobilized metal-ion affinity chromatography. hPTH1-84, hPTH38-84, and hPTH45-84 were synthesized by solid phase peptide synthesis. The identity of hPTH1-84 and hPTH45-84 fragments was confirmed by mass spectrometry. To determine whether different-sized hPTH fragments modulate the bioactivity of hPTH1-84, we studied its effects on the generation of the cellular second messenger, cAMP, which mediates the intracellular signaling of hPTH1-84, in murine preosteoblasts (MC3T3-E1) in vitro. Forskolin, an adenylyl cyclase activator, was used as a positive control for cAMP production. All experiments were performed in triplicate.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Results: In MC3T3-E1 cells, cAMP increased to 28.5±5.5, 64.4±9.9, 91.5±11.6, 114.6±15.5, and 109.1±6.5 pmol/mL 30 minutes after treatment with 1, 3, 10, 50, and 100 nM hPTH1-84. The same concentrations of hPTH28-84, hPTH38-84, and hPTH45-84 had no effects. When hPTH1-84 was added to cells concurrently with 100 nM hPTH38-84 or hPTH45-84 in 1:100, 1:300, 1:10, 1:2, and 1:1 molar ratios, cAMP responses to hPTH1-84 increased by 65.3% (95% CI, 63.2% to 67.4%; P<0.01) in the presence of hPTH38-84 and increased by 77.0% (95% CI, 65.2% to 88.8%; P<0.01) in the presence of hPTH45-84. hPTH28-84, added concurrently with PTH1-84, did not enhance cAMP generation in MC3T3 cells.

Conclusions: The small hPTH fragments, hPTH38-84 and 45-84, but not hPTH28-84, enhance the hPTH-induced generation of cAMP in MC3T3-E1, suggesting a novel biological role and a novel mechanism of action for these PTH fragments in osteoblast-like cells. It is plausible that in vivo these fragments may enhance the activity of full-length PTH by novel mechanisms. These findings may partly explain the discrepancy between PTH levels and bone histology in patients with CKD.

Funding: Other NIH Support - Fred C. and Katherine B. Andersen Foundation; and NIH, grants 5R01DK107870 and DK125252 (to RK), Private Foundation Support

Bone Expression of Sclerostin in CKD and Dialysis Patients
Marcjana Lastek, Renata C. Pereira, Lauren V. Albrecht, Isidro B. Salusky, University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA.

Background: Sclerostin, a 22-kDa glycoprotein secreted by osteocytes, negatively regulates bone formation through the inhibition of the Wnt/β-Catenin pathway. In patients with CKD, circulating sclerostin correlates negatively with bone formation but the impact of bone expression of sclerostin requires further investigation.

Methods: 87 pediatric patients with CKD underwent iliac crest bone biopsy with the quantification of sclerostin bone expression using immunohistochemistry (IHC). Subjects with circulating sclerostin values at the upper and lower extremes of each population (n=6 each group) underwent staining with two monoclonal antibodies towards sclerostin.

Results: The median (IQR) age of the cohort was 17 (14, 20) and 39% had pre-dialysis CKD (Table). Significant correlations between IHC sclerostin and bone histomorphometry were limited to the dialysis group: IHC sclerostin correlated with bone formation rate (r=-0.34, P<0.02) and osteoid thickness (r=0.3, P=0.03). In the sub-group undergoing β-catenin staining, dialysis patients demonstrated low bone staining of sclerostin independent of circulating sclerostin. CKD subjects with high circulating sclerostin levels (ranging from 58 to 110 pmol/L) demonstrated increased sclerostin staining in osteocytes when compared with CKD patients with lower serum sclerostin (ranging from 30 to 36 pmol/L). Phosphorylated β-catenin staining was higher and unphosphorylated β-catenin levels lower in bone tissues with high circulating sclerostin.

Conclusions: Together, these data support a model whereby high levels of circulating sclerostin from osteocytes contributes to altered bone remodeling through aberrant Wnt signaling activity in CKD and may provide a rationale to target therapeutic strategies using monocalonal antibodies towards sclerostin.

Funding: NIDDK Support

Table: Cohort Characteristics

<table>
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<tr>
<th>N (%)</th>
<th>CKD</th>
<th>Dialysis</th>
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<td>Age, median (IQR)</td>
<td>15 (12.7, 17.1)</td>
<td>18.3 (16.4, 19.7)</td>
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<tr>
<td>Gender, n (%)</td>
<td>Male</td>
<td>Female</td>
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<tr>
<td>23 (67)</td>
<td>11 (32.3)</td>
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<td>37 (68)</td>
<td>16 (30.2)</td>
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<tr>
<td>Race, n (%)</td>
<td>Black</td>
<td>White</td>
</tr>
<tr>
<td>1 (2.9)</td>
<td>8 (15.5)</td>
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</tr>
<tr>
<td>8 (15.5)</td>
<td>6 (11.3)</td>
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<tr>
<td>0</td>
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<tr>
<td>Disease, n (%)</td>
<td>CAKUT</td>
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<td>10 (29.4)</td>
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<td>Calcium, mg/dL</td>
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<td>9.2 (8.7, 9.7)</td>
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<td>Phosphate x score</td>
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<td>Alkaline Phosphatase, IU/L</td>
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<td>150 (90, 283)</td>
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<td>Vitamin D, ng/mL</td>
<td>25 (22.5, 29.7)</td>
<td>21 (13.2, 25.6)</td>
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<td>PTH, pg/mL</td>
<td>95 (50, 159)</td>
<td>411 (211, 991)</td>
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<td>Intact FGF23, pg/mL</td>
<td>95 (64, 140)</td>
<td>1195 (286, 3718)</td>
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<tr>
<td>c-terminal FGF23, RLU</td>
<td>199 (101, 344)</td>
<td>1461 (705, 5577)</td>
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<td>Sclerostin, pg/mL</td>
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<td>36.9 (48.3, 87.2)</td>
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<td>IHC Sclerostin</td>
<td>1.6 (0.3, 6.6)</td>
<td>1.7 (0.4, 6.8)</td>
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</table>

PO0518 The Essential Role of miRNA in Maintaining an Intact Parathyroid in the Adult
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Background: miRNA are small noncoding RNAs with vital roles in homeostasis and development. Dicer mediates the final step of miRNA maturation. To study the roles of miRNA in the parathyroid, we generated parathyroid-specific Dicer knockout (PT-Dicer−/−) mice, to specifically delete parathyroid miRNA. The PT-Dicer−/− mice had normal serum PTH levels, but failed to increase PTH when stressed by hypocalcemia or kidney failure, unlike control mice and patients. We now show that in addition to parathyroid stimulation, miRNA are central to maintaining intact parathyroid glands throughout life.

Methods: We generated PT-Dicer−/− and control mice expressing YFP (Yellow Fluorescent Protein) in the parathyroid by cre lox recombination, to track parathyroid cells by fluorescence microscopy. Histological slides from P0 (day of birth) and older mice were immunostained. qRT-PCR and Western blots were performed on thyroid tissue that includes the embedded parathyroids.

Results: Surprisingly, adult PT-Dicer−/− mice had no YFP positive parathyroid glands detected by fluorescence microscopy, as opposed to easily detected intact glands in controls. However, the glands were present immediately after birth in P0 and P1 Dicer−/− mice. At P0 and P1 there were increased levels of the cleaved caspase-3 apoptotic marker in cells co-expressing PTH and the parathyroid transcription factor GCM2. From P3 to P12, there was a gradual loss of parathyroid glands in PT-Dicer−/− mice, with the left gland disappearing last. qRT-PCR of thyroid RNA, containing the parathyroid when present, showed reduced expression of PTH miRNA in adult PT-Dicer−/− mice, compared to controls. PTH levels were also decreased in thyroid extracts as determined by Western blots. There was no change in thyms PTH mRNA that has been proposed to provide an auxiliary source of PTH.

Conclusions: Mice that do not express miRNA in the parathyroid lose their parathyroid glands after birth, indicating that miRNA are not essential for parathyroid embryonic development by rather postnatally, for maintaining intact parathyroid glands. In the absence of parathyroid glands in adult PT-Dicer−/− mice, an additional source for PTH other than cells in the thyroid or thyms contributes to normal basal serum PTH that cannot be stimulated by hypocalcemia or uremia.

PO0519 PTH Suppression Improves Cortical Bone Parameters in Aging Mice with CKD
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Background: Chronic kidney disease (CKD) and aging are each independently associated with higher risk of fracture due to significant loss of bone mass and quality. In CKD, cortical thinning and cortical porosity are driven by elevated parathyroid hormone (PTH) and directly linked to increased fracture risk in CKD patients. Overlaying CKD and aging produces cortical porosity that is higher than either condition alone. Previously, we discovered potent suppression of PTH in rodents with CKD infilled existing pores; however, it is unknown if aged bone may react similarly given attenuated osteoblast function. The goal of this study was to assess the impacts of PTH suppression on cortical porosity in young and aging CKD mice.

Methods: Male C57Bl/6J mice were used at 16 and 66 weeks of age. CKD was induced via dietary adenine (AD, 0.2% for 6 weeks + 2 weeks of maintenance on control diet). Control mice were fed normal control diet for the duration of the study. After 8 weeks of CKD induction, calcium water was provided for 4 weeks to suppress PTH (n=8/group). Outcome measures included biochemical assays and bone architecture via μCT.

Results: Aging AD mice had more than six-fold higher PTH levels than age-matched controls and more than two-fold higher PTH levels than young AD mice. Administration of calcium water led to lower PTH in both young AD and aging AD mice, 85% and 82%, respectively. Regardless of age, AD mice showed lower cortical bone area (~32%) and cortical thickness (~32%) compared to age-matched controls; mice given calcium water had lower cortical bone area (11%, 8%) and cortical thickness (20%, 10%) compared to untreated age-matched AD. Due to large variability, there were no statistical differences in cortical porosity between groups, although porosity did trend lower in both calcium water-treated young AD (~74%) and aging AD (~29%) groups compared to age-matched controls.

Conclusions: These data demonstrate the beneficial impact of PTH suppression on cortical bone in young and aging animals; however, PTH suppression alone may not be enough to sufficiently reduce cortical porosity, particularly in aging bone. This lays the groundwork for future studies to assess clinically available therapies of PTH suppression and their efficacy in reducing cortical porosity in a broad spectrum of CKD patients.

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Calcitremics Alter Periosteal and Perilacunar Bone Matrix Properties in Early CKD

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Background: Chronic kidney disease (CKD) patients have an elevated fracture risk due to hyperparathyroidism, cortical porosity, and reduced bone matrix quality. Calcimetric drugs are used to lower PTH in dialysis patients, but their impact on bone matrix quality in early CKD remains unknown. We hypothesized that tissue-level bone quality is altered in early CKD and that calcimetric treatment improves bone quality.

Methods: Male C57BL/6J rats fed a casein-based diet underwent progressive CKD with mineral and bone disorder. 18-week-old rats (stage 3 CKD, N=12) were treated with the calcitremic KP-2326 (0.6 mg/kg ip. 3x/wk). N=12 normal littermates (NL) and untreated CKD rats received the casein diet to control mineral intake. Calcim was administered 4 and 14 days prior to sacrifice at 28 weeks (stage 4 CKD). Blood was drawn and femora were harvested for MicroCT and 4-point bending. Femur sections were cut and polished for colocalized Raman spectroscopy and nanoindentation. Colocalization was run in fluid in perinosteal bone using calcimine as a guide and in concentric ellipses around osteocyte lacunae.

Results: PTH was 284% higher in CKD vs NL and KP reduced PTH by 92% vs CKD. Neither CKD nor KP altered cortical porosity and KP did not improve structural mechanical properties vs CKD. In new periosteal bone, CKD reduced carbonate substitution by 29% and elastic modulus by 15% vs NL while KP increased mineral crystallinity by 4% vs NL and restored elastic modulus to NL levels. In perilacunar bone, KP reduced carbonate substitution and increased elastic modulus vs hardness vs CKD.

Conclusions: This study demonstrates that CKD and KP alter bone matrix composition, mechanical properties on the tissue level prior to structural changes such as cortical porosity. The perilacunar data suggests that osteocytes may actively alter their surrounding matrix in CKD and that calcimetric agents may help prevent these changes prior to a decline in bone structural integrity.

Funding: NIDDK Support, Other NIH Support - NIAMS, Veterans Affairs Support

Calcitremics Alter Periosteal and Perilacunar Bone Matrix Properties in Early CKD

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Background: Chronic kidney disease (CKD) patients have an elevated fracture risk due to hyperparathyroidism, cortical porosity, and reduced bone matrix quality. Calcimetric drugs are used to lower PTH in dialysis patients, but their impact on bone matrix quality in early CKD remains unknown. We hypothesized that tissue-level bone quality is altered in early CKD and that calcimetric treatment improves bone quality.

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Funding: NIDDK Support, Other NIH Support - NIAMS, Veterans Affairs Support

The Calcimetric KP-2326 Alters the Gut Microbiota in a Rat Model of CKD-MBD

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Background: CKD-MBD therapies, including diet and phosphate binders, can alter the gut microbiota. However, it is unknown if calcimetric agents alter the gut microbiota and their derived uremic toxins.

Methods: C57BL/6J rats, a slowly progressive rat model of CKD-MBD (CKD hereafter, n=13) and normal littermates (NL, n=8) consumed a diet with 0.77% phosphorus from 18 wk of age (~ 60% of NL glomerular filtration rate (GFR)) to euthanasia at 28 wk of age (~30% of NL GFR). An additional CKD group received the pre-clinical form of etelcalcetide, KP-2326 (CKD+KP; 0.6 mg/kg IP 3 times/wk, n=13) for a total of 10 wk starting at 18 wk of age. DNA was extracted from cecal samples, the V4 region of the 16S ribosomal RNA gene was sequenced via Illumina MiSeq, and data were analyzed via QIIME2.

Results: KP-2326 reduced carbonate substitution and increased elastic modulus vs hardness vs CKD.

Conclusions: This study demonstrates that CKD and KP alter bone matrix composition, mechanical properties on the tissue level prior to structural changes such as cortical porosity. The perilacunar data suggests that osteocytes may actively alter their surrounding matrix in CKD and that calcimetric agents may help prevent these changes prior to a decline in bone structural integrity.

Funding: NIDDK Support

Oxalate Transport in Mouse and Human Intestinal Tissue

A New Physiological Model to Study Regulation of SLC26A6-Mediated Oxalate Transport in Mouse and Human Intestinal Tissue

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Background: Intestinal organisms have great utility in studying stem-cell self-organizing properties. However, barrier and transport functions cannot be determined cinematically in 3D cultures. We converted 3D intestinal organoids to two-dimensional monolayers (2D) and studied oxalate transport physiology via the oxalate transporter SLcC26A6. Furthermore, we investigated the response of intestinal organoids to high oxalate concentrations.

Methods: Male and human adult stem cell-derived 3D culture systems were grown onto 2D monolayers. Cell differentiation was compared by gene expression and western blotting. Plasma membrane transport was examined in mouse and human monolayers with radioactively labeled substrates. Monolayers were exposed to soluble oxalate and cell death was measured by Caspase-3 activation and lactate dehydrogenase (LDH) release.

Results: We demonstrated that 2D intestinal monolayers maintained the gene expression profile of 3D organoids. Furthermore, murine and human intestinal organoids demonstrated high oxalate exchange transport activity that was 4,4-diisothiocyanostilbene-2,2'-disulfonic acid (DIDS)-sensitive. Chloride-oxalate exchange was abrogated in murine organoids deficient for Slc26A6, resulting in intracellular oxalate accumulation, Caspase-3 activation and LDH release.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

Integrated Transcriptomic and Proteomic Analyses for the Characterization of Oxophil Cells in Patients with Uremic Secondary Hyperparathyroidism

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Background: Calcitremics and calcimetrics are the most powerful treatments for secondary hyperparathyroidism (SHPT); however, the mechanisms leading to calcitremic or calcimetric resistance in SHPT are unknown. Here we used transcriptomic RNA-seq and tandem mass tag (TMT) proteomic techniques to characterize oxophil cells by comparing the differences between chief and oxophil cell nodules of parathyroid glands in patients with uremia.

Methods: Transcriptomic and proteomic analyses were performed on chief and oxophil cell nodules collected from uremic patients. We sought to verify the expression of differentially expressed genes (DEGs), and detect the expression of mitochondrion-associated proteins (voltage-dependent anion channel 1 (VDAC1) and mitochondrial transcription factor A (MTF-1)), mitochondrial DNA (mtDNA) copy number was measured to assess the mitochondrial mass. Freshly excised parathyroid tissues were measured to assess the mitochondrial mass. Freshly excised parathyroid tissues were measured to assess the mitochondrial mass.

Results: Compared to chief cell nodules, the most marked expression increases in oxophil cell nodules were for proteins involved in mitochondrion-associated components and a series of metabolic processes. The mitochondria number, mtDNA content, and protein levels of VDAC1 and MT-CO2 were significantly increased in oxophil cell nodules. Moreover, oxophil cell nodules expressed PTH and GCM2, and exhibited lower expression of PCNA and Cyclin D1 but higher synthesis and secretion level of PTH. The protein expression of VDR, CaSR, and Klotho were significantly downregulated in oxophil cell nodules.

Conclusions: Oxophil cells characterized by enrich mitochondria in patients with uremia, are proliferative cells and showed higher synthesis and secretion of PTH but lower expression of SHPT regulators than chief cells, which may contribute to the pathophysiology of SHPT and the treatment resistance to calcitrol and calcimetrics.

Funding: Government Support - Non-U.S.
Conclusions: We conclude that 2D intestinal organoid cultures are suitable in vitro models to study oxalate transport from mice and humans. Using these models we demonstrate that Stc20aaf-mediated chloride-oxalate exchange protects from intracellular oxalate accumulation and cell death.

Funding: Government Support - Non-U.S.

PO0524 Optimization of Oxalobacter formigenes-Derived Small Peptides with Therapeutic Potential for Hyperoxaluria, Hyperoxaluria, and Related Kidney Stones
Haitham A. Hassan, Altayeb Alshaikh, Jonathan Zarweck. The University of Chicago, Chicago, IL.

Background: Most kidney stones (KS) are composed of calcium oxalate, and very small increases in urine oxalate enhance the stone risk. Besides KS, oxalate also potentially contributes to CKD progression and CKD - and ESRD-associated cardiovascular diseases, emphasizing the need for plasma and urine oxalate lowering therapies, and enhancing the bowel’s ability to secrete oxalate may effectively do so. We previously discovered Oxalobacter-derived secreted factors stimulating oxalate transport by human intestinal Caco-2BBe (C2) cells and reducing urinary oxalate excretion in hyperoxaluric mice by inducing colonic oxalate secretion. We identified the small peptides P8 and P9 as the major secreted factors and they have significant therapeutic potential for hyperoxaluria and hyperoxaluria. Natural peptides are often not suitable therapies due to rapid degradation by proteolytic enzymes, and P8 & P9 have multiple enzymatic cleavage sites.

Methods: Described under Results.

Results: To optimize P8 & 9 peptides and make them resistant to proteolyte degradation, their were subjected to the following structural modifications. N-terminal acetylation (P8-Ac & P9-Ac), C-terminal amimation (P8-Am & P9-Am), retroviral (P8-R & P9-R), and replacing several glycine and lysine sites with PEG6 (P8-GL) & (P9-GL) or ornithine (P8-O & P9-O), respectively. All of these modified peptides stimulated oxalate transport by Caco-2Be cells similar to the native P8 & 9, except P8-R (47.3% less functional) and P8-R (nonfunctional). The native and modified peptides were then treated with different enzymes (trypsin, proteinase K, and colonic lavage fluid [CLF: mimics the colonic environment]) to evaluate the impact of such modifications using LC-MS and/or HPLC. Results indicate that the native P8 & 9 peptides were completely degraded by the above enzymes. P8-O and P9-O have improved stability (~57-80%) against trypsin, but they were fully degraded by proteinase K and CLF. Importantly, P9-R is completely resistant to degradation by the above enzymes.

Conclusion: P8 & 9 peptides are the most stable optimized peptide, but is less functional compared to native P9. Studies are ongoing to evaluate its in vivo therapeutic effects in lowering plasma and urine oxalate levels in hyperoxaleric and hyperoxaluric mice.

Funding: NIDDK Support

PO0525 Leaky Intestinal Epithelium Causes Hyperoxaluria in CA-MLCK Mice
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Background: Most kidney stones are composed of calcium oxalate, and very small increases in urine oxalate enhance the stone risk. The intestine plays a crucial role in oxalate homeostasis, and intestinal oxalate absorption is largely passive and paracellular. To evaluate whether enhanced intestinal paracellular permeability can increase urinary oxalate excretion, mice with increased small and large intestinal paracellular leak (transgene mice expressing intestinal constitutively active myosin light chain kinase = CA-MLCK) were used.

Methods: Described under Results.

Results: CA-MLCK mice have significantly higher (1.27-fold) urine oxalate compared to controls (µM/mg creatinine; Controls = 15.10±4.48; CA-MLCK = 12.56±3.65), when compared to native P9. CA-MLCK mice and mounted in Ussing chambers, and were isolated from control and CA-MLCK mice and mounted in Ussing chambers, and were compared to native P9. Studies are ongoing to evaluate its in vivo therapeutic effects in lowering plasma and urine oxalate levels in hyperoxaleric and hyperoxaluric mice.

Funding: NIDDK Support

PO0526 Transcriptional Mapping of the Human Kidney Papilla Reveals Myeloid Immune Activation and Matrix Remodeling Pathways in Stone Disease
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Background: The role of the kidney papilla in the pathophysiology of stone disease remains unclear. The aim of this study was to identify the cellular and molecular determinants of nephrolithiasis by molecular mapping of the stone forming papilla using integrated single nuclear and spatial transcriptomics.

Methods: Renal papillary biopsies were obtained from Calcium oxalate (CaOx) stone formers and reference non-stone formers. Tissue sections were prepared according to Visium (10x Genomics) spatial transcriptomic protocol. Single nucleus RNA sequencing from papillary frozen sections was used to spatially map the signature of specific cell types within the tissue. Data analysis and visualization were performed in R (seurat, RunestonePA, ClusterProfiler) and Loupe browser. In-situ imaging of cell distribution and pathway activation were quantified using 3D immunofluorescence imaging. The levels of select proteins in urine samples were quantified by ELISA.

Results: Genes and pathways associated with reactive oxidative stress, myeloid immune activation and extracellular matrix (ECM) remodeling were significantly upregulated in CaOx biopsies relative to non-stone forming reference. Spatial transcriptomic localized the signature of specific cell types and demonstrated the increased expression of genes from those pathways such as FOS, JUN, SOD2, CCL5, VEGF, and MGP, particularly in areas within or adjacent to mineralized regions in the stone forming papilla. 3D immunofluorescence imaging confirmed the observed activated stress response and myeloid immune activation using phospo-c-JUN and CD68 staining, respectively. Additionally, the activation of myeloid and ECM remodeling pathways was validated by increased levels of MMP7 and MMP9 in the urine of patients with stone disease compared to healthy controls.

Conclusions: Using integrated transcriptomic and imaging approaches, we demonstrate that the papilla of stone patients is an active site of myeloid immune activation, ReactomePA, ClusterProfiler) and Loupe browser. In-situ mapping of cell distribution and pathway activation were quantified using 3D immunofluorescence imaging. The levels of select proteins in urine samples were quantified by ELISA.

Funding: NIDDK Support

PO0527 Assessment of Vascular Calcification Using Micro-CT Quantification in a Vitamin D Rat Model
Firas Bassiassi, David Sabarod, Blasco Ferrer, Guillermo Garauel Perez, Maria del mar Perez, Miquel D. Ferrer, Francisca Mulero, Carolino Calcedo, Sanifit Therapeutics, Palma, Spain; 2Universitat de les Illes Balears, Palma, Spain; 3Universitat de les Illes Balears, Palma, Spain; 4Centro Nacional de Investigaciones Oncologicas, Madrid, Spain.

Background: Micro-computed tomography (micro-CT) scanning could be an alternative technique of both visualization and quantification of calcium content in vessels. Our aim was to standardize the micro-CT calcium quantification methodology and evaluate its reliability in a rat model of calcification.

Methods: Six Sprague-Dawley rats were induced by three consecutively daily subcutaneous administrations of 150 µl/kg vitamin D3 and sacrificed 5 days after induction. Three of the rats were subcutaneously treated with 60 mg/kg SNF472 (G1), an inhibitor of calcification, and the rest were treated with saline (G2). One additional rat was not induced nor treated and served as negative control. Micro-CT was performed in aorta and femoral arteries with an isotropic resolution of 45 µm. 400 projections collected in one full rotation of the gantry in 10 min, x-ray tube at 80 kV and 150 µA. A phantom made of a laser cut aluminum skeleton was scanned with the same protocol to simulate bone. After the image analysis, the vessel samples were digested (1:1 HNO3:HClO4) reflecting that primary intestinal barrier dysfunction is sufficient by itself to cause hyperoxaluria. This 27% increase in urine oxalate concentration is significant since minor increases enhance the stone risk. To see if the observed hyperoxaluria is due to enhanced passive paracellular intestinal oxalate absorption, jejunal and ileal tissues were isolated from native P8 & 9. CA-MLCK mice and mounted in Ussing chambers, and unilateral proximal and distal colon samples were used for activation of myeloid and ECM remodeling pathways was validated by increased levels of MMP7 and MMP9 in the urine of patients with stone disease compared to healthy controls.

Conclusions: Using integrated transcriptomic and imaging approaches, we demonstrate that the papilla of stone patients is an active site of myeloid immune activation, ReactomePA, ClusterProfiler) and Loupe browser. In-situ mapping of cell distribution and pathway activation were quantified using 3D immunofluorescence imaging. The levels of select proteins in urine samples were quantified by ELISA.

Funding: NIDDK Support

PO0528 Commercial Support - Sanifit Therapeutics

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The Effect of the Warfarin-TG2-MVs Axis in Vascular Calcification

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Background: Warfarin is a common anticoagulant drug. How to effectively reduce vascular calcification induced by warfarin while ensuring its anticoagulant effect is an urgent problem to be solved. Previous studies have found that warfarin enhances the expression and activity of transglutaminase 2 (TG2) in vascular smooth muscle cells (VSMCs), which mediates communication between cells and extracellular matrix (ECM). Matrix vesicles (MVs) are the center of hydroxyapatite crystal precipitation, which is released to ECM and interacts with ECM protein to initiate mineralization and form calcification core. This study observed the role of warfarin-TG2-MVs axis in vascular calcification by culturing VSMCs in vitro.

Methods: VSMCs were cultured in normal or osteogenic medium (OM) and stimulated with 10 µM warfarin for 3-14 days. The expressions of SM22α, Runx2, ALP, OPN, and CTRP were detected by qPCR. In addition, the amount of MVs produced by the warfarin and OM group was significantly higher than that of other groups, and the ability to mineralize of MVs in OM group was increased. The expression of the Warfarin-TG2 axis was significantly higher in cultured VSMCs with OM and warfarin treatment. Meanwhile, the number of Ca^2+ in the medium increased significantly in the OM group. The results of calcium staining in the warfarin intervention group were all positive. Warfarin increased the expression and activity of TG2, and it gradually increased with the extension of the intervention time. The same amount of MVs were cultured for 7 days under different stimuli, and the medium was changed every other day. Then, the supernatant was collected for differential centrifugation. The amount of MVs produced by the warfarin and OM group was significantly higher than that of other groups, and the ability to mineralize of MVs in OM group was increased.

Conclusions: Warfarin stimulated the transdifferentiation of VSMCs, that the expression of osteogenic factors Runx2, ALPL and OPN were increased, while the expression of SM22α and calcification inhibitor OPG were decreased. When using OM, the above trend was more obvious. Alizarin red and von Kossa staining were performed when the cells were cultured for 14 days. The results of calcium staining in the warfarin intervention group were all positive. Warfarin promoted the expression and activity of TG2, and it gradually increased with the extension of the intervention time. The same amount of MVs were cultured for 7 days under different stimuli, and the medium was changed every other day. Then, the supernatant was collected for differential centrifugation. The amount of MVs produced by the warfarin and OM group was significantly higher than that of other groups, and the ability to mineralize of MVs in OM group was increased.

Results: Warfarin stimulated the transdifferentiation of VSMCs, that the expression of osteogenic factors Runx2, ALPL and OPN were increased, while the expression of SM22α and calcification inhibitor OPG were decreased. When using OM, the above trend was more obvious. Alizarin red and von Kossa staining were performed when the cells were cultured for 14 days. The results of calcium staining in the warfarin intervention group were all positive. Warfarin promoted the expression and activity of TG2, and it gradually increased with the extension of the intervention time. The same amount of MVs were cultured for 7 days under different stimuli, and the medium was changed every other day. Then, the supernatant was collected for differential centrifugation. The amount of MVs produced by the warfarin and OM group was significantly higher than that of other groups, and the ability to mineralize of MVs in OM group was increased.

Conclusions: Warfarin increased the expression and activity of TG2, promoted the release of MVs from VSMCs, and further cross-linked ECM to aggravate vascular calcification.

Uremic Milieu Exacerbates Muscle Regeneration After Muscular Injury in Mice

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Background: In our life, skeletal muscle injuries occur not only in strenuous exercises but also in daily activities with unexpected excessive muscle contraction. In general conditions, injured muscles are repaired to normal structure, and muscle functions are rescued. However, whether this repair process is affected in the uremic milieu has not been fully elucidated yet.

Methods: In C57BL6 male mice fed with normal diet or 0.2% adenine-conjugated diet, the muscle injury was induced by intramuscular injection with vehicle (PBS) or barium chloride (BaCl2) in tibialis anterior (TA) muscles. Then, we evaluated the TA muscle weight, histology, muscle strength, and marker gene expressions of Pi^+ satellite cells and macrophages during a pival role in muscle regeneration. We also treated differentiating mouse skeletal myoblasts with a representative uremic toxin, indoxyl sulfate (IS), and evaluated the cell morphology and marker gene expressions.

Conclusions: In an adenine-induced CKD mice, the BaCl2-induced TA muscle showed reduction of muscle wet weight, muscle fiber size, instantaneous muscle strength, and Pax7 gene expression compared to control mice. Furthermore, the gene expression of Dll1 and Notch2 regulating the Pax7 expression, CCL5 accelerating the migration of macrophages, and cell surface markers of Mu2 macrophages (CD206, CD163, and CD86) also decreased in the injured muscle of CKD mice. Treatment of murine C2C12 myoblast with IS led to not only the myotube atrophy but also smaller number of nuclei per myotube. The gene expression of Pax7, Dll1, and CCL5 increased during the C2C12 myoblast differentiation, but IS treatment worsened these expressions as seen in vivo experiments.

Conclusions: Uremic milieu deteriorated muscle regeneration with the decline of gene expression associated with satellite cells and macrophages.

Indoxyl Sulfate Induces Cardiomyocyte Hypertrophy via FGF23-FGFR4 Signaling Pathway

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Background: Both fibroblast growth factor 23 (FGF23) and indoxyl sulfate (IS) have been reported to relate with left ventricular hypertrophy (LVH) in patients with chronic kidney disease (CKD), but their inter-relationship remains unknown.

Methods: To induce LVH, 8-week-old male C57BL/6J mice were fed high phosphorus diet after deletion transglutaminase 2 (TG2) in vascular smooth muscle cells (VSMCs), which mediates communication between cells and extracellular matrix (ECM). Matrix vesicles (MVs) are the center of hydroxyapatite crystal precipitation, which is released to ECM and interacts with ECM protein to initiate mineralization and form calcification core. This study observed the role of warfarin-TG2-MVs axis in vascular calcification by culturing VSMCs in vitro.

Results: In C57BL6 male mice fed with normal diet or 0.2% adenine-conjugated diet, the muscle injury was induced by intramuscular injection with vehicle (PBS) or barium chloride (BaCl2) in tibialis anterior (TA) muscles. Then, we evaluated the TA muscle weight, histology, muscle strength, and marker gene expressions of Pi^+ satellite cells and macrophages during a pival role in muscle regeneration. We also treated differentiating mouse skeletal myoblasts with a representative uremic toxin, indoxyl sulfate (IS), and evaluated the cell morphology and marker gene expressions.

Conclusions: In an adenine-induced CKD mice, the BaCl2-induced TA muscle showed reduction of muscle wet weight, muscle fiber size, instantaneous muscle strength, and Pax7 gene expression compared to control mice. Furthermore, the gene expression of Dll1 and Notch2 regulating the Pax7 expression, CCL5 accelerating the migration of macrophages, and cell surface markers of Mu2 macrophages (CD206, CD163, and CD86) also decreased in the injured muscle of CKD mice. Treatment of murine C2C12 myoblast with IS led to not only the myotube atrophy but also smaller number of nuclei per myotube. The gene expression of Pax7, Dll1, and CCL5 increased during the C2C12 myoblast differentiation, but IS treatment worsened these expressions as seen in vivo experiments.

Conclusions: Uremic milieu deteriorated muscle regeneration with the decline of gene expression associated with satellite cells and macrophages.

PO0532

Bone and Mineral Metabolism: Causes and Consequences

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
expression levels of specific target genes. Furthermore, we determine if co-treatment with the phosphate transporter inhibitor Foscanrol blocks the observed effects.

**Results:** A 2% Pi diet promotes the elevation of plasma FGF23 levels in mice. Despite reduced TRP, increased FEP1 and urine Pi levels, the serum Pi levels are still enhanced. In animals fed a 2% Pi diet, we observed reduced renal NaPi-2a mRNA expression. Western blot data revealed immunoreaction of NaPi-2a from the apical BBM due to the high dietary Pi load. This confirmed by analysing BBM vesicles. Interestingly, mice on 2% Pi diet have a diminished renal Klotho expression, but unaltered FGF1 expression. PT-2 expression is increased and accumulated in the basolateral membrane of PT cells. Pi-mediated mRNA expression up-regulated in EK/1.2 phosphorylation was blocked by Foscanrol co-treatment.

**Conclusions:** Hyperphosphatemia might be a result of PT-2/ERK1/2-mediated downregulation of NaPi-2a stimulated by Pi itself. Our study indicates these Pi-mediated effects may be independent of FGF23. We postulate that high dietary Pi load causes a resistance of renal FGF23/Klotho signaling.

**PO0533**

**Reurrence of Hypophosphatemia Despite FGF-23 Reduction in Dmp1 Knockout Mice**

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**Background:** Fibrolast growth factor 23 (FGF23) is a phosphaturic hormone produced by bone. Hyperphosphatemic rickets diseases, such as X-linked hypophosphatemia (XLH) and autosomal recessive hypophosphatemic rickets (ARHR), are associated with FGF23 levels. Thus, lowering FGF23 and PTH is insufficient to prevent phosphaturia in Dmp1 KO mice. We sought to determine whether hypophosphatemia in the long term and in other diseases associated with FGF23 excess, including ARHR.

**Methods:** We deleted Fgfr3 in osteocytes using a Dmp1-cre in wild-type (WT) and Dmp1 knockout (Dmp1KO) mice. We studied the bone and mineral phenotype of WT, Dmp1KO/Fgf23cKO mice at 12 and 20 weeks of age.

**Results:** WT mice showed a 40% reduction in serum intact FGF23 levels and a 25% increase in Pi levels (vs. WT), confirming successful deletion. As expected, DMP1 deficiency in Dmp1KO mice induced significant elevations in serum FGF23 levels (+15-fold) and PTH levels (+5-fold), phosphaturia, hypophosphatemia, rickets and osteomalacia. Treatment with FGF23 blocking antibody has shown great promise to improve serum phosphate (Pi) levels and bone mineralization in XLH. Further studies need to determine if blocking FGF23 is efficacious in the long term and in other diseases associated with FGF23 excess, including ARHR.

**Conclusions:** Treated with Tolvaptan

**PO0536**

**Call for Harmonization of the Histomorphometric Reference Ranges for Bone Turnover in Renal Osteodystrophy**

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**Background:** Knowledge of bone turnover helps guide fracture preventive treatment in patients with chronic kidney disease (CKD). Bone histomorphometry remains the gold standard to assess bone turnover, while non-kidney retained bone biomarkers are considered a valid, but imperfect alternative. Published reports show marked variation in the histomorphometric reference values of bone turnover. Our aim was to investigate the impact of different diagnostic cutoffs on the categorization of bone turnover in a CKD population.

**Methods:** 199 patients with successful bone biopsies before or after kidney transplantation were categorized for bone turnover according to diagnostic cut-off values (published by Salusky et al and Malluche et al, respectively). We applied the diagnostic cutoffs of the histomorphometric reference ranges by Recker et al and Malluche et al to assess bone turnover in patients with chronic kidney disease (CKD) on regular dialysis in a tertiary care center.

**Results:** Increased phosphate concentrations induced an inflammatory response in HBECs, which was further exacerbated by the addition of CSE and attenuated by FGF23 treatment. Furthermore, mice on a high phosphate diet showed increased FGF23 and IL-6 levels in their lung. The increase in IL-6 was not observed in the FGF44 mice. Subacute cigarette smoke exposure led to an increase in IL-10 and IL-8 in total lung tissue, which was abrogated in the FGF44 mice.
PO0537
Effects of Patiromer on Serum Phosphate over 4 Weeks of Treatment in Hyperkalemic Patients with Hyperphosphatemia: Pooled Analysis of the AMETHYST-DN, OPAL-HK and TOURMALINE Trials
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Background: Elevated serum phosphate (sP) is associated with increased mortality in non-dialysis CKD. KDOQI guidelines suggest elevated sP should be lowered into the normal range (2.5-4.5 mg/dL). Patiromer is a non-absorbed, sodium-free, potassium (+K) binder that uses calcium as the exchange ion which, when released, likely binds to intestinal phosphate. We conducted a post-hoc analysis of pooled data from AMETHYST-DN, OPAL-HK and TOURMALINE to evaluate patiromer’s effect on sP over 4 weeks in patients with sP > 4.5 mg/dL.

Methods: Eligible patients had CKD and hyperkalemia (HK; serum K+ [sK+] > 5.0 mEq/L). Prescription of phosphate binders was not allowed. Hyperphosphatemia subgroup was defined as baseline sP > 4.5 mg/dL. Patients in the analysis received at least 1 dose of patiromer (8.4-33.6 g/day to start) and had a post-baseline sP assessment. Mean (± SD) changes from baseline in sP, sK+, serum magnesium and serum calcium at weeks 2 and 4 were evaluated.

Results: 86/578 (15%) patients had baseline sP > 4.5 mg/dL: 36% were male, mean (SD) age was 63.9 (10.5) years, 84% had diabetes, mean (SD) eGFR was 25.9 (17.2) mL/min/1.73m² and 76% had stage 4/5 CKD. Mean (SD) baseline sP and sK+ were 5.0 (0.5) mg/dL and 5.5 (0.4) mEq/L, respectively. At 2 or 4 weeks of patiromer treatment, both mean sP and sK+ levels decreased into the normal range (Table). Most frequent adverse events (AEs) were constipation (18.6%; 9/50) and diarrhea (6/86; 7%); most cases were mild or moderate in severity. AEs leading to study discontinuation occurred in 3/86 (4%) patients.

Conclusions: Patiromer decreased both sP and sK+ into the normal range in patients with elevated sP and sK+. Patiromer was well tolerated with mild/moderate gastrointestinal events. The ability of patiromer to normalize sP may be therapeutically useful in hyperkalemic patients with CKD and hyperphosphatemia.

Funding: Commercial Support - Vifor Pharma Ltd

Table: Serum phosphate, potassium, calcium, and magnesium at baseline, and after 2 and 4 weeks of patiromer treatment

PO0538
Circadian Changes in Serum Phosphate Among Patients with ESKD on Hemodialysis
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Background: Serum phosphate concentrations are known to have a circadian rhythm in healthy adults and in CKD, with a nadir in the late morning and a peak in the afternoon. Circadian changes in serum phosphate concentrations among persons on chronic hemodialysis may have important treatment implications, as serum phosphate concentrations are a therapeutic target in these patients.

Methods: We assessed serum phosphate concentrations in 118,440 persons with ESKD treated with in-center hemodialysis at Fresenius Kidney Care centers across the United States in July 2017. We used linear regression to assess the relationship between time of day and serum phosphate concentrations. We assessed unadjusted models and models adjusting for age, sex, race, region, weight, diabetes and use and dose of vitamin D analogs, calcimimetics and phosphate binders.

Results: The cohort had mean age 63 ± 13 years, 44% were female, 53% were white and 33% were black. The mean serum phosphate concentration was 5.3 ± 1.5 mg/dL. In both the unadjusted and fully adjusted models, serum phosphate concentrations varied over the day with a peak at 6:00 pm and a nadir at 10:00 am (p < 0.001). In the unadjusted model the difference from peak to nadir was 0.6 mg/dL. This difference was attenuated in the fully adjusted model to 0.2 mg/dL (Figure).

Conclusions: In a large and diverse cohort of adults with ESKD treated with hemodialysis, serum phosphate concentrations varied depending on the time of day in which serum phosphate levels were measured. Thus, the target serum phosphate range for patients treated with hemodialysis should account for when serum phosphate is being measured.

Funding: NIDDK Support, Commercial Support - Fresenius Medical Care North America

PO0539
Association of Combined Urinary Fractional Excretion of Phosphate and Serum FGF-23 with Adverse Events in Moderate and Advanced CKD: An Analysis from the CRIC Study
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Background: High levels of FGF23 are associated with adverse events in CKD. The urinary fractional excretion of phosphate (FePi) might modify this association, although data are limited in moderate and advanced CKD. We investigated the association of combined FePi and serum FGF23 with mortality, renal and cardiovascular events in patients with prevalent CKD 2-4.

Methods: Patients from the Chronic Renal Insufficiency Cohort (CRIC) were divided into four groups according to the median of FePi and FGF23: 1) low-FePi/low-FGF23, reference group; 2) high-FePi/low-FGF23; 3) low-FePi/high-FGF23; 4) high-FePi/high-FGF23. Primary outcomes were: incident heart failure; a composite atherosclerotic cardiovascular disease (ASCVD) outcome of myocardial infarction, ischemic stroke or peripheral artery disease; CKD progression; and all-cause mortality. The association of groups with the longitudinal outcomes was assessed through unadjusted and adjusted Cox proportional hazards models.

Results: We analyzed 3684 patients with a mean age of 58±11 years, 45% were male, and 42% were Black. Baseline mean eGFR was 44.3 ± 14.9 mL/min/1.73 m2. Median FePi and FGF23 were 26.5% (IQR, 19.5-36.8) and 145 (IQR, 95.6-238.3) RU/mL, respectively. The median time of follow-up was 12 (IQR, 7-13) years. The total number of events was 796 for incident heart failure, 717 for composite ASCVD, 1233 for CKD progression and 1328 for all-cause mortality. The adjusted relative risk of incident heart failure was highest in the low-FePi/high-FGF23 group (HR, 1.31; 95%CI, 1.03 to 1.67) and higher in the high-FePi/high-FGF23 group (HR, 1.58; 95%CI, 1.23 to 2.02), comparing to the low-FePi/low-FGF23 group. Composite ASCVD was higher in the high-FePi/high-FGF23 group (HR, 1.42; 95%CI, 1.11 to 1.80), but not in the low-FePi/low-FGF23 group (HR, 1.25; 95%CI, 0.98 to 1.59). All-cause mortality was higher in the low-FePi/high-FGF23 group (HR, 1.56; 95%CI, 1.30 to 1.89) and higher in the high-FePi/high-FGF23 group (HR, 1.57; 95%CI, 1.29 to 1.90). The adjusted risk of CKD progression was not different between groups.

Conclusions: In contrast to previous reports in patients with mild renal disease, the combination of high FePi and high FGF23 was associated with the highest risk of heart failure and ASCVD events in moderate and advanced CKD.
PO0540

Pill Burden and Changes in Mineral Bone Disorder (MBD) Markers in Hemodialysis (HD) Patients Switched from Sevelamer to Sucroferric Oxyhydroxide (SO): A One-Year Follow-Up in a Contemporary Cohort

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Background: About 80% of US dialysis patients are prescribed phosphate binders (PB) for serum phosphorus (sP) control; however, PB high pill burdens are associated with non-adherence and elevated sP levels. Clinical and observational studies have demonstrated that SO is effective in lowering sP with similar efficacy to sevelamer (Sev), but with a lower pill burden. The present study aims to assess the long-term changes in MBD markers and pill burden in a contemporary HD cohort switching from Sev to SO.

Methods: The study included adult, Fresenius Kidney Care maintenance HD pts receiving Sev during a 91-day baseline (BL) and first prescribed SO monotherapy during 5/2018-5/2019. The one year follow up (FU) on SO therapy was divided into four consecutive 91-day intervals (Q1-Q4). Comparisons of PB pill burden and MBD markers between BL and FU were carried out using mixed-effects linear regression and Cochran’s Q test.

Results: On average, patients (n=841) were 56.2 (13.3) years old with dialysis vintage of 50.5 (48.6) months. At BL, the % of pts was 21.2% for sP ≤ 5.5 mg/dL and 4.5% for sP > 5 mg/dL, with 8.4 Sev pills/day; after switching to SO, the % of pts increased to 35.4%-44.0% for sP ≤ 5.5 mg/dL and 11.4%-16.1% for sP > 4.5 mg/dL with 4.4-4.9 pills/day. Mean iPTH and serum calcium (Ca) decreased progressively after SO conversion.

Conclusions: Maintenance HD patients switching PB prescription from Sev to SO during 2018 and 2019 as part of routine care showed significant reductions in sP and PB pill burden, and increases in the number of patients with sP ≤ 5.5 mg/dL and sP > 4.5 mg/dL. A trend toward decreased serum Ca and iPTH levels during SO therapy was also observed.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

*P<0.05; **P<.001 (vs. BL)

PO0541

Serum Phosphorus (sP) and Pill Burden Among Hemodialysis (HD) Patients Prescribed Sucroferric Oxyhydroxide (SO): One-Year Follow-Up on a Contemporary Cohort

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Background: A previous real-world analysis included HD patients (pts) prescribed SO during 2014-2015 followed for 1 year. Improvements in sP were observed along with a reduction in pill burden. However, the present study compares the long-term effectiveness of SO in a contemporary cohort of HD patient who switched from Sev to SO as part of routine care and followed for one year were included.

Results: Adult Fresenius Kidney Care HD pts first prescribed SO monotherapy between 5/2018-5/2019 and were on FC for 3 months (baseline; BL) prior to SO therapy. The one year SO therapy was divided into four consecutive 91-day intervals (Q1-Q4). Changes in lab measurements and pill burden were compared between BL and Q1-Q4, using mixed-effects linear regression and Cochran’s Q test.

Conclusions: Maintenance HD pts switched PB prescription from ferric citrate to sucroferric oxyhydroxide experienced significant increases in % patients achieving in-range sP (+111% for sP ≤ 5.5 mg/dL and +144% for sP > 4.5 mg/dL) with a lower pill burden.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

PO0542

One-Year Follow-Up of Maintenance Hemodialysis (HD) Patients Who Switched Phosphate Binder (PB) Prescription from Ferric Citrate (FC) to Sucroferric Oxyhydroxide (SO)

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Background: A new class of iron based PBs have been prescribed to HD patients for hyperphosphatemia management. This one-year real-world data analysis in a contemporary cohort of HD patient who switched from FC to SO as part of routine care investigates changes in serum phosphorus (sP) and pill burden.

Methods: Adult Fresenius Kidney Care HD patients included in the analysis were first prescribed SO monotherapy between 5/2018-5/2019 and were on FC for 3 months (baseline; BL) prior to SO therapy. The one year SO therapy was divided into four consecutive 91-day intervals (Q1-Q4). Changes in lab measurements and pill burden were compared between BL and Q1-Q4, using mixed-effects linear regression and Cochran’s Q test.

Results: Patients (n=115) were on average 55.5 (12.6) years old with 52.8 (46.4) months HD vintage, 38% female, 54% had diabetes and 20% had CHF. There were consistent improvements in pts achieving sP ≤ 5.5 mg/dL (from 20% at BL to 35.7%-44.3% with SO; p<.0001) and in patients achieving sP > 4.5 mg/dL (from 6.1% at BL to 8.7%-16.5% with SO; p=0.02). Pts were prescribed 6.7 pills/day at BL and 4.7-5.2 pills/day with SO. SO conversion was associated with decreases in mean iPTH (620 pg/mL at BL and 496 pg/ml at Q4; p<.0001) and serum calcium (9.18 mg/dL at BL, 8.93 mg/dL at Q4; p<.0001).

Conclusions: Maintenance HD pts switched PB prescription from ferric citrate to sucroferric oxyhydroxide experienced significant increases in % patients achieving in-range sP (+111% for sP ≤ 5.5 mg/dL and +144% for sP > 4.5 mg/dL) with a lower pill burden.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

PO0543

Effects of Lanthanum Carbonate on Whole-Body Phosphorus Balance in Patients with Stage 3b-4 CKD and Normophosphatemia

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Background: In CKD, elevated phosphorus, even within the normal range, is associated with cardiovascular disease (CVD) and mortality. However, in normophosphatemic CKD, phosphate binders do not improve vascular function, an independent predictor of CVD. Whether long-term treatment with phosphate binders affects phosphorus balance in CKD is unknown. Our objective was to determine phosphorus balance in normophosphatemic subjects with CKD 3b-4 after 12 weeks of treatment with lanthanum carbonate (LC) or placebo.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Management of Serum Phosphorus (sP) Over One-Year Follow-Up in Peritoneal Dialysis (PD) Patients Prescribed Sucroferric Oxyhydroxide (SO) as Part of Routine Care

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Background: Clinical and observational studies have shown the effectiveness of SO in controlling sP in PD patients (pts). A real-world retrospective analysis in a PD cohort prescribed SO for 6 months demonstrated an association between SO prescription and lower sP. The current analysis examines the changes in sP and PB pill burden over a one-year period in PD patients converting to SO.

Methods: We included adult Fresenius Kidney Care (FCK) PD pts (n=260) first prescribed SO monotherapy during 5/2018-5/2019 who had sP measured 91 days before SO prescription (baseline; BL). Comparisons were made between BL and the four consecutive 91-day intervals of SO treatment (Q1-Q4). Means of PB pill burden and lab measures were calculated using mixed effects linear regression.

Results: At BL, mean age was 54 years old with PD vintage 18 months, 37% pts had no PB prescriptions recorded and the remaining pts were prescribed sevelamer (36%), calcium acetate (33%), lanthanum (1%), ferric citrate (13%), switched between PB (10%), or >1 PB recorded (6%). After switching to SO, % of pts achieving sP< 3.5 mg/dL increased from 32.7% at BL to 46.9% 53.8% within SO FU, % of pts achieving sP< 4.5 mg/dL increased by 13% from BL to Q4, along with fewer PB pills per day (29.3% BL vs 4.6-5.2 at FU).

Conclusions: During a one-year observation period, PD pts prescribed SO as part of routine care during 2018-2019 had significant reductions in sP and PB pills/day and increases in % of pts with sP 3.5 mg/mL or sP ≤ 4.5 mg/mL, suggesting improved sP management with concurrent reduction in pill burden.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

Impact of Tenapanor in Peritoneal Dialysis

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Background: Peritoneal dialysis (PD) utilization is being promoted worldwide as more emphasis is placed on the advantages and reduced cost of home dialysis. Serum phosphorus (sP) control for PD patients remains a challenge, particularly as residual kidney function is lost. Many PD patients receive stool softeners or laxatives to prevent constipation which may impede the treatment. Tenapanor (TEN) is a first-in-class phosphate absorption inhibitor (PAI) that targets the paracellular pathway of phosphate absorption by inhibiting the sodium-hydrogen exchanger 3 (NHE3) antiporter on the luminal surface of gastrointestinal epithelium. As a side effect of inhibiting NHE3, the sodium and water content of the stool is augmented, increasing stool frequency and volume. Here we compare the control of sP and the adverse event (AE) profile of TEN in patients with stage 3b-4 CKD and normophosphatemia. Whether this translates into beneficial clinical outcomes relevant to chronic-kidney disease-mineral and bone disorder warrants further investigation.

Funding: NIDDK Support, Veterans Affairs Support

PO0546

US Hemodialysis Facilities Switching from Cinacalcet to Etelcalcetide: Impact on Parathyroid Hormone (PTH) Levels

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Background: Some US hemodialysis (HD) facilities switched from oral cinacalcet (Cina) to intravenous (IV) etelcalcetide (Etel) as the primary calcimimetic therapy to control parathyroid hormone (PTH) levels after the introduction of Etel in 2017. While clinical trial data have indicated superior efficacy of Etel vs. Cina, real-world evidence is lacking.

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Underline represents presenting author.
PO0547

A Real-World Observational Study of Calcimimetic Use in Hemodialysis (HD) Patients with Secondary Hyperparathyroidism (SHPT) in Europe

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Background: Calcimimetics, Cinacalcet (CIN) and Etelcalcetide (ETEL), are approved for treating SHPT in adult patients on maintenance HD. Data on real-world use are needed to guide clinical practice.

Methods: In this observational study, chronic HD patients treated with calcimimetics for SHPT with a1 parathyroid hormone (PTH) measurement recorded within 90 days before calcimimetic initiation were included. Medical history, PTH, calcium (Ca) and phosphat (P) measurements, and calcimimetic use data were extracted from medical charts. Baseline period was defined as 6 months before calcimimetic initiation.

Results: Interim data for 974 HD (198 CIN and 776 ETEL) patients across 15 countries in Europe, recorded from June 2018 to March 2021, are reported. 434 (334/76) of ETEL patients had switched within 90 days after stopping CIN. ETEL patients were younger (139 vs. 117 months); 42% were female; 30% were white and 31% were black; 84% were HD 1 year, normocalcemic, without CVD. Serum Ca levels were slightly lower in facilities that switched to etelcalcetide (vs. remained cinacalcet) as the primary calcimimetic therapy. Further research is needed to evaluate whether this clear difference in real-world effectiveness translates to a reduction in hospitalizations and mortality.

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PO0548

Effects of Etelcalcetide on the Evolution of Cortical Porosity in Patients and Rats with CKD

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Background: Suppression of chronically elevated parathyroid hormone (PTH) is a key treatment goal in patients with chronic kidney disease–mineral and bone disease (CKD-MBD). High PTH leads to increased cortical porosity which is associated to increased fracture risk. We tested the hypothesis that etelcalcetide, a calcimimetic agent, suppresses cortical pore development in CKD.

Methods: For our clinical cohort, etelcalcetide was dose-titrated to maintain serum PTH at 2-5 times the upper limit of normal of the local PTH assay, corresponding to the lower half of the KDIGO recommended target level. Patients were scanned at the distal tibia by high resolution peripheral OCT before and after 9-months of treatment. For our preclinical cohort, etelcalcetide was administered to an established model of progressive CKD (Male Cy+/+ rat) for 3-5 weeks with in vivo microCT scans at the distal tibia taken at baseline and endpoint. Clinical and preclinical scans were registered across the two samples to allow for direct pore analysis.

Results: Etelcalcetide significantly suppressed PTH in both the clinical (-64%) and preclinical (-77%) cohorts. Total cortical porosity did not increase over the course of treatment in either humans (baseline 5.8%, endpoint 5.8%) or rats (baseline 3.3%, endpoint 3.7%). However, changes were detected at the individual pore level by individual cortical pore analysis. In humans, of the baseline pores, 3% were unchanged, 25% had completely infilled, 40% had become smaller and 27% had increased in size. Twenty-one percent of the total pores at the end of treatment were formed de novo during treatment. The preclinical data followed similar trends, 43% of baseline pores had completely infilled, 20% had decreased in size, 22% had increased in size and 63% of the total pores end of treatment had formed de novo.

Conclusions: PTH suppression by etelcalcetide stabilizes overall cortical porosity yet permits dynamic activity of individual cortical pores during treatment. Further studies are needed to determine if de novo cortical porosity can be prevented by more aggressive PTH reduction.

Funding: Veterans Affairs Support, Commercial Support - Amgen

PO0549

Etelcalcetide Improves Central Skeleton Bone Quality and Density in Patients on Hemodialysis

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Background: Secondary hyperparathyroidism (SHPT) is an important complication of dialysis. It is associated with osteoporosis and fractures. Etelcalcetide is an intravenous calcimimetic superior to cinacalcet in control of parathyroid hormone (PTH) in hemodialysis (HD) patients. The effects of etelcalcetide on bone quality and density are unknown. We hypothesized that etelcalcetide improves spine trabecular bone score (TBS), a marker of central skeletal trabecular bone quality, and bone mineral density (BMD) by dual energy X-ray absorptiometry (DXA) in HD patients.

Methods: Eligible subjects were ≥18 y, on HD ≥1 year, normocalcemic, without calcimimetic exposure within 3 months of enrollment. Treatment included a 3-month run-in period to determine the effects of etelcalcetide on tissue-level bone quality, bone strength and fracture resistance. Treatment of SHPT with etelcalcetide for 9 months was associated with improvements in trabecular quality and central skeleton BMD. Further studies are needed to determine the effects of etelcalcetide on tissue-level bone quality, bone strength and fracture resistance.

Funding: Commercial Support - Amgen

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Baseline DXA parameters and Change in DXA parameters following treatment with etelcalcetide

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline (Mean±SD)</th>
<th>Change (Mean±SD)</th>
<th>p-value</th>
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<td>Z-Score Total Hip</td>
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<td>0.51±0.6</td>
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<td>Z-Score Truncal Bia.</td>
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<td>-0.28±0.1</td>
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<td>Z-Score Ultrasound Radial</td>
<td>-1.23±2.2</td>
<td>-0.27±2.1</td>
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</table>

PO0550

Etelcalcetide Suppresses Trabecular and Cortical Bone Remodeling Without Altering Bone Quality in Patients with ESKD

Corinne E. Metzger,1 Matthew R. Allen,1 John G. Damrath,2 Rachel K. Surowiec,1 Joseph M. Wallace,2 Joshua C. Sung,2 Sanchita Agrawal,2 Thomas Nickolas.2 Indiana University School of Medicine, Indianapolis, IN; 1Columbia University Irving Medical Center, New York, NY; 2Indiana University Purdue University at Indianapolis, Indianapolis, IN.

Background: A key treatment goal in chronic kidney disease-mineral and bone disease (CKD-MBD) is suppression of chronically elevated parathyroid hormone (PTH). High PTH in CKD is associated with high bone turnover and fracture risk. Calcimetics, such as etelcalcetide, are pharmacologic agents used clinically to reduce PTH to target levels. The goal of this study was to test whether 9-months of etelcalcetide treatment suppress bone remodeling in patients with end stage kidney disease (ESKD) on hemodialysis with renal hyperparathyroidism (rHPT).

Methods: Five patients were enrolled. Mean age was 52±16 yrs and 80% were female. A quadruple label method was used to quantify pre- and post-treatment effects of etelcalcetide on bone turnover and quality. Paricalcitol or tetracycline double labeling (3 days, 15 day interval, 3 days). Over 3 months, etelcalcetide was dose-titrated to maintain serum PTH at the lower half of the KDIGO recommended target (2-9x the upper limit of normal of the PTH assay). Patients were maintained on etelcalcetide at the specified PTH level for 6 months. At end of treatment, demeclocycline was administered (3 days, 15 day interval, 3 days) followed by transiluminescence bone biopsy.

Results: Mean PTH (pg/mL) levels at baseline and 9-months were 616±135 and 135±16 yrs and 80% were female. A quadruple label method was used to quantify pre- and post-treatment effects of etelcalcetide on bone turnover and quality. Paricalcitol or tetracycline double labeling (3 days, 15 day interval, 3 days). Over 3 months, etelcalcetide was dose-titrated to maintain serum PTH at the lower half of the KDIGO recommended target (2-9× the upper limit of normal of the PTH assay). Patients were maintained on etelcalcetide at the specified PTH level for 6 months. At end of treatment, demeclocycline was administered (3 days, 15 day interval, 3 days) followed by transiluminescence bone biopsy.

Conclusions: This work shows that etelcalcetide corrects high bone turnover in patients with rHPT on dialysis without affecting bone quality. More research is needed to determine whether the potent remodeling suppression by etelcalcetide can be used as a primary strategy to reduce risk of fracture in patients with ESKD.

Funding: NIDDK Support, Commercial Support - Amgen

PO0551

Interim Analysis of Paricalcitol vs. Cinacalcet in Hemodialysis Patients with Secondary Hyperparathyroidism: A Multicenter, Randomized, Positive Controlled Study (PERMIT Study)

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Background: A randomized, controlled, open-label, multi-center study was conducted in China to compare the safety, efficacy and cost effectiveness of paricalcitol-dominated therapy with cinacalcet-dominated therapy in maintained hemodialysis (MHD) patients with secondary hyperparathyroidism.

Methods: Patients over 18 years old, accepted MHD over 3 months, serum intact parathyroid hormone (iPTH)≥300pg/mL, serum calcium 2.1–2.5mmol/L and serum phosphorus≥1.78mmol/L were randomized into paricalcitol-dominated therapy group (GpP) or cinacalcet-dominated therapy group (GpC) for 24 weeks. Paricalcitol or cinacalcet monotherapy was prescribed at the beginning, and combination therapy would be carried out when monotherapy was unable to meet the expected target for 2 consecutive visits (Fig 1). The primary endpoint was iPTH maintained within 150–300pg/mL. The secondary endpoints were the combination therapy rate, more than 30% or 50% decline of iPTH from baseline.

Results: 271 patients in 23 centers were screened, 154 patients were enrolled and 93 patients completed the study up to May 2021. There was no statistical difference between groups in age, gender, iPTH, Ca and P at baseline. In GpP and GpC, 44.9% (22/49) vs 36.4% patients (16/44) achieved primary endpoint (P=0.406). 89.8% (44/48) vs 77.3% (34/44) and 73.5% (36/49) vs 63.6% (28/44) patients attained iPTH decline more than 30% (P=0.099) or 50% (P=0.306). 24.7% (9/77) patients in GpP have hypercalcemia, and 42.4% (34/77) patients in GpC have hypocalcemia. The incidences of hyperphosphatemia were similar (28.6% vs 26.0%, P=0.7174). Combination therapy rate had a rising tendency, 36.8% in GpP vs 59.1% in GpC.

Conclusions: Paricalcitol-dominated therapy was as effect as cinacalcet-dominated therapy with lower incidence of hypocalcemia and combination therapy rate. (chictr.org.cn registration number: ChiCTR2000031420)

Fig 1: Study Design

PO0552

The Impact of Paricalcitol on Parathyroid Gland Size of Secondary Hyperparathyroidism Patients with Long-Term Maintenance Hemodialysis: An Observational Study

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Background: This is an observational study to assess effectiveness of paricalcitol for treating secondary hyperparathyroidism (SHPT) patients with long-term maintenance hemodialysis, via changes in biochemical indexes, such as Calcium (Ca), Phosphate (P) and Parathyroid Hormone (PTH), and size of parathyroid gland (PG).

Methods: This single-centre and small sample study included 11 Long-term maintenance hemodialysis patients with SHPT, who were undergoing SHPT treatment with paricalcitol in the Blood Purification Centre of Fengyu people’s hospital, Chongqing, China, from December 2018 to October 2019. We Administered Paricalcitol (Zemplar®) intravenously through a hemodialysis vascular access after dialysis as the following dosage: 5 µg tid for iPTH>1000 pg/ml and 10 µg tid for iPTHS>500 pg/ml. Titrations based on serum calcium and intact PTH levels. We collected biochemical indexes including Ca, P and iPTH, and imaging parameters of PG via ultrasonography (volume and number), evaluating variations between baseline and Month 11 of post-treatment.

Results: Compared to baseline, the maximum diameter lines of PG decreased significantly (mean 1.727 mm vs 10.936 mm, P=0.005) after 11 months’ treatment, though the minimum diameter lines decreased without statistical difference (mean 6.727 mm vs 10.936 mm, P=0.089). The number of glands was less in Month 11 than that of baseline (mean 2.455 vs 2.182, P=0.277) and iPTH declined significantly (mean 1045.109 pg/ml vs 5.255 mm, P=0.089). The number of glands was less in Month 11 than that of baseline (mean 2.455 vs 2.182, P=0.277) and iPTH declined significantly (mean 1045.109 pg/ml vs 5.255 mm, P=0.089). The number of glands was less in Month 11 than that of baseline (mean 2.455 vs 2.182, P=0.277) and iPTH declined significantly (mean 1045.109 pg/ml vs 5.255 mm, P=0.089). The number of glands was less in Month 11 than that of baseline (mean 2.455 vs 2.182, P=0.277) and iPTH declined significantly (mean 1045.109 pg/ml vs 5.255 mm, P=0.089). The number of glands was less in Month 11 than that of baseline (mean 2.455 vs 2.182, P=0.277) and iPTH declined significantly (mean 1045.109 pg/ml vs 5.255 mm, P=0.089).

Conclusions: Intravenous paricalcitol can decrease the size and number of parathyroid gland, and reduce iPTH concentrations in SHPT patients with Long-term maintenance hemodialysis, without significant influence for serum Ca and P levels.
Burden of Secondary Hyperparathyroidism: A Matched Comparison Using Administrative Claims Data from Germany
Philipp Csomor,1 Kim M. Schneider,2 Timotheus Stremel,1 Edelgard Kaiser,1 Dominic Meise,1,2 Vifor Pharma Ltd, Glattbrugg, Switzerland; 3Xcenda GmbH, Hannover, Germany.

Background: Secondary hyperparathyroidism (SHPT) is a frequent, early, and progressive complication in chronic kidney disease (CKD) characterized by excessive parathyroid hormone production. SHPT independently predicts serious complications like cardiovascular diseases (CVD), fractures, progression to dialysis, and death. Analysis of data on the burden of CKD patients with SHPT in the German health insurance system is lacking.

Methods: A German health insurance claims database comprising data from 2014-2018 served as a source to identify CKD stage 3 and 4 patients, who were stratified by the occurrence of incident SHPT using ICD-10-GM diagnosis and ATC prescription codes. SHPT patients were matched 1:1 to non-SHPT patients in the same CKD stage using propensity scores. Index date was the first SHPT diagnosis date in the SHPT cohorts, and a randomly chosen quarter of a CKD diagnosis within the CKD-only cohorts. Patients with evidence of dialysis or kidney transplant prior to the index quarter were excluded. Matched groups were compared with respect to the prevalence of CVD (acute and recurrent myocardial infarction [MI], chronic ischemic heart disease, congestive heart failure [HF], and atherosclerosis [ATH]), dialysis, and CKD progression in a two-year follow-up period.

Results: Overall, 1,156 incident SHPT patients in CKD3 and 517 in CKD4 and the prevalent SHPT patients were identified. Prevalence of combined CVD conditions was higher in SHPT patients (46.8% vs. 41.9% p=0.05 in CKD3, 56.5% vs. 51.8% p=0.13 in CKD4). HF was more frequent among SHPT patients (34.6% vs. 28.6% p=0.01 in CKD3 and 46.4% vs. 39.3% in CKD4 p=0.05) while acute MI was observed significantly more often among CKD4 patients in the SHPT cohort (9.1% vs. 5.8% p=0.05). ATH was more frequent in SHPT patients in CKD4 (18.6% vs. 14.3% p=0.06). SHPT patients progressed to CKD5 more often (6.1% vs. 1.2% from CKD3, 26.7% vs. 2.9% from CKD4, both p<0.01) which resulted in a higher proportion of dialysis (6.1% vs. 1.3% in CKD3, 22.1% vs. 3.7% in CKD4, both p<0.01).

Conclusions: Patients with CKD3&4 and incident SHPT presented with a significantly higher disease progression to CKD5 and dialysis and had a higher prevalence of CVD compared to patients without SHPT during a two-year follow-up period.

Funding: Commercial Support - Vifor Fresenius Medical Care Renal Pharma Ltd.

Side Selective Renal Reduction of Intact and C-Terminal FGF-23
Shilpa Sharma,1 Alfonso J. Houben,2 Abraham A. Kroon,2 Peter W. de Leeuw,2 Andrew N. Hoofnagle,1 Ronit Katz,1 Alexander Bullen,4 Charles Ginsberg,4 Joachim H. Ik,4 1University of California Los Angeles, Los Angeles, CA; 2Universiteit Maastricht, Maastricht, Netherlands; 3University of Washington, Seattle, WA; 4University of California San Diego, La Jolla, CA.

Background: Relative abundance of FGF23 measured by the C-terminal (cFGF23, which measures both intact FGF23 & C-terminal fragments) vs intact (iFGF23) assays is higher in persons with higher eGFR. Mechanisms are unclear. Individuals with vascular disease often have asymptomatic renal function. We compared side selective (R vs L) renal resection of iFGF23 and cFGF23 within the same individual.

Methods: 162 patients were referred for renal angiography at Maastricht University, the Netherlands, for clinically suspected RAS. Participants were maintained off anti-hypertensive meds for 21 days. Blood samples were obtained from the aorta and right (RV) and left renal vein (LV), and renal blood flow was measured using 133Xenon washout. Creatinine (Cr), cFGF23 (Immutopics), and iFGF23 (Kainos) were measured. Difference of side selective % reductions of each metabolite ([Aorta – (RV or LV)/Aorta]×100) was calculated among each participant. Mean “RV-LV metabolite reduction difference” was calculated across all participants.

Results: Mean age was 54±12 years, 54% were women, and all were white. Mean eGFR was 75±25 ml/min/1.73m2 and directly measured Cr clearance during angiography was 72±48 ml/min/100g. Median (IQR) aorta concentrations of cFGF23 was 82 (59, 105) RU/mL, and intact FGF23 was 47(37, 65) pg/mL. The mean difference in R vs. L Cr clearance was 6.0 ± 3.6 ml/min/100g. Side selective reduction differences of both cFGF23 & iFGF23 were significantly related to side selective Cr reduction. Side selective phosphate reduction also associated with iFGF23 reduction independent of Cr reduction, but not cFGF23 (Table). Results were similar in models adjusted for age, sex & BMI.

Conclusions: In hypertensive individuals, the kidney with greater Cr reduction also reduced plasma cFGF23 and iFGF23 more than the contralateral kidney. The kidney that removes more iFGF23 also removes more phosphate, independent of Cr removal; a finding not observed for cFGF23.
PO0557

Potassium Supplementation Decreases Plasma Fibroblast Growth Factor 23 and Increases Plasma Phosphate in Stage 3b-4 CKD Patients: Single-Arm Intervention Study

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Background: Advanced chronic kidney disease (CKD) is characterized by mineral and bone disorders (MBD) including elevated fibroblast growth factor 23 (FGF23). Recent studies in healthy subjects showed that potassium supplementation decreases FGF23. Here, we investigated whether potassium supplementation reduces FGF23 and other MBD parameters in patients with CKD.

Methods: We performed a post-hoc analysis of a 2-week open-label run-in phase from a clinical trial in patients with CKD stage G3b-G4 (NCT03235172). Patients received potassium chloride (KCl, 40 mmol/day). Baseline and post-treatment blood and urine samples were collected. Mixed model analyses were used to assess effects of potassium supplementation on MBD parameters.

Results: We included 113 patients in whom KCl supplementation increased plasma phosphate (from 1.0 ± 0.2 to 1.1 ± 0.2 mmol/L, P < 0.001) and tubular phosphate reabsorption (from 0.64 ± 0.20 to 0.69 ± 0.20 mmol/L, P < 0.001). KCl supplementation, when adjusted for estimated glomerular filtration rate, decreased C-terminal FGF23 (eFGF23) from 140.5 [Interquartile range (IQR) 105.9–217.4] to 131.5 [IQR 105.8–212.8] RU/mL, P < 0.05, intact FGF23 (from 69.6 [IQR 46.6–107.1] to 62.9 [IQR 47.1–104.6] pg/mL, P = 0.003) and vitamin D (72.5 [IQR 43.9–92.9] to 70.2 [IQR 44.2–90.1] nmol/L, P < 0.001). Parathyroid hormone, plasma calcium, 24hrs urinary calcium excretion, and IL-6 did not change. At baseline, 37 participants were vitamin D deficient (<50 nmol/L). The decrease in eFGF23 by KCl supplementation depended on baseline vitamin D status (P-interaction=0.002), and was present in vitamin D sufficient (147 [IQR 108.3–216.8] to 130.9 [IQR 105.5–218.0] RU/mL, P = 0.03), while it was not in vitamin D deficient patients (131.5 [IQR 104.0–230.7] to 133.0 [IQR 106.8–211.0] RU/mL, P = 0.32).

Conclusions: In this short-term interventional study, KCl supplementation reduced FGF23 and coincided with increased plasma phosphate levels and vitamin D. Reduction in eFGF23 by KCl was only present in vitamin D sufficient patients. Dietary potassium intake might decrease FGF23 levels and vitamin D status should be sufficient before FGF23 lowering strategies could be applied in patients with CKD.

PO0558

The Dietary Supplement Chitosan Lowers Serum Phosphorus in a Hemodialysis Patient Not Tolerating Prescription Binders

Martin Sedlacek, Multidisciplinary patient care team, FMC Lebanon dialysis unit, Lebanon, NH Dartmouth-Hitchcock Medical Center, Lebanon, NH.

Introduction: Chitosan is a chitin derived, non-toxic, biodegradable biopolymer that binds negatively charged molecules. It’s numerous industrial applications include phosphorus binding in agricultural wastewater. In humans it is used as a dietary supplement for weight loss, purportedly binding negatively charged lipids and bile acids and preventing their absorption. Here we report the case of a dialysis patient who did not tolerate prescription binders and who was able to control her serum phosphorus level for over a year by taking 3.5g of Chitosan with meals.

Case Description: A 66 y/o woman with no prior medical history and not taking any medications presented with emphysematous pyelonephritis with bilateral obstructing staghorn calculus requiring intensive care and hemodialysis. Her initial serum creatinine was 18 mg/dL. She recovered from sepsis but continued to require dialysis after discharge. Her residual creatinine clearance was 7.9ml/min six months after hospital discharge and 5.6ml/min two years later. The patient tried several prescription phosphorus binders but eventually decided to stop all prescription medications because of gastrointestinal side effects. Since over a year ago, at the recommendation of her dietitian, she purchased 500mg Chitosan tablets from the internet and used them like a phosphorus binder with meals, at a dose of 3.5 g per day. Her serum phosphorus levels have been stable and in a controlled range since (Figure 1). A quantitative analysis using ura kinetics to estimate phosphorus intake and removal reveals that Chitosan bind around 40 mg of phosphorus per gram, comparable to prescription binders.

Discussion: Chitosan acts as an over-the-counter non-calcium containing phosphorus binder that may provide an alternative option for patients who do not tolerate prescription phosphorus binders. Importantly, it may be psychologically more attractive for patients to take a dietary supplement for weight loss with their meals than a prescription medication.

Figure 1: Effect of Chitosan on serum phosphorus levels

PO0559

Longitudinal Changes in FGF-23 in Children with CKD

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Background: Cross sectional studies show that plasma FGF23 is increased early in the course of chronic kidney disease (CKD) in children and adults and associates with disease progression and adverse cardiovascular outcomes. However, longitudinal changes in FGF23 have not been described in children with progressive CKD.

Methods: We measured C-terminal FGF23 and estimated GFR at baseline and every other year in 564 children with CKD stages 2-4 enrolled in the Chronic Kidney Disease in Children (CKD) study. All subjects had 2 to 5 FGF23 measurements. We used linear mixed models to identify factors associated with baseline FGF23 level and longitudinal changes and latent group-based trajectory modeling to characterize distinct classes of FGF23 trajectories.

Results: Median age was 11 years and eGFR 55 ml/min/1.73m2. In a univariate model with repeated measures, plasma FGF23 was 12% higher for every 10% lower eGFR (P = 0.0001). In fully adjusted models, higher FGF23 at baseline was significantly associated with lower GFR, higher serum phosphorus, and glomerular diagnosis. Thereafter, FGF23 increased more rapidly in older subjects with lower GFR and higher proteinuria at baseline. We identified three distinct linear FGF23 trajectories: stable FGF23 in 62% of subjects (FGF23 slope 0% per yr); slowly rising in 32% (6% per yr) and rapidly rising in 6% (39% per yr). At baseline, median FGF23 in the trajectory groups were 90 [IQR:70,120], 166 [125, 242] and 461 [219, 924] RU/mL, respectively. Membership in the faster-rising trajectory groups was associated with lower eGFR, higher proteinuria and serum phosphorus, and glomerular diagnosis.

Conclusions: FGF23 was relatively stable in most children with CKD, but it increased more rapidly in those with traditional CKD risk factors. Further analyses of FGF23 trajectories will investigate whether FGF23 is a modifiable cause or a consequence of CKD progression and cardiovascular complications.

Funding: NIDDK Support

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212
PO0560
Two Siblings with X-Linked Hypophosphatemia (XLH) Treated with Burosumab: Is Therapeutic Regimen Recommended Now Supported by Real-World Data?
Hiroiaki Morita,1 Kiyoko Inui,2 Yoshihiko Inoue,2 Fumihiko Kiwita,2 Ashio Yoshimura,1 Junko Takagi,1 Aichi Ika Daigaku, Nagakute, Japan; 1Shiga Daigaku Fujigouka Byoin, Yokohama, Japan; 2Shinnyokohama Daichii Clinic, Yokohama, Japan.

Introduction: Burosumab, a human monoclonal antibody to FGF 23, is used now to treat XLH. In phase III study, patients were selected and controlled. What is considered as “recommended” regimen of burosumab in that population within the controlled setting might be different from that in another population in real world. The present study was conducted in an attempt to address this issue.

Case Description: Patient A and patient B with XLH are siblings in their twenties. They were successfully managed in childhood, and have enthesopathy. They had had alpha calciferol and phosphate supplementation, and started to have 1 mg/kg BW burosumab 1.5 years ago. Changes in TmP/GFR, IP, and sCr after burosumab administration are shown (Figure). A significant increase in TmP/GFR (p<0.00001) was seen. IP and sCr levels almost did not change. Nephrocalcinosis, hyperparathyroidism, and vitamin D deficiency were mild and not worsened. Changes in bone mineral density (BMD) were assessed by DEXA scan. In 2018, young adult mean (YAM) of lumbar vertebrae were 129% in Patient A, and 138% in Patient B. In 2021, these YAM values increased to 141% in Patient A and 140% in Patient B, respectively. Figure legend: Data for the past 6.5 years were retrospectively analyzed and shown as mean (column) plus standard deviation (bar). N numbers indicate the time they visited our hospital where they gave blood and spot urine samples. Dimensions of IP and sCr are mg/dL. TmP/GFR; tubular threshold maximum for phosphorus per glomerular filtration rate.

Discussion: Using real-world data, we confirmed the efficacy and safety of recommended burosumab therapy regimen for 1.5 years, so far as laboratory indices used in phase III study were concerned. However, YAM values were above-the-average and increasing in the presence of hypophosphatemia and low TmP/GFR. The future consequence of this feature in relation to time-elapsed changes in renal physiological parameters including TmP/GFR, Ca, IP, and sCr should be seen.

PO0561
Burosumab in X-Linked Hypophosphatemic Rickets Adult Patients: An Italian Center Experience
Nadia Edgide Folungo, Teresa Arcidiacono, Arianna Bologna, Elena Brioni, Monica Avino, Giuseppe Vezzoli, Nephrology and Dialysis Unit, IRCCS San Raffaele Scientific Institute, Vita-Salute University, Milan, Italy.

Background: X-linked Hypophosphatemic Rickets (XHR) is a rare disease caused by mutations in the PHEX gene leading to an increase in the serum levels of FGF23, which inhibits the tubular reabsorption of phosphates and the production of 1,25(OH)D. This causes hypophosphatemia, rickets, bone deformities, growth retardation and muscle activity impairment.

Methods: Burosumab (B) is a monoclonal antibody against FGF23, used for the treatment of XHR patients. In Italy B can be employed in adults only as compassionate use. Starting in 2020 B (1 mg/kg sc every 4w) was administered to 4 adult subjects treated with XHR: VM (M, 32 yrs), ST (F, 47), ER (M, 46) and SM (F, 20) who showed legs use. In Italy B can be employed in adults only as compassionate use.

Results: A total of 3867 hemodialysis patients (average age of 55.3±18.9 years; 61.81% of males) were included. 48 cases were diagnosed with CUA, and the prevalence was 1.24%. Among CUA patients, 68.75% of cases were male, and average age and median dialysis duration were 53.85±15.17 years and 84.00 (48.00, 138.75) months respectively. The average BMI of CUA patients was higher than that of controls, and patients with hyperparathyroidism, diabetes, atrial fibrillation, stroke, or tumors were more likely to suffer from the disease. Although only 4 CUA patients used warfarin therapy, there was still a significant statistical difference between the two groups. Multivariate analysis indicated that increased BMI, prolonged dialysis duration, warfarin therapy, concomitant with hyperparathyroidism, diabetes mellitus or tumors, low ALB, and high serum ALP levels were high-risk factors for CUA. 394 (10.32%) of 3819 hemodialysis patients who didn’t meet current diagnostic criteria for CUA had a variety of manifestations of skin lesions, mainly in lower limbs. 28.68% of these patients complained about a progressive deterioration of skin damage, and 44.67% suffered moderate to severe pain with potential CUA risks.

Conclusions: The prevalence of CUA in Chinese hemodialysis patients was 1.24% according to this regional epidemiological survey, but its actual prevalence was presumably far beyond present data. Calciphylaxis, as a disease with such a high disability and fatality rate, should attract the attention of relevant specialists.

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Calciphylaxis lesion at diagnosis (A) and 6 months later (B)

PO0564
Calciphylaxis in a Cohort with Normal Kidney Function: Improved Survival Compared to ESKD
Mohamed Hassanein, Emad Ababneh, Anas Saad, Eleanor E. Cook, Anthony P. Fernandez, Jennifer S. Ko, Steven D. Billings, Richard A. Fatica, Tushar J. Vachharajani. Cleveland Clinic, Cleveland, OH.

Background: Calciphylaxis is a rare, devastating disease, characterized by vascular calcification and is associated with increased mortality.

Methods: We studied the baseline characteristics and outcomes of 78 patients with biopsy-proven calciphylaxis that were stratified according to glomerular filtration rate (GFR) into normal kidney function (NKF): GFR ≥ 90 mL/min/1.73 m², chronic kidney disease (CKD): GFR 15 – 89 mL/min/1.73 m², and end-stage kidney disease (ESKD): GFR <15 mL/min/1.73 m².

Results: Forty-seven patients (60%) with calciphylaxis had ESKD, compared to 22 patients (28%) with CKD and 9 patients (12%) with NKF. Patients with NKF were younger (median age 55 years compared to 69 years in CKD and 65 years in ESKD, p=0.006). Across all 3 groups, there was a predominance of female gender, obesity, multiple and peripheral lesions involving the extremities. Among patients with ESKD, 39 patients (83%) were on hemodialysis (HD) and 7 patients (15%) were on peritoneal dialysis (PD). The probability of survival was significantly higher in patients with NKF compared to ESKD (p = 0.039)(figure 1). Sepsis was the most common cause of death.

Conclusions: Calciphylaxis can occur in patients with normal or abnormal kidney function. Female gender, obesity, multiple, and peripheral lesions were predominant in our cohort. Patients with NKF were younger, which may have contributed to their increased survival compared to ESKD. Sepsis due to secondary infection of necrotic wounds appears to remain the most common cause of death.

PO0565
Severe Tumoral Calcinosis of the Hip in a Hemodialysis Patient

Introduction: Tumoral calcinosis (TC) is a rare complication of patients with end-stage renal disease (ESRD) on hemodialysis (HD) in which precipitation of calcium salts occurs in periarticular soft tissue. This manifestation can lead to painful and function restricting lesions. We herein describe a case of a severe presentation of TC with associated ulceration.

Case Description: A 47-year-old female with medical history of arterial hypertension, heart failure, hypothyroidism, focal segmental glomerulosclerosis and ESRD on HD for 15 years presented to the emergency department after a right hip ulceration. The patient described a right hip hard mass with ten years of progressive growth that suffered a sudden rupture associated with sand-like secretions. Medication and dialysis compliance was reported. Vital signs were unremarkable. Physical examination showed a right hip swelling and ulcer. Laboratories revealed WBC of 19.98 10^3/µL, Hgb of 8.70 g/dL, calcium 9.9 mg/dL, phosphorus 6.6 mg/dL, 25-hydroxyvitamin D 12.72 ng/mL and PTH 288.90 pg/mL. Calcium Phosphate Product (CPP) resulted in 65.34 mg/dL. Pelvic CT scan showed a 11.4 cm x 9.6 cm mixed density calcified cystic mass with multiple fluid-calcium levels in the right hip, suggestive of TC. Treatment with intravenous Sodium Thiosulfate, Sevelamer and antibiotics were provided. Cleansing and debridement were performed by the plastic surgery team without complications. Patient was discharged and sodium thiosulfate treatment was continued at the hemodialysis center. Discontinuation of the treatment was proposed by the plastic surgery team.

Discussion: TC is associated with the dysregulation of calcium phosphate metabolism. Altered renal phosphate excretion along with vitamin D activation leading to hyperparathyroidism with elevated CPP is the proposed mechanism. The precipitation of large periarticular deposits of calcium salts leads to inflammation and chronic pain. Consequently, limiting functionality and impairing quality of life. Surgical excision can relieve symptoms, but the deposits can recur. Sodium thiosulfate has been described as a potential treatment, but further studies are necessary to assess its role in dialysis patients. The recognition of this rare disease is important as optimization of medical therapy and dialysis regimen can improve the evolution and outcome of this disorder.

PO08566
Case Series of Penile Calciphylaxis in a Large Urban Hospital
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Background: Calciphylaxis or calcific uremic arteriolopathy (CUA) is a complex syndrome of deranged mineral metabolism and vascular calcification with subsequent tissue ischemia predominantly in end stage kidney disease (ESKD) patients on dialysis. The disease has been categorized as central or peripheral but in rare cases of peripheral calciphylaxis there may be penile involvement. Due to the paucity of data on penile calciphylaxis, this study was done to ascertain the characteristics, management and mortality of patients with this condition.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Methods: An observational study involving retrospective analysis of medical records of six (6) patients with biopsy proven penile calciphylaxis treated in a large urban hospital between January 2000 and March 2021 was performed.

Results: All patients with penile calciphylaxis had ESKD with mean duration on dialysis of 5.2±3.5 years. The mean age at diagnosis was 54±9.7 years. Sixty six percent of patients were African Americans with the remainder being Caucasians. Only one of six patients was obese with mean BMI of 23.2±5.5 kg/m². Similarly only one patient was on warfarin. None of the patients was on systemic steroids or vitamin D at the time of diagnosis.

All patients had secondary hyperparathyroidism with median PTH of 264.5pg/mL (IQR 175.5). Surprisingly all patients had normal calcium phosphate products with mean lower than our previously reported level of 569pg/mL in our calciphylaxis database. The PTH was associated with calciphylaxis, majority of our patients with penile calciphylaxis were not obese. Interestingly all our patients had normal calcium phosphate products suggestive of heterogeneous mechanisms in the pathophysiology of the disease. The PTH was lower than our previously reported level of 569pg/mL in our calciphylaxis database. Our mortality rate was very high with 100% mortality within six months of penile calciphylaxis diagnosis.

PO0567

A Case of Severe Penile Pain
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Introduction: Calciphylaxis is a rare disease with skin necrosis, tissue ischemia and small to medium-sized vessel calcium (Ca) deposition and thrombosis. The prevalence of penile calciphylaxis is 0.24% in end stage kidney disease (ESKD). Given its rarity and location, it can be difficult to diagnose and has a poor prognosis. Identifying it is imperative.

Case Description: 56 year old male with ESKD on hemodialysis (HD) due to diabetes mellitus with secondary hyperparathyroidism and peripheral vascular disease was admitted with a painful, necrotic penile lesion for 1 month. Since starting HD 1 year prior, his serum phosphorous ranged 7.8-9.0mg/dL, Ca 8.0-9.0mg/dL and parathyroid hormone downwarded from 611 to 127pg/mL on hectorol, phosho and Ca therapy. CTA showed atherosclerotic stenosis of internal pudendal arteries with patent penile arteries. Interventionsal angiongram showed severe stenosis occluding distal pudendal arteries. After consensus with nephrology, interventional radiology, vascular surgery, urology, dermatology and infectious disease, the diagnosis of penile calciphylaxis was made. Treatment goals included phosphate normalization by 4 weekly HD sessions, low Ca dialysate, non Ca based phosphate binders; vasodilators sildenafil and pentoxifylline, and sodium phosphate (blocks calcification of smooth muscle cells). He is in a clinical trial for SNF427, a selective calcification inhibitor, for wound healing and pain management. His severe pain has resulted in disability and income loss.

Discussion: Penile calciphylaxis is associated with hyperparathyroidism, ESKD, and normal body mass index. Neither parathyroidectomy nor penectomy have shown mortality benefits and current treatments are not based on interventional trials. Kidney transplant may be curative. It is essential that we identify penile calciphylaxis, given its significant morbidity and mortality.

PO0569

Incident Diuretic Use and Subsequent Risk of Bone Fractures: A Large Nationwide Observational Study of US Veterans
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Background: Diuretics may affect bone metabolism by electrolyte imbalance (e.g., Ca and Na derangements). Inconsistent associations have been reported between diuretic use and fracture, presumably due to the heterogeneity of study designs and populations.

Methods: In a nationwide cohort of 2,318,267 US veterans with an eGFR≥60 mL/min/1.73m² from 2004-2006 and follow-up through 2018, we examined the association of incident diuretic use (thiazide, loop, and K-sparing diuretics, as time-dependent exposures) with incidence of any fractures (both vertebral and non-vertebral fractures), using time-dependent Cox models adjusted for sociodemographics, smoking and alcohol use, comorbidities, eGFR, vital signs, and medications (e.g., bone anabolic/antiresorptive agents, SERMs, steroids). Associations were also assessed by diuretic types.

Results: Patients were 50±15 years old; 91% were male; 14% were African American, and 18% were diabetic. Their baseline eGFR was 82±16 mL/min/1.73m². Among 2,318,267 patients, 835,054 (36.0%) started any diuretic therapy, and 146,017 (6.3%) experienced an incident fracture. After multivariable adjustment, incident diuretic use (vs. non-use) was significantly associated with higher risk of incident fracture (adjusted HR [95%CI], 1.13 [1.06-1.19]). The association was most pronounced for loop diuretics (1.37 [1.28-1.46]) but less evident for thiazide diuretics (1.07 [1.00-1.14]), and was not significant for K-sparing diuretics (1.16 [0.88-1.54]) (Figure).

Conclusions: Diuretic use, particularly loop diuretic use, was independently associated with higher risk of incident bone fractures. While our findings may be from confounding by medical indication, it might suggest a distinct pathogenic contribution of diuretics to bone metabolism and the need for careful attention to skeletal outcomes when initiating diuretics.

Funding: Veterans Affairs Support
Low Magnesium Is Associated with Weak Bone Strength in Pre-Dialysis CKD Patients: Results from the KNOW-CKD Study

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Background: In patients with chronic kidney disease (CKD), bone strength was weakened as CKD progressed. There are still controversial association of this and inadequate vitamin D status (VDBP) deficiency and osteoporosis in pre-dialysis CKD patients.

Methods: We investigated the association between serum Mg and a decrease of bone mineral density (BMD) from the prospective, multicenter cohort of pre-dialysis CKD patients (n=928). Patients were divided into tertiles according to serum Mg. The primary endpoint is a decrease of BMD, defined as decline of BMD of lumbar spine < -0.05 cm²/yr.

Results: After 4 years of follow-up, BMD decreased in 267 (28.7%) patients. In a multivariable binary logistic regression model, the lowest tertile of Mg was associated with risk of the decrease of BMD of lumbar spine (T1, serum Mg <2.2 mg/dL, OR ratio (OR) 2.79 [1.58–4.92]; T2, serum Mg 2.2–3.3 mg/dL, reference group). Similar results were obtained when sensitivity analysis was performed with BMD of femur neck. Subgroup analyses showed that low Mg was particularly associated with risk of the decreased BMD of lumbar spine in patients <50 years of age, in those without diabetes mellitus, and in those with low physical activity.

Conclusions: Low level of Mg is associated with a weak bone strength in pre-dialysis CKD patients.

The Vitamin D Metabolite Ratio May Serve as an Important Biomarker of Vitamin D Status in Patients Undergoing Therapeutic Plasma Exchange

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Background: Recent studies suggest that 25-hydroxyvitamin D [25(OH)D] may be a poor marker of vitamin D status due to variability in levels of vitamin D binding protein (VDBP). The vitamin D metabolite ratio (VMR) is the ratio of 24,25(OH)2D3: 25(OH)D3 and is thought to be independent of variability in VDBP. Therapeutic plasma exchange (TPE) on free vitamin D concentrations and the VMR remains unknown.

Methods: We measured total 25(OH)D, 1,25(OH)2D, 24,25(OH)2D3, free 25(OH)D, VDBP and VMR across TPE. Results were obtained when sensitivity analysis was performed with BMD of femur neck.

Conclusions: Low level of Mg is associated with a weak bone strength in pre-dialysis CKD patients.

Performance Status (PS) as an Effect Modifier for Association Between Vitamin D Receptor Activator (VDRA) and Outcomes Among Hemodialysis Patients

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Background: VDRA use has been reported to be associated with lower mortality and fracture among hemodialysis patients. However, PS has not been considered in previous studies.

Methods: This is a prospective cohort study based on JSDT Renal Data Registry. Subjects on hemodialysis with age 20-100 at the end of 2009 were included. Exposure variables were two-year all-cause mortality and hip fracture. Associations between VDRA use and mortality or fracture were analyzed using Cox or poisson regression, respectively and interaction between VDRA use and PS was tested.

Results: Among 210,001 subjects, 80,492 (61.7%) were on VDRA. VDRA use was not associated with all-cause mortality (HR 1.02 [0.99-1.05]) or hip fracture (IRR 0.93 [0.86-1.00]) after adjustment for confounders including PS. The use of VDRA was associated with lower mortality and incidence of fracture among those with good PS (PS0) but not with poor PS (P interaction 0.03 and 0.05, respectively). Poor PS was associated with higher corrected calcium (Ca), lower parathyroid hormone (PTH) levels, and proportion of intravenous VDRA use was lower among those with poor PS. Linear regression analysis showed that the association between higher corrected Ca levels and VDRA use were stronger among those with poor PS compared with those with good PS (P interaction 0.01).

Conclusions: VDRA use was associated with better outcomes only among those with good PS. The reasons may be higher prevalence of adynamic bone among those with poor PS suggested by lower 25(OH)D and greater increase in Ca levels by VDRA, or preclusion of higher dose VDRA prescription due to higher Ca levels.

Changes in Vitamin D Metabolites, VDBP, and VMR from Before to After a Single TPE Procedure (N=45)

PO0572

Childhood Hypercalcicuric Hypercalcaemia with Elevated Vitamin D and Suppressed Parathyroid Hormone: Long-Term Follow-Up

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Background: Hypercalcaemia with low parathyroid hormone (PTH) level, hypercalciuria, nephrocalcinosis, or nephrolithiasis, was recently reported as caused by mutations in CYP24A1 and SLC34A4 genes. These encode for vitamin D-24A-hydroxylase and for the renal phosphate transporters NaPiIIa and NaPiIIc, respectively. We aimed to describe the course of these conditions during long-term follow-up.

Methods: Ten patients with the above features were followed in our center during 1998-2019. Relevant laboratory and imaging data and results of genetic evaluation were retrieved from medical files.

Results: The median age at presentation was 9.5 months (range 1 month-11 years), six (60%) males, and the median follow-up time was 3.8 (1.1-14) years. Mutations in CYP24A1 and SLC34A4 were identified in three and one patients, respectively. Five patients presented with nephrocalcinosis, three with nephrolithiasis, and two had normal renal ultrasound. High blood calcium and 1,25-(OH)2D levels at presentation decreased during follow-up (11.1±9.9 vs. 5.0 µg/dL (p=0.012), and 307±297 vs. 66±42 ng/ml (p=0.03), respectively); this paralleled an increase in suppressed PTH levels (5.8±4.0 vs. 11.8±7.5 pg/ml, p=0.2). Substantial improvements in hypercalciuria and renal sonography findings were not observed. Two patients had impaired renal function (eGFR 84-88 ml/min/1.73m2) at the last follow-up. Interventions included appropriate diet, citrate supplementation, and thiazides.

Conclusions: In patients with the described clinical and laboratory profile, abnormal renal sonographic findings can persist despite appropriate treatment; and renal function may deteriorate. Long-term follow up and intervention to prevent nephrocalcinosis and nephrolithiasis are recommended in these children.

PO0573

Suppressed Parathyroid Hormone: Long-Term Follow-Up

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Background: Hypercalciuria with low parathyroid hormone (PTH) level, hypercalciuria, nephrocalcinosis, or nephrolithiasis, was recently reported as caused by mutations in CYP24A1 and SLC34A4 genes. These encode for vitamin D-24A-hydroxylase and for the renal phosphate transporters NaPiIIa and NaPiIIc, respectively. We aimed to describe the course of these conditions during long-term follow-up.

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Conclusions: In patients with the described clinical and laboratory profile, abnormal renal sonographic findings can persist despite appropriate treatment; and renal function may deteriorate. Long-term follow up and intervention to prevent nephrocalcinosis and nephrolithiasis are recommended in these children.
Prevalence of Vitamin D Deficiency in a Predominantly African-American Hemodialysis Patient Population

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Background: Vitamin D insufficiency and deficiency are common abnormalities and high risk groups include kidney disease patients and African-Americans. Recommendations on the evaluation of vitamin D levels in CKD and ESKD are ambiguous due to a lack of studies examining epidemiology and treatment. The COVID-19 pandemic has disproportionately affected minorities and has highlighted the need for studies as studies have examined vitamin D deficiency as a risk factor for COVID-19 complications. We present a case series examining the prevalence of vitamin D deficiency in a predominantly African-American hemodialysis patient population.

Methods: Retrospective chart review of all in-center hemodialysis patients at Emory Dialysis in Atlanta, GA. Data extracted from Sep to Nov 2020. We excluded any patients on home therapies. Serum 25(OH)vitamin D concentration total was analyzed. We defined vitamin D insufficiency as 20-29.9 ng/mL and vitamin D deficiency as a level<20 ng/mL.

Results: Patients receiving in-center hemodialysis(n=615). Average length of time on dialysis was 5 years and average age was 59.4 years. Patients were 52.5% male(n=323), 91.5%(n=563) of patients were African-American. Mean calcium level for all patients was 8.73 mg/dL and PTH level of 554 pg/mL. Mean vitamin D in all patients was 26.32 ng/mL. 98%(n=603) of patients had a vitamin D level available. All patients with vitamin D level<30 ng/mL(68.3%) and all patients with vitamin D level<20 ng/mL(40.5%). African-American patients with a vitamin D level was 552. African-American patients with vitamin D level<30 ng/mL=382 (69.2%) and African-American patients with vitamin D level<20 ng/mL=229(41.5%).

Conclusions: In comparison to others such as the DIVINE trial, we present a larger and more diverse cohort. In our study, African-Americans had a statistically significant lower vitamin D level. A case for replacing 25(OH) vitamin D even in ESKD patients, especially with regard to autocrine regulation of immune function. Future directions include examining effects of treatment on PTH and study of vitamin D deficient patients’ risks for adverse events like COVID-19 infection.

PO0576
Development of a Machine Learning Approach to Management of CKD-MBD Therapy

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Background: We developed a Quantitative Systems Pharmacology (QSP) model of CKD-MBD that predicts changes in mineral metabolism. We incorporate the CKD-MBD model into an Machine Learning (ML)-based simulation to optimize the dosing of three drugs used in CKD-MBD to test the hypothesis that Reinforcement Learning (RL) approach would improve therapeutic goals.

Methods: We performed a simulated 24 month study in a virtual cohort of 80 Stage 5d CKD patients using the QSP model of CKD-MBD treated by a simulated physician (AI-Agent 0) or RL (AI-Agent 1). Agent 0 was a Deep Neural Network trained on a set of 128,061 instances. Agent 1 was developed using RL rewarding concentrations within the target range for Ca, P, PTH and avoiding Ca < 7.0 and > 10.2 mg/dL. Results of the simulation were compared using regression analysis of the dependent variable (Ca, P, PTH, calcitriol (CTL), INFgF23, bCa(bone efflux), and vCa(vascular influx) over time with the factors RL (Agent1 vs Agent 0), P binder adherence, and equilibrium vs. steady-state. Doses of agents used to treat were compared at 24 months.

Results: Results of the statistical analysis are shown in the Table. Agent 1 using RL resulted in a greater rate of change in the dependent variables in all cases and resulted in lower model predicted concentrations of P, PTH, and FGF23 and higher concentrations.
of Ca, and CTL. The time effect on FGF23 was not significant. Ca flux from the bone and into the tissue was also decreased in Agent 1. Drug utilization was also different between methods tested at 24 months. Agent 1: 734 mg/day less P binder (p=0.015), 0.71 ug/day more calcitriol (p=0.001) and 3.84 mg/day less cinacalcet (p=0.001).

**Conclusions:** Through simulation we have shown that a machine learning approach using reinforcement learning is superior to an expert system mimicking physician dosing practices. Concentrations of Ca, P, and PTH came into equilibrium faster and at more optimal levels while predicting decreased unwanted Ca movement.

**Funding:** Veterans Affairs Support

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**PO0577**

**Role of Current Proposed Algorithm to Guide Osteoporosis Treatment in CKD: A Bone biopsy Study**

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**Background:** Recently, algorithms have been proposed to guide osteoporosis treatment in chronic kidney disease population. As suggested by Kharraiah et al, evaluation of bone turnover level by bone specific phosphate alkaline (bALP) will determine the use of anabolic or antiresorptive therapy with or without prior bone biopsy. The aim of this study is to use a cohort of CKD patients who had a bone biopsy to evaluate accuracy of this algorithm in a real-world setting.

**Methods:** Single-center retrospective cross-sectional study at CHU de Quebec, Canada from 2017 to 2021. CKD 4-5 patients with bone fragility and suspicion of low bone turnover or mineralization defects who had a bone biopsy were included. Results of bone biopsy were categorized based on the TMV classification. We compared the performance of the algorithm to identify potential contraindications to antiresorptive or anabolic therapy vs bone biopsy results. Receiver operating characteristic (ROC) curves were used to explore the predictive ability of bALP and tALP regarding low bone turnover and potential contraindication to antiresorptive therapy in our cohort.

**Results:** Twenty-six patients included (mean age 67.7 years, 11 men, 14 HD and 1 PD, 11 diabetic patients). Eleven patients had low, 8 normal and 7 high bone turnover on biopsy. According to the algorithm, no patient would have received anabolic treatment, bone biopsy would have been proposed to 10 patients and 16 would have received antiresorptive therapy. Based on the biopsy results, 8 out of these 16 patients had potential contraindications: 4 with low bone turnover and 4 with presence of mineralization defects. ROC curve for bPAL to predict low bone turnover was 0.749 (similar to tPAL). However, the AUC for bPAL to predict potential contraindication to antiresorptive therapy was lower at 0.6667 (0.6095 for tPAL).

**Conclusions:** Algorithm predicting bone turnover markers can help clinicians in approaching these patients. However, bone biopsy is still needed in many patients to better tailor anti fracture therapy until more accurate non-invasive markers are available.

**Funding:** Private Foundation Support, Government Support - Non-U.S.

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**PO0578**

**Different PTH Responsiveness and Bone Turnover in Japanese as Compared to European Patients Treated with Hemodialysis**

**Pieter Evenepoel,** Hanne S. Joergensen, Hirokata Komaba, Sandro Mazzaferrero, Marc G. Vervoort, Etienne Cavaler, Masafumi Kogawa, on behalf of the CKD-MBD working group of the JSN, and EUROD, an initiative of the CKD-MBD working group of ESKD-ETDA-Katholike Universiteit Leuven, Leuven, Belgium; Katholike Universiteit Leuven Universiteit Ziekenhuizen Leuven, Leuven, Belgium; Aarhus Universitetshospital, Aarhus, Denmark; Universita degli Studi di Roma La Sapienza, Rome, Italy; Umberto 1 Policlinico di Roma, Roma, Italy; Universite de Liege, Liege, Belgium; Amsterdam Universitair Medisch Centra, Daarheen, Netherland; Tokai Daigaku, Ichihara, Japan.

**Background:** Parathyroid hormone (PTH) targets are lower in Japanese compared to European patients on dialysis. Whether this translates to lower bone turnover may depend on PTH responsiveness. This study tested the hypothesis that skeletal PTH responsiveness differs between Japanese and European hemodialysis patients.

**Methods:** Whole PTH (Roche), bone-specific alkaline phosphate (bAP, iSYS), and tartrate-resistant acid phosphatase type 5b (TRAP5b, iSYS) were centrally assessed in 378 prevalent hemodialysis patients from Japan and Belgium, matched 1:1 on age, gender, diabetes, and dialysis vintage. Patients with PTH levels at the extremes (>± normal range or >± 15 XULN) were excluded.

**Results:** Patients were well matched in age (59±12 yrs), gender (66% male), diabetes (34%), and dialysis vintage (39 [22-63] months). Japanese patients had lower PTH levels (109 vs 161 pg/mL, p=0.001) and bone turnover markers (bAP 15.3 vs 24.5 ug/L; TRAP5b 3.35 vs 5.79 U/L, p<0.001 both). Scatterplots and linear regression revealed higher bone turnover markers in European patients for any given level of PTH (Figure).

In a multivariable model, Japanese nationality, male gender, higher BMI, and higher PTH were negative predictors of the TRAP5b/PTH ratio (Table).

**Conclusions:** Skeletal PTH responsiveness is lower in Japanese as compared to European patients on dialysis; thus, differences in PTH sensitivity cannot reconcile the current discrepancies in PTH target range.

**Funding:** Private Foundation Support

**Table:** Determinants of Ln (TRAP5b/PTH) by multivariable linear regression

<table>
<thead>
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<th>Coefficient</th>
<th>Value</th>
<th>p-value</th>
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<tr>
<td>bAP</td>
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<td>&lt;0.001</td>
</tr>
<tr>
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<td>&lt;0.001</td>
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<tr>
<td>BMI</td>
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</table>

Stepwise selection of variables. Model adjusted R² 52%, p<0.001.

Scatterplots of bone turnover markers over PTH

**PO0579**

**Association of Metabolic Acidosis with Impaired Bone Quality**

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**Background:** Chronic kidney disease (CKD) is a state of impaired bone quality and strength, usually presenting as renal osteodystrophy. Metabolic acidosis (MA) is an important complication of CKD that alters bone quality and strength and is associated with increased fracture risk. Few studies have investigated bone tissue-level effects of MA in humans with CKD. We hypothesized that CKD patients with MA would have altered bone tissue-level mineral content.

**Methods:** This retrospective cross-sectional analysis included 22 patients with eGFR <90 mL/min/1.73m², including those receiving kidney replacement therapy, recruited from the general nephrology clinics of Columbia University Irving Medical Center. Patients were considered to have MA for serum bicarbonate <22mEq/L. Transiliac crest bone biopsy was assessed for bone formation and mineralization measures from quantitative histomorphometry of tetracycline double labels, tissue mineral density (TMD) by microCT and bone mineral density distribution (BMDD) by quantitative backscatter electron imaging (qBEI). Spearmann correlations (ρ) were adjusted for eGFR. Univariate Wilcoxon tests assessed between group differences.

**Results:** Twelve participants had MA. There were no differences in age, sex or race/ ethnicity. After eGFR adjustment, there was a correlation between serum bicarbonate and TMD (ρ=0.60, p=0.004). Bone formation and mineralization measures did not differ. TMD by microCT showed a trend. Measures of calcium content by BMDD differed between groups.

**Conclusions:** MA is associated with lower TMD and altered calcium content in patients with CKD. Further investigation is needed to determine whether impairments in TMD and BMDD are associated with decreased bone strength and are corrected by bicarbonate supplementation.

**Funding:** NIDDK Support
Impact of Urinary Calcium Excretion on Bone, Cardiovascular System, and Kidney Function in Caucasian Osteoporotic Patients: A Longitudinal Long-Term Follow-Up Study

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Background: Urinary Calcium excretion (UCaE) is expected to reflect the bone activities, however this relationship in osteoporotic (OP) patients (pts) is not well understood. Moreover, the influence of UCaE on kidney function and cardiovascular (CV) system is controversial.

Methods: Longitudinal study for OP pts who had bone biopsies between January 2008 and December 2013. All pts were white, had 24 urine collection for UCaE, DEXA scan for BMD, bone histology, and at least two follow ups with a minimum of 1-y. Exclusion criteria included active malignancies and infections, liver failure, ESKD, organ transplant, or secondary OP.

Results: Study included 118 OP pts with median follow up of 5.3 (1-11) y. The mean age was 61 ± 12 y and 89% of pts were women. The mean eGFR at baseline was 83 ± 19 ml/min Trabeicular bone volume was low in 95% of pts, 59% had high turnover bone turnover disease (HTBD) and 61% had low turnover bone disease (LTBD), while mineralization was defective in 9%. Serum calcium and 25 vitamin D were within normal range in vast majority of pts. At baseline, lumbar spine (LS) T-score was -1.9 (-5.5 to 3.9), and total hip (TH) T-score was -1.6 (-4 to 2). Pts with HTBD had lower LS T-scores (p=0.02). Hypercalcuria found in 23%. Mean UCaE was 195 ± 116 mg/d with no difference between LTBD and HTBD pts. CKD pts were older (p=0.001), had higher PTH (p<0.001), and lower UCaE (p=0.04). BMD significantly decreased (>2%) in 46% of pts at TH, and 42% at LS. BMD losers at TH were older, had lower UCaE, and lower serum albumin. Lower UCaE was significant predictor of BMD loss after adjustment of age, eGFR, and serum albumin (p=0.039, β=1.01, 95% CI (1-1.01)). Fractures occurred in 18% of pts during follow up. Fractures were higher in pts with UCaE<100. GFR declined (>3.3%/y) in 19% pts with no difference in UCaE; in pts with declined vs stable GFR. Pts with kidney stones (13%) tended to have higher UCaE. New CV events occurred in 14% of pts. Pts with CV events tended to be older (64 ± 61 y) and had lower UCaE (169 ± 199 mg/d).

Conclusions: LTBD is common in OP pts. UCaE is not different between LTBD, and HTBD pts. CKD pts had less UCaE. Lower UCaE predicted bone loss and fracture risk in white OP pts.
Case Description: A 59-year-old man with ESKD had longstanding well-controlled mineral bone disorder. He developed worsening hyperphosphatemia of unclear etiology, and eventually presented with symptomatic hypercalcemia with corrected calcium level of 12.9 mg/dL. Biochemistry and imaging were consistent with hypercalcemia of granulomatous lung disease. CT chest showed numerous conglomerations of centrilobular nodules in multiple lobes of both lungs (Figure 1A). Transbronchial biopsy showed giant cell granulomas containing crystalline material and calcified inclusions (Figure 1C, 1D). Infectious and rheumatological work-up was unrevealing. Detailed patient interview revealed that he had been sanding drywall without respiratory protection due to N95 mask shortage in the global pandemic. No treatment was initiated because the environmental exposure had already terminated. Over a few months, the imaging (Figure 1B) and biochemical findings resolved. A year later, the patient has well controlled mineral bone disorder on calcium-containing phosphate binders again.

Discussion: Our report demonstrates how systematic work-up and careful history-taking are critical in diagnosing esoteric conditions associated with hypercalcemia. It also illustrates indirect health-related effects of the coronavirus-19 pandemic on non-infected ESKD patients.

A: CT scan showing granulomas, B: Resolution of granulomas in 4 months, C: Transbronchial biopsy with granulomatous inflammation, D: Crystalline material in granulomas

PO0584

Holy Fanconi, My Bone Is Breaking!

Introduction: Tenofovir-induced Fanconi syndrome can be insidious with severe hyperphosphatemia from renal losses leading to subclinical fractures.

Case Description: A 72 y/o woman with CKD stage 3a, chronic hepatitis B and osteoporosis was referred for hyperphosphatemia. She had recently presented to the ER with diziness/weakness, chronic bone pain and poor appetite. She was found to have a critically low phos of 1.0 mg/dL. X-rays revealed old C-spine and femur fractures. Labs were also notable for K 3.2 mmol/L, Cl 111 mEq/L, bicarb 18 mEq/L, Cr 1.1 mg/dL, Ca 8.4 mg/dL, PTH 120 pg/mL and normal vit D. Medications included tenofovir disoproxil fumarate (TDF) started 5 years prior for hep B, and ibandronate for osteoporosis. The hyperphosphatemia was initially attributed to poor nutrition vs bisphosphonate therapy. However, fractional excretion of phos (FEphos) resulted at 78% consistent with renal loss of phos. PTH normalized in tandem with Ca repletion (Figure).

The hypophosphatemia was initially attributed to poor nutrition vs bisphosphonate therapy. Common causes of severe hypercalcemia were ruled out. Supporting this response or an early monoclonal protein. QuantiFERON Gold was indeterminate but negative for tuberculosis. Mycobacterium Tuberculosis PCR in urine was negative. She developed hypercalcemia, which peaked at 13.7 mg/dL (ionized calcium 1.83 mmol/L). The ultrasound showed right kidney hypertrophy to 16.3 x 9.9 x 10.5 cm, but no abscess formation or liquefaction. Imaging showed no osteomyelitis, lytic lesions or suspicious masses. Kappa/lambda ratio was at 0.8 and IFE gel showed a faint band in lambda suggestive of a specific immune response or an early monoclonal protein. Quantiferon Gold was indeterminate but imaging did not show pulmonary tuberculosis. Seven separate urine samples had negative acid fast stain and culture. Mycobacterium Tuberculosis PCR in urine was negative. She completed a prolonged course of antibiotics and over the six months of follow-up, her serum calcium and albumin normalized, and 1.25-Vitamin D fell to 16 pg/mL. Her serum creatinine decreased to 2.17 mg/dL. Right kidney size decreased to 9.8 x 5.7 x 5.4 cm and normal contour and sonographic appearance.

Discussion: Tenofovir nephrotoxicity occurs via disruption of proximal tubular mitochondrial function. In our patient, prolonged 5-year exposure to TDF with renal phos wasting led to inadequate bone mineralization and subsequent osteomalacia, which may have been aggravated by concurrent bisphosphonate therapy. Subclinical bone fractures led to chronic pain, deconditioning and poor nutritional status. TAF is a produg of tenofovir thought to be less nephrotoxic than TDF because its pharmacokinetics requires lower doses for efficacy. Other forms of tenofovir nephrotoxicity include ATN, chronic interstitial nephritis and nephrogenic diabetes insipidus.

A: CT scan showing granulomas, B: Resolution of granulomas in 4 months, C: Transbronchial biopsy with granulomatous inflammation, D: Crystalline material in granulomas

PO0585

An Unusual Culprit of Severe Acute Refractory Symptomatic Hypocalcemia: Keyboard Cleaner
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Introduction: 1,1-Difluoroethane is commonly found in gas dusters and aerosol products. It has emerged as a recreational drug due to its acute euphoric effect. Side effects from difluoroethane abuse include hypocalcemia, acute kidney injury, cardiac arrhythmias and seizures. We report a case of 1,1-difluoroethane abuse presented with severe acute symptomatic hypocalcemia post Zoledronic acid therapy for Paget’s disease.

Case Description: A 35 year old male with a past medical history of Paget’s disease presented with generalized muscle cramps, facial twitching and upper extremities spasms for a day. He received IV Zoledronic acid as outpatient a day prior to the onset of symptoms. He also reported a significant history of inhalant abuse with keyboard cleaners. Physical examination were unremarkable other than a positive Trousseau sign. EKG showed prolonged QTc interval of 523 ms. Initial labs revealed corrected serum calcium 4.30 mg/dL, phosphorus 1.8 mg/dL, alkaline phosphate 455 U/L, parathyroid hormone (PTH) 201 pg/mL, 25-Hydroxyvitamin D 7.0 ng/mL and 1,25-Dihydroxyvitamin D 146 pg/mL. Over the course of 5 days, he received a total of 24 g of IV Calcium gluconate and 30 g of oral Calcium carbonate. His symptoms subsequently resolved and serum corrected calcium normalized to 8.04 mg/dL and PTH decreased to 169.7 pg/mL on day 5 of hospitalization. He was discharged on day 6 with plans to follow up with primary care physician for monitoring of serum calcium level.

Discussion: Incidence of severe symptomatic hypocalcemia related to Zoledronic acid therapy in Paget’s disease is uncommon (1%). Our patient was treated with Zoledronic acid in the past without complication. Besides, he lacks the risk factors for bisphosphonate-induced hypocalcemia which include hypoparathyroidism, hyperparathyroidism, hypoponoresis and renal failure. Low 25-Hydroxyvitamin D on presentation is likely due to the effect of secondary hyperparathyroidism in response to hypocalcemia. Thus, we conclude that 1,1-difluoroethane is most likely the major precipitating factor for hypocalcemia seen in this case. Healthcare provider should be aware of uncommon causes of hypocalcemia such as difluoroethane as a differential once common causes have been ruled out, especially in certain susceptible populations given the ease of access for abuse and potentially fatal associated adverse effects.

PO0586

Severe Hypercalcemia in a Patient with Acute Lobar Pneumonia
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Introduction: Acute lobar pneumonia is a form of focal acute bacterial pyelonephritis without abscess formation or liquefaction.

Case Description: A 62-year-old Native American woman with a childhood history of left nephrectomy and treatment for tuberculosis was admitted for sepsis due to pyelonephritis and pan-sensitive E. coli bacteremia. Her creatinine was 5.2 mg/dL on admission, improved to 3.5 mg/dL with intravenous ceftriaxone, then increased to 4.2 mg/dL after transitioning to oral antibiotics six days later. At the same time, she developed hypercalcemia, which peaked at 13.7 mg/dL (ionized calcium 1.83 mmol/L). PTH was undetectable. Her 1,25-dihydroxy vitamin D (1,25-Vit D) was elevated at 120 pg/mL. The ultrasound showed right kidney hypertrophy to 16.3 x 9.9 x 10.5 cm, but no perinephric abscess or hydrenephrosis. MRI abdomen showed wedge-shaped and cortical hyperintense striations through the kidney, the largest measuring 2.3 cm (Figure 1). Imaging showed no osteomyelitis, lytic lesions or suspicious masses. Kappa/lambda ratio was at 0.8 and IFE gel showed a faint band in lambda suggestive of a specific immune response or an early monoclonal protein. QuantiFERON Gold was indeterminate but imaging did not show pulmonary tuberculosis. Seven separate urine samples had negative acid fast stain and culture. Mycobacterium Tuberculosis PCR in urine was negative. She completed a prolonged course of antibiotics and over the six months of follow-up, her serum calcium and albumin normalized, and 1,25-Vit D fell to 16 pg/mL. Her serum creatinine decreased to 2.17 mg/dL. Right kidney size decreased to 9.8 x 5.7 x 5.4 cm and had normal contour and sonographic appearance.

Discussion: Acute hypercalcemia was likely due to a rare pathological activation of calcium hydroxylase (CYYP2c7b) in renal proximal tubule cells due to inflammatory response. Common causes of severe hypercalcemia were ruled out. Supporting this etiology, resolution of hypercalcemia correlated with resolution of renal inflammation.
Identification of Factors Affecting Changes in the Agatston Coronary Artery Calcification Score in Maintenance Hemodialysis Patients
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Background: Coronary artery calcification (CAC) has been implicated in cardiovascular disease, one of the leading causes of death in patients on maintenance hemodialysis (MHD). The Agatston CAC score is the most widely used scoring system for CAC evaluation. The factors affecting changes in the CAC score in MHD patients remain unknown. We characterized the associations between change in Agatston CAC score and clinical parameters in MHD patients.

Methods: A total of 288 patients on hemodialysis at Ichiyokai group facilities between January 2018 to February 2021 were retrospectively analyzed. Clinical parameters and Agatston CAC scores, determined by multi-detector computed tomography, were assessed at baseline and after 1 year. Patients with Agatston CAC score ≥ 30 were enrolled. A multiple regression analysis for change in Agatston CAC score was performed. The independent variables were sex, age, Agatston CAC score, glucose, albumin-corrected serum calcium, serum phosphate, β2-microglobulin, hemoglobin, blood urea nitrogen, albumin, angiotensin-converting enzyme (ACE) inhibitor/angiotensin II receptor blocker (ARB) use, calcimimetic use, and vitamin D use.

Results: The mean change in Agatston CAC score was 205.2 ± 545.1 and the mean percentage change in Agatston CAC score was 21.2% ± 43.5%. The multiple regression analysis for change in Agatston CAC score identified Agatston CAC score (regression coefficient [RC] = 0.3795, p < 0.001), serum phosphate (RC = 0.1230, p = 0.0317), albumin-corrected serum calcium (RC = −0.1165, p = 0.0049), and ACE inhibitor/ARB use (RC = −0.1262, p = 0.0298) as significantly related factors (R² = 0.2011, p < 0.001).

Conclusions: In patients on MHD, change in Agatston CAC score is positively associated with Agatston CAC score and serum phosphate, and negatively associated with albumin-corrected serum calcium and ACE inhibitor/ARB use.

PO0588
Qatar National Program for Screening and Management of Vascular Calcification in Hemodialysis Patients

Background: Vascular calcification (VC) is an independent and important risk factor for cardiovascular events in (HD) patients. Trials aiming to reduce the progression of VC did not show a great success. We are presenting data from our national program for screening and management of VC in hemodialysis patients in State of Qatar.

Methods: All ambulatory HD patients in Qatar where included. Data were collected in 2020 from the Qatar national electronic medical record and it included all imaging studies (X-ray, echocardiogram, US, CT). VC then were classified into mild, moderate or severe. Patients with VC were started on a newly created protocol to decrease calcium load (shift to non-calcium phosphate binder, reduce active vitamin D, and liberalize calcimimetic dosing). Figure 1 shows new pathway of screening and management of VC in HD patients.

Results: Total patients were 650 During the study period. 559 were screened for VC (86%). 433 (75%) had VC. We were able to classify 286 patients (67%) of them based on severity of VC on radiological findings to mild 201(70%), moderate 59(21%) or severe 26(9%). Following interventions, percentage of patients with calcium level of normal range (2.1-2.55mmol/l) increased by 5% from 83% in March 2020 to 88% in December 2020 (p value=0.004). Phosphorus level was maintained in the range 0.81-1.8mmol/l by 72% calcium based phosphate binder tables used weekly decreased by 30%.

Conclusions: we created a screening and management protocol for VC in HD patients. Our protocol was successfully implemented and the initial outcomes was very promising. A follow up imaging to identify progression of VC should be considered in further studies.
Methods: Randomized, open-label, parallel-group clinical trial (control/experimental; 2:8 per group). The experimental group received 360mg of Mg carbonate daily for 15±1.5 months. At the beginning and at the end of the study, blood and urinary biomarkers of bone mineral metabolism were measured; pulse wave velocity (PWV) was determined with Mobil-O-Graph device as an indicator of arterial stiffness, the Agradao index was calculated and bone mineral density was measured by densitometry.

Results: The included patients were in both groups mostly men and similar with respect to age and GFR. Serum Mg concentration were 1.9±0.1 vs 2.0±1.1 mg/dl in control and experimental group respectively. At the baseline, no differences were found in demographic characteristics, comorbidities, treatments, PWV or biomarkers of bone mineral metabolism. The experimental group did not present hypermagnesemia or any other adverse event. The increase in urine Mg confirmed the therapeutic adherence. There was a decrease in GFR: 4ml/min in control and 1.7ml/min in experimental group, with no changes in serum Mg (both not statistically significant). An inverse correlation was found between urine Mg and the albumin/creatinine ratio (p=0.039). At the end of follow-up, serum Mg was inversely correlated with PWV (p=0.015). Urinary Mg was inversely correlated with iFGF23 (p=0.007). A non-significant trend of decrease in the Agradao index was observed in the experimental group. There were no changes in bone mineral density.

Conclusions: In CKD3-4 patients the Mg supplements reduce arterial stiffness without changes in bone mineral density.

PO0592
Phosphate, Blood Pressure, and Endothelial Cell Dysfunction in a Population Study
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Background: Hyperphosphatemia contributes to medial vascular calcification in chronic kidney disease (CKD) patients. There is emerging evidence that phosphate (Ph) is also associated with microvascular disease in individuals with normal kidney function, with in vitro data supporting a toxic effect of Ph on endothelial cells. We hypothesized there would be an association between serum Ph, blood pressure (BP), and endothelial cell dysfunction (ECD) markers in a large, diverse cohort.

Methods: Using data from the Dallas Heart Study, a multi-ethnic population-based cohort, we used serum Ph as the predictor variable and conducted linear regression analysis to determine its association with systolic BP and serum asymmetric dimethylarginine (ADMA) from a single visit. We controlled for numerous demographic and clinical variables including parathyroid hormone (PTH), calcium, vitamin D, estimated glomerular filtration rate (eGFR), and albuminuria.

Results: There were 3301 participants with a mean age of 43 years. The median systolic BP was 122 [112, 134] mmHg. The GFR was 102 [88, 114] ml/min. Serum calcium, Ph, PTH, and vitamin D levels were 9.2 [9, 9.5] mg/dL, 3.2 [2.8, 3.5] mg/dL, 3.73 [27, 51] pg/mL, and 17 [12, 23] ng/mL. Serum Ph and PTH were independently associated with both systolic BP and ADMA (Table 1), although there was a negative relationship between Ph and BP.

Conclusions: Even in the physiologic range, serum Ph and PTH were independently associated with higher ADMA, an ECD marker, in a diverse population while accounting for known predictors of hypertension including age, diabetes, and kidney function. Higher systolic BP was predicted by higher PTH, but lower Ph. The presence of these associations in individuals with preserved renal function warrant further studies in CKD, where hypertension and hyperphosphatemia are both more prevalent.

Funding: Veterans Affairs Support

Multivariate Linear Regression Analysis

Model also controlling for race, sex, diabetes, serum albumin, estimated glomerular filtration rate, LDL cholesterol, urinary albumin to creatinine ratio

PO0593
Hyperphosphatemia Is Associated with Vasoconstriction and Endothelial Cell Dysfunction in Hemodialysis Patients
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Background: Hyperphosphatemia is associated with increased mortality in hemodialysis (HD) patients. High phosphate (Ph) causes vascular structural changes including medial calcification. While there is in vivo evidence that high Ph can induce endothelial cell dysfunction (ECD), little is known about the relationship between Ph and vasoconstriction or ECD in HD patients.

Table 1
Phosphate Indices and Atherosclerotic Cardiovascular Disease in CKD Patients: The CRIC Study

Methods: We studied hypertensive HD patients with the following outcome data: pre-HD systolic blood pressure (BP), total peripheral resistance index (TPRI) obtained with non-invasive cardiac output monitor, and serum levels of endostatin-1 (ET-1) and asymmetric dimethylarginine (ADMA). The most recent pre-HD serum Ph was the predictor variable. We conducted correlation and multivariable linear regression analyses while controlling for other clinical variables.

Results: Among the 60 participants, the mean age was 50 years. There were 62% male, 58% Black, and 60% with diabetes. Serum Ph had significant correlations with systolic BP, TPRI, ET-1, and ADMA (Figure 1). Multivariable regression analysis showed independent associations for Ph with all outcomes except ADMA (Figure 2), but PhTdid have an independent association with ADMA.

Conclusions: Hyperphosphatemia is independently associated with vasoconstriction in HD patients. Serum Ph is also associated with ECD, but this is in part confounded by PTH. These data show the adverse cardiovascular consequences of hyperphosphatemia extend beyond vascular calcification. Further human studies are needed to determine 1) if lowering Ph improves endothelial function in HD patients and 2) if pharmacologic therapy aimed at improving ECD reduces the cardiovascular burden associated with hyperphosphatemia.

Funding: NIDDK Support, Veterans Affairs Support

PO0595
Bone-Vessel Relationships, the Association Between Calcifications of the Iliac Arteries with Vertebral Fractures in Hemodialysis Patients: Results from the VIKI Study

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Background: Vascular calcification and fragility fractures are common age-related disorders and associated with high morbidity and mortality especially in end-stage renal disease. Skeletal disorders occur in dialysis patients. Few studies have provided data on the prevalence of vertebral fractures (VFs) and their association with large artery calcifications. We evaluated the relationship of iliac arteries calcifications (IACs) and abdominal aorta calcifications (AACs) with the risk for VFs in hemodialysis (HD) patients.

Methods: The VIKI Study is a cross-sectional study involving 387 HD patients from 18 Italian dialysis centers. Biochemical data included bone health markers such as vitamin K levels, vitamin 25(OH)D, alkaline phosphatase, parathormone, calcium, phosphate, osteocalcin and Matrix GlA Protein. The presence of VF, IACs and AACs was determined through standardized spine lateral radiographs. A >20% reduction of vertebral body height was considered a VF. We quantified vascular calcifications by measuring the length of calcium deposits along the arteries classifying the degree of severity for the IACs and AACs according to a specific score (mild: 0.1–3 cm; moderate: 3.1–5 cm; and severe >5 cm) previously validated for AACs.

Results: The prevalence of IACs was 56.1%, and of AACs 80.6%. After adjusting for confounding variables, the presence of IACs was associated with 73% higher odds of VF (p=0.028), whereas we found no association (p=0.294) for AACs. The presence of IACs associated with VF irrespective of calcification severity. Patients with IACs had lower levels of the vitamin K2, menaquinone 7 (MK7) (0.99 vs 1.15 ng/ml; p=0.003), and deficiency of this marker became greater when adjusting for triglyceride levels (0.57 vs 0.87 ng/ml; p=0.001).

Conclusions: The presence of IACs, regardless of their extent, appears to be a clinically relevant risk factor for VFs. The association is further enhanced by including vitamin K, a main player in bone and vascular health, in the model. Prospective studies are needed to confirm these findings both in chronic kidney disease patients and in the general population.

Funding: Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO0596

Oral Calcitriol Use, Vertebral Fractures, and Vascular Calcifications in Hemodialysis Patients: Results from the Vitamin K Italian (VIKI) Study

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Background: Chronic Kidney Disease patients are characterized by alterations in bone and vascular metabolism associated to adverse clinical outcomes such as fractures, cardiovascular events and mortality. Dysregulation of vitamin D hormonal system, in levels of calcium, phosphate, PTH, FGF23/Klotho are the main responsible of these changes. We want to evaluate if oral calcitriol use can play a protective role on fractures in hemodialysis (HD) patients.

Methods: We included 387 HD patients of the VIKI database, a multicenter cross-sectional study. Biomarkers measured: vitamin K, VKDPs, vitamin 25(OH)D, D, ALP, PTH, Ca, P. Spine radiograph performed to define the presence of Vertebral Fractures (VF) and Vascular Calcification (VC). VF was indicated as ≥20% reduction of vertebral body height and VC were quantified by measuring the length of calcium deposits along the arteries.

Results: 45.7% of patients were treated with oral calcitriol. No biochemical differences were observed between the treated and untreated patients. VFs were significantly lower in patients receiving oral calcitriol (48.6% vs 61%, P=0.015), the presence of VCs was similar (aortic: 81.9% vs 79.5% respectively, P=0.552; iliac: 52.0% and 59.5%, P=0.167). In a multivariable logistic regression analysis, after adjustment for all potential confounders, oral calcitriol was associated with a marked reduction (-40.2%) of the odds of fractures (OR: 0.598, 95% CI: 0.363-0.985, P=0.043).

Conclusions: In conclusion, we found a significant association between oral calcitriol use and lower VF rate in HD patients. Further prospective and interventional studies are needed to confirm these findings.

Funding: Private Foundation Support

PO0597

Significant Associations Between Vascular Calcification and Bone Mineral Density in CKD

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Background: Vascular calcification (VC) demonstrated as a predictor of cardiovascular mortality in chronic kidney disease (CKD) patients (pts). There are uncertainties in term of factors that may explain the links between low bone mineral density (BMD) and mortality in CKD. We aimed to study associations between VC and BMD in CKD pts.

Methods: We studied 90 consecutive CKD pts. The following VC assessments used: 1) lateral lumbar X-rays and the scoring system to assess VC of the abdominal aorta using a semi-quantitative scoring (Kauppila,1997); 2) Ankle-brachial index (ABI) assessment; 3) lateral lumbar X-rays and the scoring system to assess VC of the abdominal aorta using a semi-quantitative scoring (Kauppila,1997); 4) Carotid intima-media thickness (CIMT). Measures included tibial cortical(Cort) and trabecular(Trab) BMD by peripheral quantitative CT, CAC, carotid intima-media thickness(cIMT), pulse wave velocity(PWV) and carotid distensibility, expressed as z-scored(BMD, cIMT, PWV).

Results: 98 participants(age 13.8;IQR 10.7,16.5 yrs) were assessed at baseline and 55 again after 1.5(1.3 to 1.8) years. At baseline 10% had CAC, increasing to 18% at follow-up. Median cIMTz and PWVz were 2.17(1.14, 2.86) and 1.45(0.16, 2.57) at baseline. At follow-up cIMTz and PWVz increased, and distensibility decreased in participants with static linear growth compared to children with linear growth (Fig 1A). TrabBMDz decreased from -0.26 to -0.38, p=0.01, particularly in growing children(Fig 1B); there was a non-significant decrease in CortBMDz (-0.47 to -1.13, p=0.09). On multivariable regression, baseline TrabBMDz was positively associated with cIMTz (β 0.35, p=0.001,Fig 1C).

Conclusions: In growing people with CKD, an increase in vascular measures was seen despite an increase in BMD. Progression of vascular changes may be attenuated in the growing skeleton. Providing adequate calcium for optimal bone mineralization whilst avoiding vascular calcification remains challenging.

Funding: Government Support - Non-U.S.
treatments and surgical interventions as well as the morbidity related to symptomatic stone disease, medical prophylaxis for stone recurrence is an attractive approach. Efficacy of thiazides for kidney stone prevention was tested in 11 trials in the past. However, all these trials had major methodological deficiencies. Nowadays, thiazides are widely used in the treatment of recurrent nephrolithiasis and arterial hypertension, but at significantly lower doses than those used in previous trials. However, this practice was not supported by randomized evidence. Thus, evidence for benefits and harms of thiazides in the prevention of kidney stones remains unclear.

Methods: NOSTONE is a multicenter, randomized, placebo-controlled, double-blind, parallel-group trial aiming to assess the dose-response relationship of three different dosages of hydrochlorothiazide (12.5mg, 25.0mg, 50.0mg) compared to placebo in the kidney stone prevention. The primary outcome incidence of stone recurrence at 3 years is a composite of symptomatic and radiologic recurrence (comparison of basal and end-of-study low-dose CT). The study included patients from 12 hospitals throughout Switzerland.

Results: The study was approved by all competent authorities by the end of February 2017. Recruitment started in Bern on March 9th 2017. All study sites are operative since June 30th 2017. The target number of 416 patients randomized in the trial was reached October 31st 2018 and recruitment stopped. In March 2020 the first patient randomized in the trial completed the treatment phase. All patients are expected to reach end of treatment by the end of August 2021 (www.nostone.ch).

Conclusions: The NOSTONE study will provide physicians with crucial information for the treatment of kidney stones. The impact of the results of this study will affect many patients currently under treatment with hydrochlorothiazide for the prevention of recurrent nephrolithiasis.

Funding: Government Support - Non-U.S.

PO0600
Body Mass Index (BMI) and Kidney Stone Risk in Calcium Kidney Stone Formers
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Background: The role of obesity among calcium kidney stone formers remains poorly defined, and it is unknown whether there are effect modifications of stone risk by diabetes or insulin resistance (IR).

Methods: We examined the independent associations between BMI and 24-hour urine stone risk profile among 167 calcium kidney stone formers (CSF), and analyzed the effect modifications by diabetes and IR measured by Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) in non-diabetics. Study participants were recruited from Lifespan Kidney Stone Clinic. We used linear regression and adjusted for demographics.

Results: The study population (n=167) had a mean age of 53 years, 77 (46%) were male, and 135 (81%) had diabetes. Mean BMI was 29 (Interquartile range IQR 25 to 33). Higher BMI was associated strongly with diabetes (p<0.001). Among 159 non-diabetic CSFs, mean BMI was 28 (IQR 25 to 31), and BMI had a strong positive association with HOMA-IR (p=0.001). 33% of non-diabetic CSFs had hypertension (vs. 100% in diabetics), 21% of non-diabetic CSFs had hyperlipidemia (vs. 89% in diabetics). HOMA-IR ranged from 0.42 to 28.2 (mean 4.3). Overall, in the whole study population, BMI had significant positive associations with urine ammonium, urine uric acid (UUA), and UUA supersaturation (p=0.004, <0.0001, <0.0001 respectively). The strong association between BMI and urine ammonium was only observed among diabetics (r=0.006), with a similar trend observed among non-diabetics with high IR (p=0.09 when HOMA-IR>10, p=0.9 when HOMA-IR=5–10, p=0.2 when HOMA-IR<5). On the contrary, the uricosuric effect of higher BMI was only observed in nondiabetics (p=0.09 when HOMA-IR>10, p=0.2 when HOMA-IR=5–10, p=0.9 when HOMA-IR<5). Lastly, BMI did not have significant associations with serum levels of vitamin D and uric acid, plasma parathyroid hormone concentration and measurements of other urine stone risk factors.

Conclusions: In our cohort of CSFs, higher BMI had strong associations with urinary uric acid and ammonium excretions, and these associations appeared to be modified by the presence of diabetes or IR.

Funding: Clinical Revenue Support

PO0601
Examining the Clinical Effectiveness of Calcium Oxalate Stone Treatments
Joseph T. Gutbrod, Charles C. Keys McKay, Elaine M. Worcester, Megan Prochaska, 1 and 2 are co-first authors University of Washington Division of the Biological Sciences, Chicago, IL.

Background: Lowering urine calcium oxalate (CaOx) supersaturation (SS) is a primary clinical focus for CaOx kidney stone (KS) prevention and can be achieved by increasing urine volume, or decreasing uric acid or oxalate excretions. Common clinical strategies for this include advising patients to increase fluid intake, restrict dietary sodium, restrict dietary oxalate, or prescribing a thiazide-type diuretic. Several of these strategies have been validated in the controlled setting of randomized trials but efficacy in the real-world clinical setting is less clear. We investigated the efficacy of these treatment strategies in a clinical setting, observing whether trial-based findings on CaOx KS treatment hold true.

Funding: Clinical Revenue Support

PO0602
Effect of Hydroxyurea (HCT) on Urine Chemistry in Calcium Kidney Stone Formers
David S. Goldfarb,1 Kumar Rohit,1 Avinash G. Adiga,1 Briony L. Norris,1 Lee Yang,2 Frank Moderslitskiy,1 David A. Bushinsky,2 Jeffrey D. Rimer,2 John R. Asplin,2* NYU Langone Health, New York, NY; 2LithoLink Corp, Chicago, IL; 3University of Rochester Medical Center, Rochester, NY; 4University of Houston, Houston, TX; 5The Royal Melbourne Hospital, Melbourne, VIC, Australia; 6University of Alabama, Tuscaloosa, AL.

Background: Potassium citrate is a mainstay of treatment to prevent recurrent calcium-containing kidney stones. However, it can increase urine pH and calcium phosphate (CaP) supersaturation (SS). HCA, extracted from Garcinia cambogia, is a potent inhibitor of calcium oxalate crystal growth in vitro and should not provide "potential base", as citrate does. Urinary excretion of HCA has not been well-studied.

Methods: We enrolled 2 groups: calcium stone formers (SF, n = 9) and non-stone forming (NSF, n = 9) controls (after excluding 2 SF and 2 NSF whose urine creatinine excretion on the 2 collections differed by more than 20%). Mean age 49.3 years. Thiazides and citrate were held for 2 weeks prior to study. Participants recorded a self-selected diet for 2 days and performed 24-hour urine collection on day 2. HCA was purchased online from Amazon.com (Super CitiMax Garcinia Cambogia); 2 caps = 900 mg of HCA. Participants took 900 mg 3 times daily orally for 7 days. Diet from days 1 and 2 was replaced by a diet where days 6 and 7 of the HCA arm of the study, 24-hour urine was collected on day 7. Urine was sent to Litholink, Inc. (Chicago, IL) for analysis. Urinary excretion of hydroxyurea and citrate were measured using LC/MS.

Results: According to label, 6 pills would provide 2700 mg (13.2 mmol) of HCA per day, we measured content as 3198 mg (15.6 mmol). Citrate content is supposed to be 0, but we found 126 mg (0.66 mmol) per day. Both NSF and SF had appearance of HCA in the urine: 1.86 ± 0.80 and 2.07 ± 0.67 mmol/day (p = 0.56). Urine chemistry seen in Table 1. In NSF, pH and citrate did not change. In SF, pH increased, citrate did not. K went down in both groups.

Conclusions: Administration of HCA, a potential inhibitor of Ca stone formation, leads to significant urinary HCA excretion. Citrate excretion was not affected. Urine pH increased, suggesting some alkalizing effect. The difference in NSF and SF may be due to the lowering start pH in SF. The effect of HCA on stone formation remains to be determined.

Funding: Clinical Revenue Support

Urinary chemistry after HCA

| Parameter | NSF | HCA NSF | p-value
<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>pH</td>
<td>6.67 ± 0.62</td>
<td>6.63 ± 0.58</td>
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<tr>
<td>Calcium</td>
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<td>0.087</td>
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<tr>
<td>Cr</td>
<td>0.57 ± 0.58</td>
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PO0603
Factors Reducing Kidney Stone Risk in Patients with Enteric Hyperoxaluria (EH)
Megan Prochaska, Julianna Bianco, Francesca M. Chu, Elaine M. Worcester. University of Chicago Division of the Biological Sciences, Chicago, IL.

Background: There have been no trials examining efficacy of interventions aimed at decreasing stone risk in patients with EH. We drew upon data for patients in a kidney stone clinic and made recommendations with consistent methodologies over time. We asked how doctors made therapeutic choices and which therapies were effective at decreasing stone risk.

Methods: We selected 100 patients with EH from the Kidney Stone Evaluation and Treatment Program at the University of Chicago between 1970 and 2018. We analyzed 24-hour urine collections before and after patients’ first clinic visit using multivariate linear regression and t-tests to compare effects of fluid intake and oxalate-focused interventions on outcomes.

Results: Compared to those who did not receive the advice, advice to increase fluid intake resulted in a larger pre- to post-advice increase in urine volume (0.6 vs. 0.99/L/day, p<0.001) and decrease in CaOx SS (-3 vs. -1, p<0.001). Compared with those who did not receive the advice, advice to restrict dietary sodium alone resulted in a larger pre- to post-advice decrease in urine sodium (-28 vs -13mg/day, p=0.002) but there was no change in urine calcium or CaOx SS without concurrent thiazide. Thiazide prescription resulted in a significant pre- to post-advice decrease in urine calcium for patients who also sodium restricted (-19mg/day, p<0.001) and those who did not sodium restrict (-58mg/day, p<0.001) with a trend towards a larger decrease in those who did both (p=0.06). Thiazide prescription resulted in a significant pre- to post-advice decrease in urine CaOx SS for patients who also sodium restricted (-3.3, p<0.001) and those who did not (-2, p<0.001).

Conclusions: In a real-world clinical setting, advice to increase fluid intake fluid or a thiazide diuretic prescription and reduction in sodium intake lowered CaOx SS and CaOx KS risk in follow up.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
High Oxalate Concentrations Increase Risk for Sudden Cardiac Death in Dialysis Patients

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Background: The clinical significance of accumulating toxic terminal metabolites such as oxalate in kidney failure patients is imperfectly defined. Our study evaluated whether oxalate concentrations are associated with risk of all-cause mortality and cardiovascular events in a cohort of patients with kidney failure requiring chronic dialysis.

Methods: To relate all-cause death and cardiovascular events to serum oxalate, we performed a post-hoc analysis of a randomized controlled trial conducted between March 1998 and October 2002 that comprised 1255 European hemodialysis patients with diabetes who were followed up for a median of 4 years (4D Study). The results obtained via Cox proportional hazards models were confirmed by competing risk regression and restricted cubic spline modeling in the 4D cohort, and validated in a separate cohort of 104 US dialysis patients after a median follow-up of 2.5 years.

Results: A total of 1108 patients with a mean (SD) age of 66.3 (8.3) years had baseline oxalate measurements with a median (IQR) oxalate concentration of 42.4 (30) micromolar. During follow-up, 548 patients died, including 139 (25.4%) patients who died from sudden cardiac death. A total of 413 patients reached the primary composite cardiovascular events in a cohort of patients with kidney failure requiring chronic dialysis. Between 2007 and 2015 from national VHA data. We defined the primary outcome as an inpatient or emergency department diagnosis of acute myocardial infarction, unstable angina or stroke or a procedural code for percutaneous coronary intervention or coronary artery bypass graft surgery. We performed Cox proportional hazards regression to identify the risk of a cardiovascular event by level of 24-hour sodium and potassium excretion. We found that patients with lower 24-hour urine sodium excretion have a higher risk for cardiovascular disease. Patients with higher 24-hour sodium or potassium excretion are independently associated with cardiovascular events. In those not told to increase fluid intake urine volume increased from 1.3 to 2.0 L/day (p < 0.001). In those not told to increase fluid intake urine volume increased from 1.7 to 2.0 L/day (p = 0.003). Volume increased more in the advice group (p = 0.03). No interventions aimed at reducing oxalate absorption (low fat diet, calcium supplement, increased diet calcium, cholesterolemia, and low oxalate diet) had a significant effect on urine oxalate. In those getting advice, urine oxalate was 68 mg/day at baseline and 91 mg/day on follow-up (p = 0.90) compared with 50 mg/day at baseline and 51 mg/day on follow-up (p = 0.77) in the non-intervention group. In a multivariate model, fluid intake advice was associated with a decrease in calcium oxalate supersaturation (95% CI 1.43-0.90) while oxalate-focused interventions were not (95% CI 1.2-2.3).

Conclusions: Advice to increase fluid intake is associated with decreased risk of stone formation. Advice to reduce fluid intake is not associated with a decreased risk of stone formation on follow-up. This lack of effect may be the result of patient physiology or lack of compliance with treatments and advice.

Funding: NIDDK Support

PO0605

Association of Serum Sclerostin Levels with Mortality in Maintenance Hemodialysis Patients: An 8-Year Prospective Cohort Study

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Background: Sclerostin is a osteocyte-derived inhibitor of bone formation and is increased in kidney failure. Sclerostin might be involved in the pathogenesis of vascular calcification, but few studies examined the association between sclerostin and mortality in hemodialysis patients.

Methods: We analyzed a cohort of 654 maintenance hemodialysis patients enrolled in the Tokai Dialysis Prospective Cohort Study. The primary exposure variable was the baseline serum sclerostin level, measured using a sandwich ELISA (Biomedicina Medizinprodukte GmbH & Co KG). The primary outcome was 8-year all-cause mortality. Mortality risk was assessed using Cox regression models adjusted for potential confounders.

Results: Median (IQR) serum sclerostin level was 163 (120-215) pmol/L. Patients with higher sclerostin levels were likely to be male; have diabetes; have better nutritional status, higher hemoglobin, and lower intact PTH and bone turnover markers. No associations were observed between serum sclerostin and cardiovascular comorbidities.

Conclusions: Serum sclerostin levels were not associated with mortality in maintenance hemodialysis patients. Further research is required to determine the role of sclerostin in vascular calcification and cardiovascular disease in kidney failure.

Funding: Government Support - Non-U.S.

PO0606

Association Between 24-Hour Urine Sodium or Potassium Excretion and Cardiovascular Events in Veterans with Urinary Stone Disease

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Background: Urinary stone disease (USD) is associated with an increased risk of major adverse cardiovascular events. Recent studies that estimated 24-hour urine sodium or potassium excretion demonstrated an association between these variables and USD. Whether oxalate concentrations are associated with risk of all-cause mortality and cardiovascular events in a cohort of patients with kidney failure requiring chronic dialysis.

Methods: We identified 6,401 Veterans with USD and a 24-hour urine sodium measurement and 4,950 Veterans with USD and a 24-hour urine potassium measurement between 2007 and 2015 from national VHA data. We defined the primary outcome as an inpatient or emergency department diagnosis of acute myocardial infarction, unstable angina or stroke or a procedural code for percutaneous coronary intervention or coronary artery bypass graft surgery. We performed Cox proportional hazards regression to identify the risk of a cardiovascular event by level of 24-hour sodium and potassium excretion. Patients with USD underwent 24-hour urine testing for stone prevention, direct 24-hour urine testing for sodium and potassium excretion may provide insight into cardiovascular risk for patients with USD.

Results: Patients with lower 24-hour urine sodium excretion had a higher risk for cardiovascular disease. Patients with higher 24-hour sodium or potassium excretion are independently associated with cardiovascular events. Patients with USD undergoing 24-hour urine testing for stone prevention, direct 24-hour urine testing for sodium and potassium excretion may provide insight into cardiovascular risk for patients with USD.

Conclusions: Patients with lower 24-hour urine sodium excretion have a higher risk for cardiovascular disease. Patients with higher 24-hour sodium or potassium excretion are independently associated with cardiovascular events. These findings differ prior studies that used spot urine samples to identify patients who are at risk for cardiovascular disease, suggesting that direct measurement of 24-hour urine sodium or potassium excretion more accurately identifies patients who are at risk for cardiovascular disease.

PO0607

Indoxyl and Cresyl Sulfate Are Respectively Linked to Phosphocalcic Metabolism Abnormalities and to Cardiovascular Morbidity in Hemodialysed Patients

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Background: Indoxyl sulfate (IS) and Cresyl sulfate (CS) are uremic toxins generated by the intestinal amino acid catabolism. Blood levels of these toxins increase in patients with CKD and are linked to cardiovascular events.

Methods: Therefore, we studied the relationship between serum levels of free IS and CS and prevalent ion metabolism variables and cardiovascular and cerebrovascular events, stroke (stroke, heart failure, aneurysm and myocardial infarction) in 139 hemodialysis patients (age 68±13 years, weight 65±13 kg, dialysis vintage 69±71 months). We divided patients according to tertiles of free serum IS and CS.
Results: Patients in the highest tertile of serum free IS showed shorter dialysis vintage and higher body weight gain during dialysis sessions than patients in the other two tertiles. Patients in the highest tertile of IS showed lower body weight and serum concentrations of alkaline phosphatase, 1, 25(OH)D3, and PTH compared to the lowest tertile. No relationships of serum free CS concentrations with phosphate and calcium metabolism variables were observed. Kaplan-Meier survival analysis shows an increased cardiovascular mortality in patients in the highest tertile (blue line in the figure) compared to those in the lowest and middle tertiles taken together (red line; p=0.01). This association was not found considering IS tertiles.

Conclusions: Our findings suggest that serum IS could predispose to adynamic bone disease; while CS may have higher cardiovascular toxicity.

PO0609
Rac1 Promotes Kidney Collecting Duct Integrity by Limiting Actomyosin Activity
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Background: A polarized collecting duct (CD) is critical for an intact kidney. The branched kidney collecting system is formed from the ureteric bud (UB). This requires a complex actin cytoskeleton and balanced actin activity allowing normal tissue polarization, morphology, and function. The small Rho GTPase, Rac1, is a key molecular switch that controls actin polymerization and branching. We investigated the role of Rac1 in kidney collecting system morphogenesis by selectively deleting it in mice at the initiating stage of UB development.

Methods: We crossed Rac1flox/flox (f/f) with Hoxb7-Cre deleting Rac1 in the ureteric bud starting at E10.5 and followed kidney development throughout adulthood. We also analyzed the role of Rac1 in regulating signaling, migration, spreading, tubulogenesis and polarity by utilizing primary inner medullary collecting duct Rac1 null cells.

Results: The kidneys of Hoxb7::Rac1f/f exhibited only a mild branching morphogenesis defect as Rac1 is expressed after most UB branching is complete. However, with aging the CD developed a disruption of epithelial integrity, resulting in fibrosis, and a urine concentration defect. Despite intact integrin signaling, Rac1 null CD cells had profound spreading, adhesion and polarity abnormalities that were independent of the major downstream Rac1 effector, Pak1. Instead, Rac1 null cells demonstrated defective WAV2-Arp2/3 dependent actin cytoskeletal branching which resulted in excessive actin-myosin activity and severe abnormalities in epithelial cell shape. The functional and morphological defects caused by Rac1 deficiency were reversed by direct myosin II inhibition using low dose blebbistatin.

Conclusions: Unexpectedly, Rac1 does not play a major role in early branching morphogenesis of the renal collecting system, however it is required for adult CD integrity. Mechanistically, Rac1 controls Arp2/3-dependent cytoskeletal branching which limits actomyosin hyperactivity allowing normal epithelial polarization, function and morphology.

Funding: NIDDK Support, Veterans Affairs Support, Private Foundation Support

PO0610
Stromal Transcription Factor 21 Is Critical for Development of the Interstitium and Nephron Progenitor Cells via Interaction with Wnt/β-Catenin Signaling
Gal Finger,1 Yoshio Mazaewa,1 Shintaro Ide,1 Tuncer Onay,1 Tomokazu Souma,1,2 Deborah R. Winter,1 Susan E. Quaggin,1 Tomoko Hayashida,1,2 Northwestern University Feinberg School of Medicine, Chicago, IL; 1Ann and Robert H Lurie Children’s Hospital of Chicago, Chicago, IL; 2Northwestern University Feinberg School of Medicine, Chicago, IL.

Background: Reciprocal signaling between the collecting duct progenitors and the stromal progenitor cells (NPC) is the primary driver for kidney development. In addition, recent studies implicate input from the interstitial progenitor cells in multiple aspects of kidney development. However, the mode of interstitial cell action on kidney development is poorly understood. We previously showed that the Transcription factor 21 (Tcf21) in interstitial progenitors is required for normal ureteric bud branching. Here, we examined roles for Tcf21 in renal interstitial progenitors in mediating stromal functions during kidney development.

Methods: Stromal Tcf21 was evaluated with the FdCCIre;Tcf21f/f mouse model. Tcf21 expression was analyzed by standard histological methods. MK3 and M15 metanephric mesenchymal cell lines were used for analyses of β-catenin signaling.

Results: In the FdCCIre;Tcf21f/f kidney, absence of Tcf21 from FdCCIre;Tcf21f/f mouse kidney by standard immunohistological analyses. MK3 and M15 metanephric mesenchymal cell lines were used for analyses of β-catenin signaling.

Conclusions: Stromal Tcf21 expression is necessary for normal development of the renal interstitium. The role of Tcf21 in mediating stromal functions during kidney development is poorly understood. We previously showed that the Transcription factor 21 (Tcf21) in interstitial progenitors is required for normal ureteric bud branching. Here, we examined roles for Tcf21 in renal interstitial progenitors in mediating stromal functions during kidney development.
activity upon β-catenin stabilization, while mutated-Tcf21 failed to increase TCF/LEF activity. Immunoprecipitation assay showed that Tcf21 is bound to β-catenin at basal and activated states in vitro.

Conclusions: Together, our findings suggest that Stromal-Tcf21 is essential for medullary stroma development, by enhancing Wnt/β-catenin signaling to promote stromal cell proliferation and differentiation. Stromal Tcf21 is also required for the development of the adjacent nephron epithelia.

Funding: NIDDK Support

PO0611

ZEB2 Is Essential for FOXD1+ Kidney Stromal Progenitor Cell Differentiation During Kidney Development

Sudhir Kumar, Xueping Fan, Hila Milo Rasouly, Richa Sharma, David J. Salant, Weining Lu. Boston University School of Medicine, Boston, MA.

Background: FOXD1+ derived stromal cells are essential for normal kidney development. They give rise to pericytes and resident fibroblasts that support the kidney vasculature and also cooperate with cells that give rise to the developing nephron. However, FOXD1+ derived stromal progenitors may also serve as precursors of myofibroblasts in kidney fibrosis. The signals that regulate the differentiation of FOXD1+ stromal progenitors are not well understood. Given that zinc finger E-box-binding homeobox2 (ZEB2), a SMAD-interacting transcription factor, is expressed in developing kidney stromal cells, we examined the role of ZEB2 in kidney stromal cell differentiation in the developing mouse kidney.

Methods: We generated Zeb2/foxd1 conditional knockout mouse (cKO) by crossing Zeb2/foxd1 mice with Foxd1Cre/Cre mice and analyzed the phenotype of homozygous Zeb2+/−/foxd1Cre/foxd1Cre mice (Zeb2 cKO) and their wild-type littermate controls. Kidney histology and function were assessed in Zeb2 cKO and Foxd1Cre/foxd1Cre mice. Cell fate mapping was performed using tdTomato mice. Expression analysis were performed by immunostaining and Western blotting of several markers for stromal progenitors, collagen, pericytes, fibroblasts, myofibroblasts, endothelial cells, renal tubules, and SMAD proteins in Zeb2 cKO and wild-type controls. Nephrogenesis was analyzed by immunostaining using nephron morphogenesis markers SIX2, WT1, nephrin, and Jagged1.

Results: Deletion of mouse Zeb2 in FOXD1+ stromal progenitors produced dysplastic and hypovascular kidneys. The Zeb2 deficient FOXD1+ stromal progenitors in these kidneys took on a myofibroblast cell fate that led to kidney fibrosis and kidney failure. Cell marker studies confirmed that these myofibroblasts expressed pericyte and resident fibroblast markers including PDGFRα, CSPG4, Desmin, GLI1, and NTSE. Notably, increased differentiated cell composition associated with loss of Zeb2 in FOXD1+stromal progenitors was accompanied by increased expression of activated SMAD1/5/8, SMAD2/3, and SMAD4.

Conclusions: Our study identifies a key role of ZEB2 in maintaining the cell fate of FOXD1+ stromal progenitors during kidney development and loss of ZEB2 leads to differentiation of FOXD1+ stromal progenitors into myofibroblasts and kidney fibrosis.

Funding: NIDDK Support

PO0612

Uncovering the Podocyte Foot Process Proteome

Gary F. Gerlach, Lori L. O’Brien. University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC.

Background: Podocyte foot process integrity is vital for kidney function and health. Disruptions to podocyte architecture, or effacement, is one of the most common observations in kidney disease. However, the full complement of players responsible for maintaining podocyte foot process integrity is still unknown. The membranous cellular environment and specialized junctional complexes have previously hindered their isolation and testing.

Methods: The discovery of a proximity-dependent bioIId2 interaction (BioID) moiety that utilizes a promiscuous biotin ligase has opened new avenues to generate proximity-dependent proteomes. Podocin (Nphp2) localizes to the slit diaphragm and is one of the most abundant foot process proteins. Therefore, we developed a novel genetic mouse model via knock in of the BioIId2 moiety that utilizes a promiscuous biotin ligase to study proximal foot process proteins. To achieve this, we generated a transgenic mouse model to identify the in vivo proteome of the podocyte foot process localized within the vicinity of podocin.

Results: We validated our transgenic podocin-BioID model by assessing correct expression and localization of the fusion protein via western blot, immunofluorescence (IF), and electron microscopy (EM). Injection of podocin-BioID mice with excess biotin leads to the significant biotinylation of proteins within podocytes. We isolated the biotinylated proteins and performed mass spectrometry analyses (MS) to uncover novel proteins localized to the foot process. In silico analysis of the top proteins uncovered from MS identified ‘cell junctions’, ‘adhesion’, and ‘adhesion’ as the top gene ontology terms. One novel candidate we uncovered is the Immunoglobulin-like domain-containing receptor protein (Ildr2) protein. We confirmed Ildr2 is expressed in mouse podocytes by immunofluorescence and utilized publicly available single cell RNA-seq data to confirm its restricted, conserved expression in both mouse and human podocytes.

Conclusions: Current efforts are aimed at knocking out Ildr2 specifically in the podocytes of mice and interrogate novel components of the foot process proteome leading to a new set of potential players and biomarkers for kidney disease.

Funding: NIDDK Support; Other NIH Support - NIAMS:5F32AR073649-05 to GFG, Private Foundation Support

PO0613

Autophagy Deficiency in Urothelial Cells Activates Progressive NF-κB Signaling

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Background: The urothelium is a specialized epithelium that functions as a urine permeability barrier along the upper urinary tract and bladder. We have shown that conditional knockout (CKO) of exocyst gene Exo5 in ureteric bud cells disrupts the urethral stratification process during ureter development, which subsequently triggers cell death and ureter obstructions. This Exo5-CKO mouse is a novel model of congenital obstructive uropathy (COU) and may be useful for elucidating the underlying pathological mechanisms of COU. Here, we investigated the role of exo-cyst-mediated autophagy in the stress responses of urothelial cells.

Methods: Cre/loxP Exo5cre conditional knockout was accomplished with Ksp-Cre and Upk3CreERT2 mouse driver strains for both embryonic and adult urothelial knockout. An immortalized human urothelial cell line (SV-HUC-1) was used for cellular assays. Autophagic flux and cell stress signaling were measured by immunofluorescence and western blotting.

Results: We report that urethelial Exo5 cKO ablation disrupted autophagy and promoted non-canonical NF-κB signaling during ureter development in Ksp-Cre mice. Adult urothelial Exo5-CKO knockout mice also showed disrupted autophagy, with an accumulation of lysosomes in the bladder urothelium. In SV-HUC-1 cells, EXO4 co-immunoprecipitated with ATG7, and silencing of Exo5 led to an accumulation of LC3II and p62, indicating poor autophagic flux. Direct inhibition of autophagy with BafA1 or PIP34i induced an early canonical RelA NF-κB response followed by a delayed p52 non-canonical NF-κB response and eventual cell death.

Conclusions: Here, we report that Exo5-CKO contributes to autophagy in urothelial cells, and impaired autophagy triggers progressive NF-κB signaling. The initial stress response activates canonical RelA NF-κB signaling, which is associated with survival mechanisms and inflammation. However, when the injury is not resolved, a delayed p52 non-canonical NF-κB signaling follows. Under these conditions, the canonical NF-κB mediators NFKB, TWEAK and its receptor Fasl4 were highly responsive. Further investigation of this progressive NF-κB signaling series in urothelial cells may be critical for understanding the etiology of COU and any lingering chronic response after COU is resolved.

Funding: NIDDK Support

PO0614

Mechanisms of VEGFR3 Signaling in Glomerular Development

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Background: Dysregulation of Vascular Endothelial Growth Factor Receptor 3 (VEGFR3), known primarily for its role in lymphangiogenesis, is causally linked to the development of kidney diseases, including renal fibrosis and cystogenesis. However, the mechanisms of VEGFR3 signaling in kidney development, how it influences kidney disease, and the vascular beds involved remains uncertain.

Methods: We performed a detailed expression profile of VEGFR3 in the developing mouse kidney from embryonic age (E)13.5 through 3 months. We generated a transgenic mouse model to investigate the role of Vegfr3 in the kidney vasculature (Vegfr3+). Conditional and cell-specific excision of the floxed allele was performed using the Rosa26/Cre-TetOCre, Cdh5-CreERT2, and Prox1-Cre/ERT2 driver strains to evaluate global, pan-endothelial, and lymphatic endothelial cell deletion of Vegfr3 respectively. Additionally, breeding of mice carrying podocyte-specific deletion and overexpression of the VEGFR3 ligand, VEGF-C, are underway to define ligand-dependent and independent function of VEGFR3 in the glomerulus. Mice underwent a detailed phenotypic evaluation and kidney sections were processed for histology.

Results: VEGFR3 undergoes dynamic expression through development in glomerular endothelial cells (GECs), beginning with high expression in the angiogenic sprouts which involute into a capillary cleft of the developing nephron. Constitutive deletion of Vegfr3 during mid-embryonic development resulted in reduced viability, lymphatic vascular defects, a reduction in kidney size, and a reduction in average cross-sectional glomerular count on serial sectioning (mean difference -3.767 ± 1.238, p <0.005). Additionally, deletion of Vegfr3 at embryonic day 11.5 demonstrated marked disruption of glomerular development with cavernous capillary malformations. Immunofluorescence and electron microscopy revealed glomerular structures surrounded by simplified podocytes, abnormal attachment of endothelial cells with reduced fenestrations, and poor formation of the glomerular basement membrane. VEGF-C mutant mice will be characterized once available.

Conclusions: VEGFR3 expression in GECs and is integral to normal glomerular development. The mechanisms of VEGFR3 signaling in GEC crosstalk with podocytes will be essential to define prior to the development of therapeutics targeting this pathway.

Funding: NIDDK Support, Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO0615

The ATP-Binding Cassette Protein ABCG2 Marks Kidney Resident Endothelial Colony-Forming Activity in Multiple Endothelial Clusters Identified by Single-Cell RNA Sequencing
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Background: Side-population cells (SP) were originally identified in hematopoietic stem cells based on their ability to efflux the DNA binding dye Hoechst 33342, an activity thought to be mediated by members of the ATP-binding cassette protein family such as ABCG2. We hypothesized that ABCG2-expressing endothelial cells (EC) are enriched in colony forming cell (ECFC) activity, and may contribute to vascular homeostasis in kidneys.

Methods: The fate of ABCG2 expressing EC was investigated using adult Abcg2-CreERT Td-tomato Rosa26 reporter mice (ABC2-TT). Transgene with tamoxifen (TMX; 50 µg/kg) 1X followed by FACs analysis for TdTomato in EC. For single-cell RNA sequencing, mouse kidney ECs were isolated following digestion with collagenase, and CD45-depleted/CD31-positive magnetic selection. Isolated single cells were sequenced using the 10X platform. Data were analyzed with Seurat.

Results: 24 hours following TMX, 2.9% of kidney EC (CD31+/CD45-) expressed TdTomato. The percentage of Td-Tomato+ EC progressively increased to 5.3% (p<0.4) by 1 week and 15.4% (p<0.0001) by 6 weeks post-injection. To determine the EC subtype expressing ABCG2-expressing ABCG2-associated progenitor activity, scRNAseq was conducted on isolated kidney endothelial cells of ABCG2-TT mice 24 hours following TMX injection. A total of 10 endothelial clusters were identified. Analysis of top expression genes suggested these clusters correspond to different kidney EC populations such as peritubular capillaries, venules, arteries, arterioles, AVR, DVR and lymphatics. The expression of the reporter was based on identification of WPRE response element expressed Rosa mice following Cre activation. Interestingly, no single discrete cluster of ECs expressing WPRE were identified. Rather, a variable percentage (4.3 to 38.7%) of WPRE expressing cells were identified in each cluster.

Conclusions: Taken together these data suggest that ABCG2+ expressing cells contribute to vascular maintenance in adult kidney and that such cells are found in most kidney EC populations. In addition, reporter expressing EC cells do not represent a transcriptionally distinct subset of EC but are transcriptionally similar to the surrounding tissue endothelial cell subsets.

Funding: NIDDK Support

PO0616

Stromal-Derived Ntn1 Influences Renal Vascular Formation and Kidney Development
Samuel E. Honeycutt, Yubin Xiong, Deanna M. Hardesty, Lori L. O'Brien. University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC.

Background: Renal vascular networks are critical to maintaining fluid homeostasis. Despite their important roles, formation and patterning of the renal endothelium and its effect on kidney development are poorly understood. Ntn1-1 is an ideal candidate for regulating endothelial network formation. In turn, the endothelium releases angiogenic factors that may influence the formation of surrounding tissues.

Methods: To investigate the role of netrin signaling during kidney development, we deleted Ntn1 from SPs and interrogated the embryonic phenotype using immunofluorescence, high-resolution and 3D microscopy, and cellular analyses.

Results: Conditional knock-out (cKO) of Ntn1 results in hypoplastic kidneys, extended nephrogenesis, and arterial mis-patterning. Using 3D light-sheet microscopy, we extended nephrogenesis, and arterial mis-patterning. Using 3D light-sheet microscopy, we found changes points (33%), total area (25%) and branch level (26%). Bulk RNA-seq of E15.5 kidneys was performed to gain insights into the resulting phenotypes. We found changes in metrics across most parameters including branch number (17%), vessel length (23%), end points (33%), total area (25%) and branch level (26%). Bulk RNA-seq of E15.5 kidneys were isolated following digestion with collagenase, and CD45-depleted/CD31-positive magnetic selection. Isolated single cells were sequenced using the 10X platform. Data were analyzed with Seurat.

Conclusions: Taken together these data suggest that ABCG2+ expressing cells contribute to vascular maintenance in adult kidney and that such cells are found in most kidney EC populations. In addition, reporter expressing EC cells do not represent a transcriptionally distinct subset of EC but are transcriptionally similar to the surrounding tissue endothelial cell subsets.

Funding: NIDDK Support

PO0617

Three-Dimensional Visualization of Neontal Glomerulogenesis in the PodoTRAP Model by Simplified Tissue-Clearing Approach

Background: The process of glomerulogenesis is complex and the dynamics and spatio-temporal coordination involved in the formation of the glomerular architecture are poorly understood. Conventional histopathological methods and 2D-microscopy techniques allow only a limited visualization and reconstruction of processes in the developing kidney which can only be fully appreciated in a 3-dimensional context.

Methods: To specifically study the organisation, maturation and arrangement of podocytes during glomerulogenesis, we used neonatal kidneys from PodoTRAP transgenic animals (P0, P3, P7) in combination with a modified synthetic (EC)-based clearing approach for immunostaining and subsequent 2-photon microscopy. We used IMARIS for comprehensive morphometric analysis and 3D-reconstruction of podocytes and glomeruli during postnatal kidney development.

Results: Tissue clearing is a technique to render biological samples transparent, thereby allowing for high resolution 3D-microscopic imaging of structures deep within the tissue without the need for conventional tissue-sectioning. We used this technique for 3D-imaging, reconstruction and analysis of different glomerular developmental stages (renal vesicles, 5-phase, capillary loop, maturing glomerulus) in transparent kidneys of P0, P3, P7 as well as adult PodoTRAP mice. Eci-clearing followed by 2-photon microscopy achieved significantly higher imaging depth compared to uncleared kidneys (100µm vs. ~150µm). GFP podocytes in ECI-treated PodoTRAP kidneys were readily identified due to robust cellular epithellofluorescence, with GFP signal intensities increasing as podocyte maturation progressed. Amongst others, we conducted comprehensive quantification of glomerular volume increases during postnatal kidney development.

Conclusions: The combination of ECI-clearing and 2-photon microscopy in the PodoTRAP model is well suited for high-resolution 3D-imaging of renal tissue including detailed morphometry of maturing glomeruli in whole neonatal mouse kidneys. Moreover, this approach could also be useful for holistic histopathological analyses and assessments in various glomerular disease models including FGSS.

Funding: NIDDK Support, Private Foundation Support

PO0618

OSR1 Couples Intermediate Mesoderm Cell Fate with Temporal Dynamics of Vessel Progenitor Cell Differentiation
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Background: Transcriptional regulatory networks refine gene expression boundaries throughout organogenesis to define the precise dimensions of organ progenitor territories. Kidney progenitors originate within the intermediate mesoderm (IM), but the pathways that establish the boundary between the IM and its neighboring vessel progenitors are poorly understood.

Methods: We employ a combination of loss-of-function and gain-of-function genetics, RNA in situ hybridization, immunohistochemistry, and transgenesis in the zebrafish model system.

Results: Here, we delineate new roles for the zinc finger transcription factor Osr1 in kidney and vessel progenitor development. Zebrafish osr1 mutants display decreased IM formation and premature emergence of neighboring lateral vessel progenitors (LVPs). These phenotypes contrast with the increased IM and absent LVPs observed with loss of hand2 and osr1 are both expressed in the posterior lateral mesoderm, but hand2 expression decreases dramatically prior to LVP emergence. Induction of osr1 expression after gastrulation is sufficient for inhibiting LVP development and rescuing IM and pronephric formation.

Conclusions: Together, our data demonstrate that osr1 modulates both the extent of IM formation and the temporal dynamics of LVP development, suggesting that a balance between levels of osr1 and hand2 expression is essential to demarcate the dimensions of kidney and vessel progenitor territories.

Funding: NIDDK Support, Private Foundation Support

PO0619

Membrane Phosphoinositides and Renal Epithelial Cell Polarity Determination in the Xenopus Pronephros In Vivo
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Background: Though only minor components of cell membranes, phosphoinositide lipids (PIs) participate in numerous signaling processes and in membrane identity determination. Many studies of cultured mammalian cells have established PIs are distributed with polarity among plasma membrane (PM) domains, and that their polarized distributions are required for the delivery of distinct populations of apical and basolateral membrane proteins. The extent to which PIs drive these processes in actual renal epithelial cells in vivo has never been examined. Here we examined the distribution of PIs in the pronephros of Xenopus Tropicalis tadpoles using MCherry-tagged Pleckstrin Homology (PH) domains that selectively bind different PIs (PH-AKT, PH-PLCD1, which bind to PI(3,4,5),PH-JP3 and PH(4,5)P2 respectively) with the goal of assessing whether and how PI localization affects cell polarization and the trafficking of proteins to their sites of ultimate functional residence in renal epithelial cells in situ.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Antonuvian Calcium Signaling in Human and Zebrafish Podocytes

Methods: mRNA encoding MCherry-PH-AKT or MCherry-PH-PLCδ1 was injected into zebrafish embryos and their distribution in newborn podocytes and differentiated neurons was assessed at stage NF45 via fluorescence microscopy. Knockdown (KD) of PTEN, a lipid 3 phosphate that regulates membrane PI composition, was achieved via injection of targeted morpholinos and confirmed by western blotting. The effects of PTEN KD on PH-AKT distribution were assessed.

Results: In MDCK cells PH-AKT and PH-PLCδ localize to the basolateral and apical PMs, respectively. Their distributions are quite different in the nephron, with both sensors showing a markedly apical signal in the proximal portion of the tubule and diffuse staining in the distal part. PH-AKT staining dramatically re-distributed in mouse podocytes to the lateral domain of renal cells upon PTEN KD but this treatment does not alter the localization of protein markers of epithelial PM polarity.

Conclusions: These studies constitute the first effort to assess the role of PI3K in epithelial cells in vivo, and future research will reveal the role of calcium signaling in podocyte foot process formation.

Funding: NIDDK Support

PO0620

Autonomous Calcium Signaling in Human and Zebrafish Podocytes
Controls Kidney Filtration Barrier Morphogenesis
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Background: Mutations in nephritic syndrome genes that lead to elevated cytoplasmic calcium in podocytes cause disruption of filtration barrier function and nephrotic syndrome. Whether calcium signaling plays a role in the initial formation of the filtration barrier is not known. Here we show that calcium signaling is active during podocyte differentiation, occurs independently of neighboring cell types, and is required for foot process slitting.

Methods: The calcium biosensor GCaMP6s was expressed in zebrafish podocytes during larval development using a podocin:Gαl4 x UAS:GCaMP6s transgene cross to evaluate calcium signaling during development. Calcium signals in differentiating podocytes in human kidney organoids were detected using Fluo-4. Filtration barrier formation in zebrafish was evaluated by electron microscopy.

Results: Immature zebrafish podocytes generated calcium transients that correlated with interactions with forming glomerular capillaries. Calcium transients persisted until 4 dpf and were absent after glomerular barrier formation was complete. Similar calcium transients were detected in maturing human organoid glomeruli. Calcium transients were not affected by deficiencies in heart, endothelium or endoderm, and persisted in isolated glomeruli, suggesting that they were generated cell autonomously. Inhibition of phospholipase C gamma, a key component of the calcium signaling pathway, blocked calcium transients in podocytes, while lanthanum was ineffective, indicating the source of calcium is podocyte intracellular stores. Calcium transients were not affected by deficiencies in heart, endothelium or endoderm, and persisted in isolated glomeruli, suggesting that they were generated cell autonomously. Inhibition of phospholipase C gamma, a key component of the calcium signaling pathway, blocked calcium transients in podocytes, while lanthanum was ineffective, indicating the source of calcium is podocyte intracellular stores. Calcium transients were not affected by deficiencies in heart, endothelium or endoderm, and persisted in isolated glomeruli, suggesting that they were generated cell autonomously. Inhibition of phospholipase C gamma, a key component of the calcium signaling pathway, blocked calcium transients in podocytes, while lanthanum was ineffective, indicating the source of calcium is podocyte intracellular stores.

Conclusions: Our results establish cell-autonomous calcium signaling as a prominent and conserved feature of podocyte differentiation and demonstrate the requirement for intracellular calcium elevations for podocyte foot process formation.

Funding: NIDDK Support

PO0621

Zebrafish Kidney Regeneration as a Model for Engraftment of Stem Cell-Derived Kidney Replacement Tissue
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Background: In vivo engraftment of iPSC derived mammalian kidney organoids is emerging as a potential goal for kidney regenerative medicine. A major challenge in engraftment is establishing patent tubule conduits between organoid graft and host tubules to allow fluid filtration and excretion. Stem cell-derived nephrons are continuously made during zebrafish kidney growth and correlates with expression of multiple genes associated with metastatic cell invasiveness. Manipulation of Wnt signaling is an opportunity to engineer kidney tubule interconnections.

Funding: NIDDK Support, Private Foundation Support

PO0622

Evidence for Convergence of NF-κB and Growth Hormone (GH) Signaling on Stem Cell Activation in the Adult Zebrafish Kidney
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Background: Adult progenitor cells in the mesonephric kidneys are required both during neo-nephrogenesis replacing injured tubules but also during overall growth. Single-cell RNA transcription profiles of adult kidney progenitor cells point to at least two receptor systems that may initiate stem cell-based nephrogenesis: growth hormone (GH) and interleukin receptors. Here we present evidence for both injury (NF-κB activation) and growth-related pathways (GH) in stimulating stem cell-based nephrogenesis.

Methods: Adult zebrafish kidneys were injured by gentamicin, and ganciclovir i.p. injection. NF-κB signaling was determined four days post injury (dpi) by NF-κB:GFP detection of the NF-κB reporter line Tg(NF-κB:EGFP) and NF-κB-associated gene expression using qRTPCR. Requirement of NF-κB signaling during regeneration was evaluated by photoactivating the NF-κB signaling pathway. GH signaling was evaluated after either GH or ganciclovir injection by quantification of progenitor marker Islx1a:GFP in Tg(lhx1a:Gfp) and stem cell marker expression by qRTPCR. Inhibitors of GH downstream signaling were used to determine GH signaling impact after kidney injury. Bulk RNAseq from ganciclovir-injured selected GFP- and mcherry+ single cells by FACS was performed from kidneys 7 dpi by gentamicin injection using Tg(lhx1a:EGFP::cdb17::mcherry) fish.

Results: Ganciclovicin-induced kidney injury leads to an increase in tubular NF-κB nuclear translocation at 4 dpi and is associated with an upregulation of NF-κB downstream target gene expression detected by qRTPCR. Ganciclovicin also causes GH receptors mRNA upregulation at 7 dpi along with the kidney progenitor markers osr1 and evx4. GH injection induced the formation of new nephrons as marked by Tg(lhx1a:GFP) expression in new nephron aggregates.

Conclusions: Multiple pathways may converge on adult kidney stem cells to activate new nephron formation. Growth and growth hormone may induce new nephron formation in response to increased body mass and need for osmoregulation. Kidney injury and nephron replacement correlate with nuclear translocation of NF-κB in injured tubules, suggesting the possibility of cytokine-mediated nephrogenesis in response to injury.

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PO0623

Dual Tubular Par1a/b cKO Is Protective Against Renal Fibrosis
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Background: Partitioning defective Par1a/b proteins are highly homologous serine threonine kinases and contribute to kidney development. Tubular Par1a/b expression increases following folic acid and unilateral ureteral obstruction (UUO). Loss of Par1a/b expression during development impairs Notch signaling pathway expression. Notch signaling activation contributes to renal fibrosis. We hypothesized that Par1a/b expression is maladaptive following injury and promotes renal fibrosis.

Methods: Using publically available single cell RNA sequencing data, we examined the cell types where Par1a (Mark3) and Par1b (Mark2) were expressed following UUO. Localization was confirmed using immuno-fluorescence with antibodies specific for Par1a and 1b. Conditional Par1a and 1b flox mice were generated using CRISPR/Cas9 gene editing. Dual tubular conditional Par1a knockout (cKO) mice (Paclt-rtTA:tet-O-Cre:Mark2hox:lox:Markhox:lox) mice were generated. Deletion of Par1a (Mark3) or Par1b (Mark2) was confirmed following doxycycline induction. UUO was performed in adult (10 week old) male tubular Par1a/cKO mice and controls; phenotype was examined at 7 days. Tubular Par1a/cKO deletion was induced by feeding mice doxycycline in chow starting 7 days prior to UUO. Controls were uninduced (−dox) transgenic littermates from the same mice colony. Six mice/group were studied. To detect renal fibrosis, Picro-Sirius Red staining of collagen was performed. Polarized light and Image J was utilized to quantify fibrosis on 200x images.

Results: Single cell analysis demonstrated increased expression of Par1a/b in proliferating and injured proximal tubules following UUO. This was confirmed by co-expression of Par1a in kidney and Sox9 positive tubules following UUO. Dual tubular Par1a/cKO deletion was protective against fibrosis, with % fibrosis decreasing from 1.6 to 0.65 percent 7 days following UUO (p=0.0048).

Funding: NIDDK Support, Other NIH Support - Maine INBRE grant (GM103423), Government Support - Non-U.S.

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PO0624
TRIM72-Containing Exosome for Kidney-Targeted Expression and Protection
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Background: TRIM72 is a myokine and appears to confer protection to the kidney in ischemia-reperfusion (IR) injury. There are low levels in the kidney. We did experiments to see if TRIM72 could be transferred to the kidney so it could be used therapeutically.

Methods: Exosomes were purified from C2C12 myotubes differentiated from C2C12 myoblasts by differential centrifugation. C2C12 exosomes were given to TRIM72 null mice twice weekly for 4-weeks by tail-vein injection. Five-days post the last exosome injection, real time PCR and western blotting was used to examine tissue expression. For comparison, samples obtained from wildtype littermates served as positive controls.

Results: TRIM72 mRNA remained detectable five days post the final C2C12 exosome infusion. Moreover, TRIM72 mRNA delivered by exosomes reconstituted TRIM72 to the same organ distribution as in wildtype littermates, with high levels in kidney, skeletal muscle and moderate levels in heart and skin. TRIM72 protein expression was detected in tissues according to TRIM72 mRNA distribution. Compared to a TRIM72-deficient exosome derived from NIH3T3 condition media, treatment with C2C12 exosome mitigated high serum creatinine level of IR injured wildtype mice. This suggested a sustained TRIM72 expression and protection in kidney when delivered in exosome format.

Conclusions: Adaptive transfer of C2C12 exosomes demonstrated TRIM72 could be reconstituted to its native organ distribution and expression in TRIM72-deficient mouse. TRIM72-containing exosome mitigated elevated serum creatinine level of IR injured mice. Pharmacologic administration of TRIM72-containing exosome might be a promising approach for the treatment of kidney disease.

Funding: NIDDK Support, Other NIH Support - NIA

PO0625
Development of Noninvasive Clinically Applicable In Vivo Tracking of Extracellular Vesicles Using MRI
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Background: Extracellular vesicles (EVs) derived from amniotic fluid stem cells (AFSC) hold great potential for the treatment of chronic kidney diseases (CKD). We showed that AFSC-EVs are renoprotective in a mouse model of CKD, Alport syndrome. However, there is an important unmet need for real-time in vivo monitoring of these therapeutic EVs to determine biodistribution to inform about safety, targeting, and effectiveness. While current optical imaging solutions like bioluminescence and fluorescence are useful for EV tracking studies in animal models, there is limited utility in clinical applications. Here we present a novel in vivo tracking solution for therapeutic EVs in Alport mice, utilizing clinically applicable MRI technology.

Methods: To generate trackable EVs, AFSC were labeled with a novel magnetic agent (VSCM). EVs secreted by the labeled AFSC were isolated by ultracentrifugation. The magnetic label did not affect the physiological characteristics of the cells and did not change identity, purity and potency (therapeutic effect in vivo) of EVs. MRI phantom studies confirmed the in vitro/vivo detectability of labeled EVs. Importantly, as expected MRI studies showed that EV homing to the kidney injected intracardially into Alport mice was more efficient vs the retro-orbital route, and Prussian blue staining of sections confirmed EV homing to the kidney.

Conclusions: We have developed a clinically applicable novel magnetic nanoparticle agent that can be used to label and track the biodistribution of EVs in the kidney and other organs using non-invasive, safe, and effective MRI technology that’s widely available. This technology is highly adaptable and can be deployed in both preclinical and clinical settings.

Funding: NIDDK Support, Other NIH Support - NIA

PO0626
Extracellular Vesicles Rescue Alport Glomerular Endothelial Lipid Dysfunction
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Background: Glomerular endothelial dysfunction plays a key role in the development of chronic kidney disease (CKD). We have previously shown that glomerular endothelial cells (GEC) are damaged in Alport syndrome mice (ASC, characterized by mutated collagen IVα3α5α5), manifested by enlarged fenestrations and damaged glyocalix in the early stage of the disease. In the present study we report on the altered fatty acid utilization pathways leading to GEC dysfunction in ASC, and the role of extracellular vesicles derived from amniotic fluid stem cells (AFSC-EVs) in re-establish lipids homeostasis.

Methods: GEC were isolated from tTomato-reporter AS and WT mice at 4 months of age by FACS and transcriptome was analyzed and compared by bulk RNA-seq. Tissue samples from patients with AS were used to confirm our findings by immunohistochemistry. In vitro, silencing experiments using human primary GEC were performed to study the role of decreased fatty acid synthase (FASN) in GEC dysfunction, and AFSC-EVs (which contain FASN in their cargo) were applied as a rescue strategy to normalize FASN level and restore lipid homeostasis. Data were confirmed using AFSC-EV

Conclusions: We report for the first time a lipid metabolic dysfunction in Alport GEC, and the ability of AFSC-EVs to rescue this phenotype. Therefore, better understanding of the functional role of GEC in ASC should lead to the development of targeted new therapies for the treatment of this and other forms of CKD.

Funding: Private Foundation Support

PO0627
Administration of Mesenchymal Stromal Cell-Derived Exosomes Is an Effective Rescue Therapy for Progressive AKI in Rats
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Background: Preclinical and clinical studies have shown Mesenchymal Stem Cells (MSCs) to be effective for prevention of AKI [NCT00733876]. Yet studies where MSCs are given 48 hrs. post-insult, a time at which most patients with severe AKI are diagnosed and when no rescue therapy is available, show them to be ineffective or even damaging due to compromised renal blood flow in capillary beds, where introduction of large cells has the potential to cause further deterioration of renal function [NCT01602328]. While MSCs’ renoprotection is largely due to their release of beneficial cytokines and exosomes, their potential negative impact on renal blood flow is a concern. Administration of MSC-derived exosomes is known to exert beneficial effects that are similar to those of the parent cells. We hypothesized that since MSC-derived exosomes can prevent AKI, their small size and ability to move through the microvasculature might allow them to also be an effective rescue therapy for late stage AKI where MSCs are ineffective.

Methods: MSCs from Sprague Dawley (SD) rats were used. Their purified exosomes were characterized for size by nanoparticle tracking analysis, protein concentration, gene expression of relevant markers, FACS (CD44 and CD29), and rHCR. I/R AKI (50-52 min bilateral renal pedicle clamp) was induced in 3 groups of SD rats (6/group). SCr was assessed at baseline, Days (D) 1 and 2. If the SCr value on D2 was greater than that on D1, then on D3, rats were given i.e. 1 ml of Vehicle, 4×10e10, or 2×10e9 ASCs. Studied Endpoints: SCr at Days 0-9; survival and renal injury.

Results: In contrast to what is found when MSCs are administered to rats immediately upon reflow, when administered to rats 48 hrs post-I/R AKI, 2×10e6 MSCs proved ineffective at ameliorating injury, while MSC-derived exosomes significantly and sustainably improve renal function by D5 post-injury.

Conclusions: MSC-derived exosome therapy administered 2 days post-insult, when renal blood flow is compromised, but also when most clinical instances of AKI are diagnosed, is superior to MSC therapy for rescue of AKI, likely due to the mirrored paracrine content, but significantly smaller size of exosomes compared to MSCs. Our results support the hypothesis that MSC-derived exosomes could be used as a rescue therapy for non-spontaneously recovering AKI.

Funding: Commercial Support - SymbioCellTech

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Human Induced Pluripotent Stem Cell-Derived Kidney Organoids to Model Idiopathic and Congenital Nephrotic Syndrome

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Background: Recent advances in human stem cell-derived kidney organoid models have opened new avenues to accurately model podopathy/athelia in 3D in vitro. The aim of this study is to develop and characterize human induced pluripotent stem cells (iPSC)-derived 3D kidney organoids as a first step in modeling idiopathic and congenital nephrotic syndrome (NS) in vitro.

Methods: Human iPSCs were successfully cultured into kidney organoids and characterized using scRNA sequencing, immunocytochemistry, TEM and RNAscope. The prostate sodium (PS) model and FSOS plasma treatment were used to model idiopathic NS. Podocin mutant organoids were used to study congenital NS.

Results: Kidney organoids showed a clear podocyte population expressing, amongst others, podocin, nephrin, PLAR2, WT1, VEGFA and collagen IV alpha 3. The slit diaphragm was confirmed by TEM. To model podocyte injury, organoids were exposed to GATA3+PDGFRβ activated FSGS, a specific active FSGS organoid-mediated injury and organoids showed clear podocyte cytoskeleton rearrangements and the induction of pNPHS1-1176 protein expression. The induced podocyte injury was rescued by heparin sulphate, illustrating recovery of injury associated mechanisms in 3D podocytes. The PS model was able to induce podocyte specific as their 2D iPSC-derived podocyte counterparts did not express pNPHS1-1176. Organoids exposed to active FSGS plasma for 4h showed increased granule formation, a podocyte stress marker, in NPHS1 + podocytes which was less abundant when treated with remission plasma. To model congenital nephropathy, erythroblasts from a pediatric patient with compound heterozygous mutations p.Arg138Gln (exon 3) and p.Arg166Ter (exon 4) in the podocin (NPHS2) gene were successfully reprogrammed in iPSC. Ablation localization and weak podin expression was shown in organoids. Using CIRSIPR/Cas9 the exon 3 mutation was repaired and podin expression was restored.

Conclusions: We successfully developed human iPSC-derived kidney organoids that will serve as a state-of-the-art tool to accurately study podopathy/athelia in a dish.

Funding: Other NIH Support - The Dutch Research Council

Five-Year Outcome in Patients with ESRD Who Received the Bioengineered Human Acellular Vessel for Dialysis Access

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Methods: HA Vs are bioengineered by culturing human vascular smooth muscle cells (SMC) on a biodegradable polymer matrix within bioreactors that provide pulsatile mechanical strain. After a quantitative decellularization process, the final complete vessel contains 5-year follow-up functional and histological data on 29 patients who were enrolled in the study (at Month 27) through at least 5 years post-implantation. This current report contains 5-year follow-up functional and histological data on 29 patients who were previously enrolled in our initial Phase 2 trial.

Results: At Month 60, 1 subject maintained primary patency, two subjects maintained primary-assisted patency, and ten subjects maintained secondary patency. Secondary patency was estimated at 58.2% (95% confidence interval: 39.2 to 73.1%) at 5 years, after censoring for deaths (n=8) and withdrawals (n=1). No infections of HA V conduits were reported during follow up period.

Conclusions: This long-term follow up shows that the HA provides durable and functional hemedialysis access for patients with end-stage renal disease who dialyze three times per week.

Mechanistic Elucidation of Nephron Progenitor Cell Expansion Using a Small Molecule, TCS21311, That Replaces BMP7 and Promotes Cell Proliferation

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Background: Nephron progenitor cells (NPCs) give rise to all epithelial components of the nephron, which is the smallest functional unit of the kidney. The development of a stable supply of NPCs is expected to contribute to kidney regeneration research. Although most reports on the development of NPC expansion culture use BMP7, the detailed mechanisms of action of BMP7 are unknown. To elucidate the roles of BMP7 and improve the NPC expansion culture method, we sought small molecules that can replace BMP7 in the culture system.

Methods: We isolated NPCs from Six-2-GFP reporter mice and screened 4,395 chemical compounds using a previously reported expansion culture system. The activity of analogous chemicals from the hits was examined. We predicted the molecular targets of the hit compounds by chemoinformatics analyses of molecular structures. Known downstream signaling pathways were examined by immunoblotting, and differentially expressed genes (DEGs) were analyzed by removing BMP7 from the NPC expansion culture. Furthermore, we improved the expansion culture method using mouse embryonic and human induced pluripotent stem cell (iPSC)-derived NPCs by adding the hit compounds to the expansion culture condition including BMP7.

Results: The chemical screening identified a JAK3 inhibitor, CP690550, in the mouse NPC expansion culture. Although several JAK3 inhibitors as well as some JAK2/3, JAK1/2 and JAK2 inhibitors showed similar activity, one JAK3 inhibitor, TCS21311, showed especially potent effects. A structural analysis of TCS21311 confirmed that JAK3 is its primary target. A pathway analysis of the DEGs by the BMP7 removal indicated STAT3 pathway activation. The phosphorylation of Smad1/5 was increased by TCS21311 even in the absence of BMP7, suggesting a mechanism by which TCS21311 replaces BMP7 via JAK3-STAT3. Furthermore, the addition of TCS21311 to the expansion culture containing BMP7 resulted in more efficient proliferation of mouse embryonic and human iPSC-derived NPCs.

Conclusions: These results will contribute to understanding the roles of BMP7 in NPC proliferation and to the stable supply of NPCs.


The Transcription Factor GATA3 Regulates Hyaluronan-Mediated Stromal-Cell Responses During Kidney Injury, Repair, and Fibrosis

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Background: Stromal-mediated processes are critical in determining fibrosis progression. Stromal cells are essential for kidney development and homeostasis, but are also myofibroblast precursors and their maladaptive responses tip the balance from tissue repair to scarring. Our work shows that GATA3 is crucial for developing and mature renal stroma and its expression marks a distinct fibroblast subset associated with improved tissue outcomes following injury. Hyaluronan-(HA), a matrix glycosaminoglycan, is a key regulator fibroblast heterogeneity and predominance of distinct HA synthes (HAS) is its primary target. The development of analogous chemicals from the hits was examined. We predicted the molecular targets of the hit compounds by chemoinformatics analyses of molecular structures. Known downstream signaling pathways were examined by immunoblotting, and differentially expressed genes (DEGs) were analyzed by removing BMP7 from the NPC expansion culture. Furthermore, we improved the expansion culture method using mouse embryonic and human iPSC-derived NPCs.

Conclusions: These results will contribute to understanding the roles of BMP7 in NPC proliferation and to the stable supply of NPCs.


PO0629

PO0630

PO0631
PO0632

The Regenerative Response to Renal Injury of the African Spiny Mouse Is Epigenetically Regulated Through H3K27 Methylation

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Background: Lysine methylation of histones plays an important role in regulating gene expression. When tri-methylated, chromatin regions marked by H3K27me3 are inaccessible for transcription. EZH2 is the Polycomb group methylates H3K27, with opposing action carried out by histone demethylases JMJD3 & UTX. EZH2 activation and subsequent increase in H3K27me3 has been associated with renal fibrosis. We hypothesize that in the African spiny mouse, a mammalian model of kidney regeneration, demethylation of H3K27 is associated with regenerative wound healing after ischemia-reperfusion injury.

Methods: Experiments were carried out on kidneys of spiny mouse and house mouse in normal kidneys and kidneys 1 & 3 days after unilateral ischemia-reperfusion injury. Mass spectrometry was used to profile histone modifications. Expression of key genes involved in methylation of H3K27 were quantified using RNA-sequencing, and protein concentration was quantified by western blot. H3K27me3 marks were visualized by immunofluorescent staining. Genes marked by H3K27me3 were identified using CUT&RUN ChIP-sequencing.

Results: H3K27me3 is significantly increased in mouse kidney after ischemia-reperfusion injury whereas no change in the repressive mark was noted in spiny mouse when quantified by mass spectrometry and western blot. H3K27me3 marks are abundant in fibrotic mouse kidneys and distributed throughout kidney tissue, while H3K27me3 is reduced in repaired kidneys of spiny mouse. RNA-sequencing demonstrated a 4-fold increase in Ezh2 in mouse after injury vs 2-fold increase in spiny mouse. During the course of injury, Trim24 expression increased in spiny mouse but decreased in expression in mouse. We previously identified nephrogenic progenitor genes potentially associated with regenerative wound healing in spiny mouse, including Cdhl1, Cdhl6 and J19. CUT&RUN identified these genes as repressively marked by H3K27me3 in mouse but available for transcription in spiny mouse.

Conclusions: This work suggests that the regenerative response to renal injury in spiny mouse is orchestrated at least in part through the methylation of histone H3K27. Modification of the histone methylation landscape through small molecular modulators may redirect the outcome of kidney injury from fibrosis to regeneration.

Funding: NIDDK Support

PO0633

Effect of Hypoxic Preconditioning on Angiogenesis and Senescence in Human Adipose Tissue-Derived Mesenchymal Stem Cells


Background: Hypertension (HTN) and chronic kidney disease (CKD) alter the angiogenic and immunomodulatory properties of human adipose-derived Mesenchymal Stem Cells (AMSCs). Hypoxic conditions modify growth potential, paracrine functions and gene expression of AMSCs. We tested the hypothesis that AMSCs in CKD patients, preconditioned with hypoxia, will have reduced senescence, enhanced migratory, proliferative and angiogenic functions compared to healthy kidney donors.

Methods: We cultured AMSCs (P3-P4) from healthy kidney donors (Controls), patients with HTN and CKD, each group under normoxia (20% O2) and hypoxia (1% O2). We tested AMSC migration and proliferation, quantified angiogenic and inflammatory factors (VEGF, HGF, TNF-α, TGF-β) in cell culture supernatant, and analyzed gene expression (VEGF, HGF, PI3K/AK1/P16, P21) using RT-PCR.

Results: The table shows characteristics of enrolled patients. Hypoxia suppresses AMSC migration in support and HTN patients while enhancing it in CKD patients and increasing proliferation in all groups. Hypoxia enhances VEGF secretion in controls and CKD while downregulating HGF gene expression in controls and HTN group. In CKD patients, TGF-β secretion was higher at baseline and under hypoxia, TNF-α was elevated. Senescence (gene expression of P16/P21) was not different among the groups at baseline but hypoxia attenuated it in all groups.

Conclusions: Hypoxic preconditioning of AMSCs increases migration, proliferation, upregulates VEGF secretion and gene expression, and downregulates pro-senescence genes. These results support hypoxic preconditioning to enhance the regenerative potential and overcome challenges in autologous stem cell therapy for nephropathies.

Funding: NIDDK Support

PO0634

Effect of Hypoxia on the Regenerative Capacity of Adipose Tissue-Derived Mesenchymal Stem Cells in an Experimental Model of Atherosclerotic Renal Artery Stenosis


Background: Atherosclerotic renal artery stenosis (ARAS) is a risk factor for parenchymal renal disease. Autologous mesenchymal stem cells (MSCs) therapy reduces kidney fibrosis and inflammation in ARAS. Studies have shown that hypoxia preconditioning (Hx) improves MSC function by affecting DNA hydroxymethylation (5-hmC). But the effect of Hx MSCs in vivo ARAS model has not been evaluated. We hypothesize that Hx MSCs would improve renal histology better than normoxic (Nx) MSCs and also compare 5-hmC differences between MSC groups.

Methods: MSCs isolated from abdominal fat of ARAS pigs were cultured under normoxia (20% O2) or hypoxia (1% O2) till 70-80% confluence. Autologous Nx or Hx MSCs (10^6 cells each) were injected into the swine renal artery 6 wks after induction of ARAS (N=4 each) and compared to Normal and Untreated ARAS pigs (N=5 each). 4 wks later, ex vivo renal trichrome and CD3(T-cell) staining was performed. MSC gene groups with significant 5-hmC fold change levels were grouped on Panther’s database.

Results: ARAS pigs treated with either Nx or Hx MSC show reduced renal fibrosis and interstitial inflammation (CD3 cells) versus untreated ARAS pigs (Fig1A-B). Intestinal fibrosis was less with Nx MSC therapy versus Hx MSC therapy (Fig1A). Intestinal inflammation showed a decreasing trend with Hx MSC therapy versus Nx MSC therapy (p=0.09). Epigenetic analysis showed higher DNA 5-hmC levels of profibrotic and inflammatory genes in ARAS MSC versus Normal Pig MSC (Fig1C). 5-hmC levels of some of these genes were lower in Hx MSC (Fig1D).

Conclusions: In swine model of ARAS, intra-arterial renal delivery of autologous MSCs with or without hypoxia preconditioning reduces kidney fibrosis and interstitial T-cell infiltration. Hx MSCs’ effect was not different from Nx MSC. But, enhanced DNA hydroxymethylation of profibrotic and inflammatory genes in ARAS MSC could be mitigated by hypoxia preconditioning.

Funding: NIDDK Support
PO0635

In Vivo Data to Support Induced Pluripotent Stem Cell-Derived Renal Progenitors as Potential Cell Therapy for Kidney Disease


Background: Novel therapies are needed to deliver life changing medicines to renal patients and cell therapy is a relatively new strategy of kidney therapy. We have developed novel methodology to produce kidney organsoids for target validation. Here we have used this learning, to derive human renal progenitor cells (RPC) and examine their differentiation in-vivo using 2 delivery models.

Methods: We used iPSC modified to contain a GF reporter of nephrin expression, to generate human RPC differentiated to day 6 and 10 using a previously described kidney organoid protocol. We then used kidney capsule implantation and intravenous delivery in naïve and Ischemia/Reperfusion Injury (IRI) NOD/SCID background mice respectively. For kidney capsule, we compared RPC implantation number (3 and 5x10⁶ naïve and Ischemia/Reperfusion Injury (IRI) NOD/SCID background mice respectively. For kidney capsule, we compared RPC implantation number (3 and 5x10⁶ naïve and Ischemia/Reperfusion Injury (IRI) NOD/SCID background mice respectively.

Results: For kidney capsule, we compared RPC implantation number (3 and 5x10⁶ naïve and Ischemia/Reperfusion Injury (IRI) NOD/SCID background mice respectively. For kidney capsule, we compared RPC implantation number (3 and 5x10⁶ naïve and Ischemia/Reperfusion Injury (IRI) NOD/SCID background mice respectively. For kidney capsule, we compared RPC implantation number (3 and 5x10⁶ naïve and Ischemia/Reperfusion Injury (IRI) NOD/SCID background mice respectively. For kidney capsule, we compared RPC implantation number (3 and 5x10⁶ naïve and Ischemia/Reperfusion Injury (IRI) NOD/SCID background mice respectively.

Conclusions: These observations clearly demonstrate the use and differentiation potential of RPC in a pre-clinical setting. These studies may aid design and delivery modality, for any future effort in examining RPC therapy for renal disease.

Funding: Commercial Support - AstraZeneca

PO0636

Synthetic Peptide Hydrogels as Support Matrices for the Generation of Distinct Cell Populations Within Induced Pluripotent Stem Cell-Derived Kidney Organoids

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Background: Kidney organoids display improved maturity with reduced variability are needed to produce models that faithfully mirror the in vivo organ. We propose that organoid development will benefit from the kidney like organelles guided by a tunable, fully defined microenvironment. Synthetic self-assembling peptide hydrogels are ideal systems to support organoid development that more accurately mimics the in vivo environment due to the simplicity of the structure formed at the molecular level, their low immunogenicity, cell retention, biodegradability, and tuneable mechanical properties.

Methods: Peptide hydrogel properties were investigated via transmission electron microscopy and rheology. Organoids were characterized by immunofluorescence and single cell RNA sequencing using the 10x Genomics platform.

Results: The self-assembling peptide hydrogels (SAPHs) were comprised of a fibrous structural architecture similar to that of natural polymer networks. The mechanical properties of the SAPHs were dynamic with Alpha4 increasing in G' stiffness (G' = 2.5 kPa) and fibrotic tissue (G' = 400 Pa), human kidney tissue (G' = 8-10 kPa) were generated. SEM revealed that hydrogel pore size was dependent on crosslinking concentration in the hydrogel formulations. PCNA and cleaved caspase-3 staining of organoids embedded within scaffolds demonstrated high cell proliferation and viability in all hydrogel constructs by day 26 of differentiation. The formation of glomerular, proximal tubular and distal tubular structures, that were supported by basement membrane and interstitial cells was confirmed in all conditions using qRT-PCR and immunofluorescent analysis. Significantly enrichment of MEIS1/2/3+ve interstitial cells was noted in organoids differentiated within stiffer hydrogels. Interstitial expansion and increased extracellular matrix deposition was confirmed using H&E and Masson’s trichrome staining within stiff GelMA scaffolds.

Conclusions: We propose the utility of GelMA hydrogels as faithful extracellular supports for the specification of hiPSC-derived kidney organoids. These scaffolds represent a mechanically tunable microenvironment to investigate the effects of the biological milieu on renal development and disease perturbations.

Funding: Government Support - Non-U.S.

PO0637

Gelatin Methacryloyl (GeMA) as a Tumour Biophysical Environment for the Derivation of Human Induced Pluripotent Stem Cell-Derived Kidney Organoids

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Background: The translational utility of hiPSC-derived kidney organoids relies on our ability to comprehensively mimic both the biochemical and biophysical properties of the cellular milieu in vitro. An improved understanding of how the mechanical environment affects the renal progenitor niche during development and how perturbations to such biophysical environments effects cell fate are required. Within this context, Gelatin methacryloyl (GeMA), a derivative of collagen, represents a mechanically amendable scaffold to probe cell fate dynamics.

Methods: We proposed the GeMA hydrogels were differentiated within photo-crosslinked GeMA hydrogels of defined mechanical strengths. Hydrogels were characterised using rheological analysis and SEM. Enrichment of renal cell types in response to the various mechanical microenvironments was subsequently investigated.

Results: Hypothesis driven studies have reported certain limitations of experiments on animals for assessing nephropathy. Due to species differences in tubular transporters, a model of continuous NPH is desirable. Organoids in a pre-clinical setting may aid in understanding peptide hydrogels, as they are factory-made materials that provide a tissue engineering platform with tunable mechanical properties.
exogenous nephrons were extracted for the immunohistochemical evaluation. In addition, ciliogenesis and nephrogenesis were assessed via immunofluorescence and live confocal imaging. The enhanced conditions also provided more stringent control over nephron spatial arrangement. PT-enhanced organoids provide an ideal model to better understand human PT maturation, inherited and acquired PT disease, and drug toxicity implications. The enhanced conditions also provided more stringent control over nephron spatial arrangement. PT-enhanced organoids provide an ideal model to better understand human PT maturation, inherited and acquired PT disease, and drug toxicity implications.
and we found that expression of the prostaglandin cyclooxygenase enzyme (Cox1) and prostaglandin regulator Pgc1a was reduced in ETag deficient embryos. Treatment with dmPGE2 or Cox1 overexpression was sufficient to rescue renal and cilia defects.

**Conclusions:** These data position ETag as a novel link between ciliogenesis and nephrogenesis through regulation of prostaglandin signaling, and highlight ETag as a potential new target for future ciliopathic treatments.

**PO0645**

**IL-33 as a Novel Target for the Treatment of Diabetic Kidney Disease**

**Background:** Diabetic kidney disease (DKD) has classically been thought as a microvascular disorder, although inflammation has emerged as a key pathophysiological mechanism involved in the development of diabetic kidney injury. Consequently, inflammatory mediators have aroused as promising therapeutic targets.

**Methods:** IL-33 is a broad acting cytokine, expressed in endothelial and epithelial barriers, that mediates local tissue inflammation. It exerts its function by binding to a heterodimer formed by its specific receptor ST2 and co-receptor IL-1RAcP. Due to the evidence of the role of IL-33 in kidney injury, we generated MEDI3506, a potent IL-33 blocking mAb for the treatment of DKD.

**Results:** Transcriptomic analysis showed that expression of IL-33 RNA is upregulated in both the glomeruli and tubulointerstitium of DKD patients in two independent cohorts. Assessment of expression in both human and experimental DKD demonstrated that IL-33 is among the most regulated inflammatory genes. Preliminary data on IL-33 protein levels in human kidney biopsies indicates that IL-33 is increased in DKD versus controls. Preclinically, the db/db uninephrectomy model of DKD showed IL-33 protein levels in kidney lysates positively correlated with histological glomerular damage from week 7 to 21. More importantly, blockade of ST2 signalling by using a mAb, prevented the progression of albuminuria. In vivo mechanistic studies using primary human glomerular endothelial cells (GECs) and mesangial cells (MCs) showed that both cell types expressed ST2 and upregulated IL-33 in response to TNFα and IFNγ, commonly upregulated in diabetic kidney microenvironment. Moreover, GECs and to a lesser extent MCs, displayed a significant IL-33 induced proinflammatory cytokine release (e.g. IL-8, IL-6...) mediated by MAP kinase activation and NF-κB translocation. All these effects were inhibited by MEDI3506.

**Conclusions:** Upregulation of IL-33 in diabetic kidney, generates localised chronic kidney inflammation through autocrine signalling in GECs and MCs. This data suggest that targeting IL-33 with MEDI3506 as a promising therapeutic intervention for DKD, currently in Phase II trial.

**Funding:** Commercial Support - AstraZeneca

**PO0644**

**Treatment of Diabetic NOD/SCID Mice with Human “Neo-Islets,”**

**3D Organooids of Mesenchymal Stromal and Pancreatic Islet Cells,**

**Normalizes Blood Glucose Levels: Significance for Clinical Trials**

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**Background:** We reported that allogeneic “Neo-Islets” (NI) are immune protected and permanently correct autoimmune diabetes in NOD mice by omental engraftment and endocrine cell redifferentiation. This new “endocrine pancreas” delivers in vitro hormones physiologically into the hepatic portal vein. Further, treatment of insulin-dependent dogs with allogeneic canine NIs (ongoing FDA-approved Pilot Study) consistently improved glycemic control without the need for antirejection drugs. The current preclinical study was undertaken in anticipation of a Phase 1 Clinical Trial with two objectives: to determine (a) whether human NIs (NIHs) can restore euglycemia, and (b) whether redosing of suboptimally controlled diabetic animals could restore euglycemia in streptozotocin (STZ)-diabetic NOD/SCID mice, as has been previously shown for mouse and dog cell-derived NIs.

**Methods:** Passaged cells that were to be used to treat diabetic NOD/SCID mice were characterized for gene expression profiles by rPCR. For in vivo testing, NOD/SCID mice were made diabetic with STZ, then randomized based on blood glucose levels into groups of 6 each, treated with insulin pellets, and once blood glucose levels were stabilized near normal animals were treated i.p. either with 2×10e5 human cell-derived NIs/kg bw (n=6) or vehicle (n=6), then followed for 8 weeks. Once blood glucose levels were determined to be no longer significantly improved compared to controls without administration of exogenous insulin, mice in each group were again treated with either 2×10e5 NIs/kg bw or vehicle, and followed for an additional 6 weeks. Therapeutic efficacy was assessed by survival, 2× weekly blood glucose monitoring, and glucose tolerance tests administered 57 and 41 days post the 1st and 2nd doses, respectively.

**Results:** Human NI therapy significantly improved glycemic control and survival vs. Vehicle. A 2nd dose given to the initial group normalized blood glucose levels long-term.

**Conclusions:** Despite the limitations of the diabetic NOD/SCID model, these data show that human NIs are curative, and in conjunction with data from the dog study, where allogeneic NI therapy reduces the need for insulin without need for antirejection drugs, have high translational relevance and support the planned conduct of human NI clinical trials.

**Funding:** Commercial Support - SymbioCellTech

**PO0643**

**Single-Cell Analysis of Senescent Epithelia Reveals Targetable Mechanisms Promoting Fibrosis**

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**Background:** Progressive fibrosis and maladaptive organ repair result in significant morbidity and millions of premature deaths annually. Senescent cells accumulate with ageing and after injury and are implicated in organ fibrosis, but the mechanisms by which senescence influences repair are poorly understood. Here, we address the role of senescence in maladaptive repair and identify new anti-fibrotic targets.

**Methods:** We analyse human kidney tissue samples post deobstruction and corresponding murine models to test involvement of senescent cells in maladaptive repair via pharmacological depletion. We use single cell RNA-Seq to examine these cells in more detail. We validate our findings using in-vitro models of senescence and fibroblast activation. Finally we use murine models of injury to test inhibition of in silico targets as anti-fibrotic.

**Results:** We demonstrate for the first time in man that senescence and fibrosis persist in kidneys in the aftermath of a resolved obstructive injury. Using a relevant murine model of injury and repair we show senescent epithelia persist after relief of ureteric obstruction and that depletion of senescent epithelia reduces fibrosis and promotes repair. We next characterise senescent epithelia in murine renal repair using single cell RNA-Seq for the first time. We extend our classification to human kidney and liver disease, identifying conserved pro-fibrotic molecules which we validate in vitro and in human disease. Inhibition of one of these molecules is essential for TGFβ mediated fibroblast activation. Importantly for translation, inhibition of this molecule in vivo significantly reduces kidney fibrosis after injury.

**Conclusions:** Our data shed light on the role of senescent epithelia in renal disease and identify a new anti-fibrotic molecule. Analysis of signaling pathways of senescent epithelia connects the important pathways such as the cell stress response to organ fibrosis, permitting rational design of anti-fibrotic therapies.

**Funding:** Private Foundation Support
Endogenous Interleukin 33 Contributes to the Progression of Diabetic Nephropathy
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Background: Inflammation and fibrosis play a crucial role throughout the course of Diabetic Nephropathy (DN). Interleukin 33 (IL-33) is an early alarmin for inflammatory damage and also shows a relationship with fibrosis in multiple organs. However, it was little discussed in the field of chronic kidney disease. Here, we try to explore the role of IL-33 in DN.

Methods: 21 patients with DN diagnosed by renal biopsy were retrospectively included; 6 kidney tissue adjacent to carcinoma were collected as normal kidney samples; 5 healthy controls were included. IL-33 levels in serum and urine were measured and IL-33 of renal tissue were evaluated. db/db mice were used as an animal model to evaluate the IL-33 expression in the early stage of DN. IL-33KO mice with STZ injection combined with unilateral nephrectomy were used as an animal model to explore the regulatory effect of endogenous IL-33.

Results: In human samples, DN group showed a significantly higher level of IL-33 than that in the normal kidney tissue (P<0.0001). The level was positively related to the degree of kidney fibrosis (Spearman’s r=0.072, P=0.007). The expression pattern of IL-33 in DN is different from that in normal condition. Further immunohistochemistry staining suggested that IL-33 is expressed mainly by fibroblasts in the kidney of DN. And IL-33 level in DN group was also showed a higher level in urine (P=0.017). In animal models, IL-33 increased in the kidney of db/db group compared with dbm (P=0.011) during the early stage of DN, which was before the decrease of renal function and appearance of pathological lesions. In the IL-33 knockout mouse of STZ-induced diabetes combined with unilateral nephrectomy, the 32 weeks old IL-33KO group had lower blood glucose levels (P<0.001), reduced urinary albumin/creatinine level than (P=0.021) wild type group. In the renal tissue also showed severe tubulointerstitial fibrosis, inflammatory cell infiltration, and glomerular mesangial expansion in wild type group, all of which were significantly attenuated in the IL-33KO group.

Conclusions: IL-33 is involved throughout the course of DN. The increase of IL-33 may play as an early warning factor in the disease and may participate in aggravating diabetic nephropathy by mediating the process of fibrosis. Based on our findings, IL-33 may have the potential to be a target for further mechanism research and treatment of DN.

Beneficial Effects of Tumor Necrosis Factor α Blockade in a Mouse Model of Diabetic Nephropathy
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Background: Recent studies indicate that immune activation may play a role in pathogenesis of diabetic nephropathy (DN). We have previously described a mouse model exhibiting characteristics of human DN including high-grade albuminuria and glomerulosclerosis. In this model, glomerular immune and inflammatory pathways, including networks associated with tumor necrosis factor (TNF)-α signaling are upregulated. In this study, we examine the functional impact of the TNF-α pathway in DN.

Methods: In a model of DN, TNF-α was significantly reduced after etanercept blockade in the treatment of DN. Moreover, we noted that IL-33 increased in the kidney of db/db mouse compared with dbm (P=0.011), which was before the decrease of renal function and appearance of pathological lesions. In the IL-33 knockout mouse of STZ-induced diabetes combined with unilateral nephrectomy, the 32 weeks old IL-33KO group had lower blood glucose levels (P<0.001), reduced urinary albumin/creatinine level than (P=0.021) wild type group. In the renal tissue also showed severe tubulointerstitial fibrosis, inflammatory cell infiltration, and glomerular mesangial expansion in wild type group, all of which were significantly attenuated in the IL-33KO group.

Conclusions: IL-33 is involved throughout the course of DN. The increase of IL-33 may play as an early warning factor in the disease and may participate in aggravating diabetic nephropathy by mediating the process of fibrosis. Based on our findings, IL-33 may have the potential to be a target for further mechanism research and treatment of DN.

A Novel Anti-Inflammatory Renoprotective Effect of GLP-1 Receptor Agonists in Type 1 Diabetes: Shifting Macrophage Polarization
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Background: Diabetic kidney disease (DKD) is a serious complication of diabetes. Increased evidence has shown a vital role of the immune system in the pathogenesis of DKD. Macrophages infiltrate the glomeruli and can polarize into an M1 pro-inflammatory phenotype versus an M2 anti-inflammatory one. Moreover, studies from our group and others highlighted the role of NADPH oxides induced ROS production in the progression of DKD. Several hypoglycemic agents were investigated for their renoprotective effects. Among these agents, Liraglutide, a GLP-1 receptor agonist. However, its role in modulating DKD development still needs to be elucidated, especially in type 1 diabetes mellitus (T1DM). In this study, we aim to investigate the reno-protective effect of Liraglutide in regulating the NADPH oxides family of enzymes which are well known for their role in ROS production. More importantly we will assess the involvement of Liraglutide with macrophage polarization, a major component of the immune system.

Methods: C57BL/6J adult male mice were allocated into three groups: control, STZ-induced T1DM, STZ-induced T1DM group treated with liraglutide (0.3mg/kg, SC twice daily) for a duration of 13 weeks. Functional, histopathological, biochemical and molecular studies were performed on kidney tissues for all groups.

Results: Liraglutide treatment improves kidney injury as assessed by blood urea nitrogen (BUN), creatinine, histological features, and more importantly proteinuria. The renoprotective effect of liraglutide was further validated via histopathological findings; increased M2 macrophage infiltration, reduced collagen deposition and extracellular matrix expansion. Of interest, these results were associated with decreased mRNA expression of M1 inflammatory markers and increased mRNA expression of the M2 anti-inflammatory ones. In addition, liraglutide treatment alleviated ROS overproduction by reducing NADPH oxidase enzymatic activity paralleled by a decrease in DUOX-1 and DUOX-2 isoforms protein expression and mRNA levels.

Conclusions: To the best of our knowledge, this is the first study to show a renoprotective effect of liraglutide in DKD through shifting macrophage polarization towards the M2 anti-inflammatory phenotype possibly via inhibiting NADPH oxides induced ROS production.

Funding: Private Foundation Support, Clinical Revenue Support

Interferon-γ Signaling and the Progression of Early Diabetic Kidney Disease
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Background: Inflammation plays an important role in pathogenesis of diabetic kidney disease (DKD). However, the pathways by which circulating pro-inflammatory factors activate intrarenal signaling and mediate DKD progression remain poorly defined. Using multicellular data integration we aimed to identify links between circulating factors in early DKD and activation of kidney signaling pathways and DKD progression.

Methods: Transcriptomic data from kidney biopsies of Pima Indians with type 2 diabetes and early DKD (n=74) were used to identify differentially expressed genes (DEGs) and their upstream regulators (URs) associated with end-stage kidney disease (ESKD). Plasma proteomics (n=162) was used to identify ESKD-associated circulating proteins. URs were selected if their regulation in plasma was consistent with the prediction based on transcriptomic analysis. Activation scores were computed based on the downstream signaling cascade at the transcriptomic level and then associated with structural lesions and health outcomes in DKD patients. The findings were validated in podyocyte-specific JAK2 transgenic Ins2aKO mice (Pod-Jak2TG-Akita) which develop progressive DKD and in human kidney organoid cultures.

Results: Five URs of ESKD-associated DEGs in both glomeruli (Glm) and tubulointerstitium (TI) were identified, with interferon gamma (IFNG) exhibiting the most significant association. IFNG receptor expression was detected in multiple kidney cell types by single cell RNAseq analysis. Higher IFNG pathway kidney activation scores in Glom and TI were associated with increased risk of ESKD and faster GFR decline over time. Increased expression of the IFNG pathway reduced kidney IFNG score and ameliorated albuminuria and mesangial expansion in Pod-Jak2TG-Akita mice. IFNG significantly increased IFNG activation score in human organoids, which was reduced by baricitinib, an inhibitor of JAK1 and JAK2, which are major IFNG signaling mediators.

Conclusions: Increased circulating IFNG levels and IFNG pathway activation in kidney tissue in early DKD may lead to DKD progression. Therefore, the IFNG pathway may be a target for intervention in early DKD.

Funding: NIDDK Support
Nrf2 Activators Induce Inflammamome Attenuation: Possible Role in Diabetic Nephropathy

Background: Kidney diseases remain a worldwide public health problem characterized by sustained inflammation. Inflammamome has recently emerged as crucial regulators of renal inflammation. In particular, the NLRP3 inflammasome is involved in the activation of caspase-1 and the maturation of IL-1β and IL-18, which have been strongly associated with diabetic nephropathy. DJ-1 is a redox-sensitive chaperone with reported antioxidant and anti-inflammatory properties in the kidney, in part due to the regulation of transcription factor Nrf2, which regulates the expression of several antioxidant genes. The 20 amino acid (aa) peptide ND-13, is a new experimental treatment that consists of 13 highly conserved aa from the DJ-1 sequence.

Methods: In this study, we determined NLRP3 inflammasome activation in peripheral blood mononuclear cells (PBMCs) of diabetic nephropathy patients and the capacity of Nrf2 inducers to attenuate inflammasome activation. Mouse bone marrow macrophages were treated with Bardoxolone (1µM), an Nrf2 inducer, and ND-13 (1µM) for 24 hours.

Results: The IL-1β concentration is the medium increased by the stimulation of the NLRP3 inflammasome by LPS/ATP, and decreased in macrophages pre-treated with Bardoxolone (65.0±26.0% vs. 4.0±0.5%) but not in macrophages pre-treated with ND-13. Concentration-response curve demonstrates the capacity of Bardoxolone to inhibit NLRP3 inflammasome activation by LPS/ATP. Additionally, in presence of H2O2 (100mM), ND-13 significantly decreased IL-1β release after NLRP3 activation (8.8±4.2% vs. 9.4±0.05%), suggesting the capacity of the ND-13 peptide to reduce NLRP3 inflammasome activity under pathological conditions. PBMCs isolated from the blood of controls patients, patients with diabetes, and patients with diabetes and renal disease were cultured in vitro and stimulated with LPS/ATP. Compared to controls and diabetic individuals, patients with diabetic nephropathy presented a trend to increase IL-1β release.

Conclusions: All these data point out that inflammasome pre-activation could have a role in the pathogenesis of diabetic nephropathy, that Nrf2 pathway stimulation is a promising approach to decrease immune cells inflammasome pre-activation, and that ND-13 could be a new approach to protect the renal damage associated to inflammasome overactivation in renal diseases.

Funding: Government Support - Non-U.S.

Renal Type 1 Pericytes in the Development of Diabetic Kidney Disease
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Background: Pericytes are described as regulators and keepers of the vascular system. They can recognize and respond to inflammatory stimuli, through secretory and paracrine mechanisms. Other than their role in vascular remodeling, these cells trigger DKD-associated injury and inflammation. We showed that pericytes from DKD context had increase LAP-1 expression, IL-6, and the macrophage M1/M2 ratio of db-nko+S17092 were significantly less IL-6 compared to db macrophages (2±1 vs. 7±1 µg/ml, P<0.05). The absence of salt sensitivity in db with db BM was associated with less IL-6 levels and lower M1/M2 macrophage ratio in the kidney.

Conclusions: Thus, blocking the ACE N-domain and the consequent AcSDKP accumulation in immune cells, pericytes from DKD context, may be a potential target in M2 phenotype resulting in less renal inflammation and no salt sensitivity in diabetes.

Funding: Other NIH Support - NHLBI
PO0654

Follistatin, an Activin A Antagonist in an Accelerated Mouse Model of Diabetic Kidney Disease
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Background: We previously demonstrated that circulating activin A, an inflammatory mediator implicated in cellular senescence-induced adipose tissue dysfunction and profibrotic kidney injury, is increased in human diabetic kidney disease (DKD) and directly correlates with kidney dysfunction. We hypothesized that follistatin, an activin A antagonist, could negate the injurious effects of activin A in DKD.

Methods: An accelerated type 2 diabetes (db/db; 10-week-old) mouse model was generated by implantation of osmotic minipumps loaded with angiotensin (Ang)-II (1000 ng/kg/min, n=14). Mice were randomized to intraperitoneal follistatin (5ug/g) or vehicle at days 15 and 18 post-pump with euthanasia at day 28. Kidney injury markers included: proteinuria, kidney injury marker (KIM)-1, tumor necrosis factor soluble receptor 1 (TNFRs1), collagen 1 and histological changes were measured. Kidney gene expression of activin A and macrophage chemotactrant protein-1 (MCP-1) were measured by qPCR.

Results: Im plantation of AngII (dbAngII) pumps induced proteinuria, mesangial matrix expansion, glomerular sclerosis, and increased fibrosis in db/db mice compared to saline-pump controls (dbSaline; Figure 1A-D). Collagen I, TNFrsR1, MCP-1, KIM-1, and activin A gene expression was increased in dbAngII mice (Figure 1E). Follistatin therapy reduced activin A gene expression and other kidney markers in addition to morphology. Conclusions: Follistatin attenuated diabetic kidney injury, reduced activated A expression and decreased macrophage chemot actants. Activin A may be a novel therapeutic target for halting DKD progression.

Funding: NIDDK Support, Other NIH Support - Diacomp

PO0655

The Functional Role of Neat1 in Diabetic Kidney Disease
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Background: Long non-coding RNA Nuclear Paraspeckle Assembly Transcript 1 (Neat1) serves as a key structural component of paraspeckle assembly, which has been implicated in a variety of biological processes. Increased Neat1 expression is associated with inflammatory responses and the pathogenesis of acute kidney injury. Yet, it remains unknown whether Neat1 also regulates inflammatory pathways in chronic kidney disease (CKD), especially in diabetic kidney disease (DKD).

Methods: Streptozotocin (STZ)-induced DKD was established in C57BL mice with a low-dose injection protocol for 5 consecutive days. Neat1 gene was specifically knocked down in the kidney by shRNA gene silencing via ultrasonic-mediated microbubble gene transfer. After 10 weeks, all mice were sacrificed for analysis of kidney function, morphology, and expression of inflammatory and fibrotic markers.

Results: Neat1 expression was induced in STZ-induced diabetic kidneys. Overexpression of IL-6 and CCL-2 in diabetic mice was attenuated by Neat1 knockdown in which kidney function was preserved with less kidney tubular injury compared to diabetic control mice. Expression of fibrotic markers, such as fibronectin and collagen-I was decreased in diabetic mice with Neat1 knockdown. Conclusions: Neat1 plays a pathogenetic role in DKD and its knock-down could alleviate diabetic kidney injury. Funding: Research Grants Council of Hong Kong (Collaborative Research Fund, grant no. C7018-16G), and Hong Kong Society of Nephrology/HK Kidney Foundation Research Grant 2019.

PO0656

Cell Surface GRP78 Regulates TGF-β1-Mediated Profibrotic Responses via TSP-1 in Diabetic Kidney Disease
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Background: Diabetic kidney disease (DKD) is the leading cause of kidney failure in North America, characterized by glomerular accumulation of extracellular matrix (ECM) proteins. High glucose (HG) induction of glomerular mesangial cell (MC) profibrotic responses plays a central role in its pathogenesis. We recently showed that the endoplasmic reticulum resident GRP78 translocates to the cell surface in response to HG, where it mediates Akt activation and downstream profibrotic responses in MC. Transforming growth factor β1 (TGFβ1) is known to be increased in DKD and by HG in MC. Here we determined whether GRP78 regulates the expression of TSP-1 and thereby TGFβ1 activation in HG.

Methods: Primary rat and mouse MC were treated with 30mM HG. TSP-1 upregulation and deposition into the ECM and TGFβ1 activation were assessed using standard molecular biology techniques.

Conclusions: Data support an important role for CSGRP78 in regulating HG-induced TSP-1 transcriptional induction via PI3K/Akt signaling. Functionally, this enables TGFβ1 activation in response to HG, with consequent increase in ECM proteins. Means of inhibiting CSGRP78 signaling represent a novel target for preventing the DKD-associated fibrosis. TGFβ1 is a central mediator of DKD, but its inhibition is not feasible due to adverse effects. Thus, indirect methods of attenuation are of current interest.

Funding: Government Support - Non-U.S.

PO0657

Histone Acetyltransferase p300 Inhibition Attenuates Kidney Fibrosis Under Diabetic Conditions
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Background: Diabetic nephropathy, the major cause of chronic kidney disease, is associated with progressive renal fibrosis. Transforming growth factor (TGF)-β1 plays important roles in extracellular matrix accumulation in diabetic nephropathy. Recently, acetyltransferase p300 has been shown to mediate intracellular TGF-β1 activity through facilitating Smad function. Therefore, in this study, the effect of p300 inhibition on kidney fibrosis under diabetic conditions was investigated to assess the therapeutic potential of p300 modulation.

Methods: Primary tubular epithelial cells (TECs) from C57BL/6 mice were treated with TGF-β1 with or without histone acetyltransferase p300 siRNA transfection of A485, a selective inhibitor for p300. For in vivo experiments, kidney samples were obtained from streptozotocin induced diabetic mice were administrated with A485 (1mg/kg) oral gavage for 6 weeks.

Results: In vitro, TGF-β1 (5ng/ml) treatment significantly upregulated p300, PAI-1, connective tissue growth factor (CTGF), fibronectin, and type I collagen mRNA and protein expressions in TECs. These increases were attenuated significantly when TECs were transfected with p300 siRNA. Similar findings were found when the cells were treated with p300 specific inhibitor A485 (100nm). In vivo, the mRNA and protein expression of p300, PAI-1, connective tissue growth factor (CTGF), fibronectin, and type I collagen were significantly increased in kidney samples from DM mice compared to non-diabetic control mice. Oral A485 administration abrogated these increases significantly. In addition, the increased blood urea nitrogen and albuminuria levels were significantly attenuated with oral A485 treatment in the diabetic mice. Immunohistochemistry and Birundo staining also revealed that fibronectin expression was significantly higher and tubulointerstitial fibrosis was significantly worse in diabetic mice kidneys compared with control mice. These changes were ameliorated by A485 treatment.

Conclusions: These findings suggest that inhibition of histone acetyltransferase p300 could improve diabetic-induced tubular fibrosis and may be a potential therapeutic strategy for diabetic nephropathy.
PO0658
Recombinant Slit2 Attenuates Renal Fibrosis in a Mouse Model of Diabetic Nephropathy
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Background: We recently described Akita+/- Ren-/- mice as a model that replicates many features of human diabetic nephropathy (DN), including hyperglycemia, hypertension, albuminuria, reduced glomerular filtration rate, glomerulosclerosis and interstitial fibrosis. Previously, we showed that recombinant N terminal Slit2 (Slit2) inhibited renal fibrosis in mouse models of postischemic renal fibrosis and obstructive ureteral obstruction. To date, however, the anti-fibrotic effects of Slit2 have not been tested in a model of DN. Here we examine the effects of Slit2 therapy in the Akita+/- Ren-/- mouse.

Methods: At 6 weeks of age, Akita+/- Ren-/- and Akita-/- Ren-/- mice were randomized to receive three weekly intraperitoneal injections of Slit2 (2 μg) or saline, and followed for a further 20 weeks.

Results: When compared with saline-treated Akita+/- Ren-/- mice, Slit2-treated Akita+/- Ren-/- mice demonstrated improved survival (66.67% vs. 50%) and decreased systolic blood pressure (142±6 mmHg vs 167±8.5 mmHg). Structurally, Slit2-treated Akita+/- Ren-/- mice displayed decreased glomerulosclerosis (glomerular picrosirius red score: 0.22±0.02 vs. 0.28±0.02) and interstitial fibrosis (picrosirius red staining: 0.08±0.01 vs. 0.10±0.01, a-smooth muscle actin (αSMA) staining: 0.02±0.00 vs. 0.05±0.01, and vimentin staining: 0.11±0.01 vs. 0.15±0.01). Slit2 treatment attenuated the nuclear translocation of the pro-fibrotic factor YAP and TAZ (28.55±0.01 vs. 0.15±0.01, a-smooth muscle actin (αSMA) staining: 0.02±0.02 vs. 0.28±0.02, a-smooth muscle actin (αSMA) staining: 0.02±0.00 vs. 0.05±0.01).

PO0660
Role of GRP56 in Glomerular Endothelial Cell Injury in Diabetic Kidney Disease
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Background: GEC injury is a key pathogenic event in early Diabetic kidney disease (DKD). However, the mechanisms of GEC injury in DKD remain unclear and the treatments by targeting specifically GEC injury are lacking.

Methods: By taking advantage of transgenic mice expressing enhanced yellow fluorescent protein (EYFP) under the endothelial-specific Flk1 promoter, we were able to sort GECs from both control and diabetic mice for RNA sequencing. We identified G-protein coupled receptor-56 (GRP56) as a highly upregulated gene in diabetic GECs. Then, we confirmed the role of GRP56 in GEC injury in DKD by both in vitro and in vivo studies.

Results: We searched the recent single-cell RNA-seq data and confirmed that GRP56 expresses predominantly in GECs in the glomeruli. We found that both mRNA and protein expression of GRP56 increased in human DKD and correlated negatively with eGFR, suggesting an important role of GRP56 in human DKD. In cultured GECs, GRP56 expression was upregulated by high glucose and advanced glycation endproducts (AGE). Collagen III, a major ligand of GRP56, was able to suppress eNOS phosphorylation and expression through activation of GRP56. We demonstrated that GRP56 reduced eNOS phosphorylation likely through G12/13-mediated RhoA pathway and inhibited eNOS expression via Gi-mediated inhibition of cAMP/PAK/CLA pathway in cultured GECs.

Conclusions: Taken together, these findings suggest a critical role of GRP56 and its underlined mechanism in regulation of GEC injury in early DKD.

Funding: NIDDK Support, Veterans Affairs Support

PO0661
Transcriptional Profiling of Renal Endothelial Compartments During Progression of Murine Diabetic Nephropathy
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Background: Kidney endothelial cell (EC) injury and capillary rarefaction are key pathogenic events in diabetic nephropathy (DN). The molecular mechanisms and spatial and temporal patterns of EC responses in DN remain elusive. We hypothesized that single-cell RNA sequencing (scRNAseq) would reveal transcriptional changes in specific kidney EC populations during murine DN progression.

Methods: Kidney EC (n=5,464) collected from 6-, 11-, and 20-week-old B6Tg ob/ob mice and lean littermates were analyzed by scRNASeq using SmartSeq2. By a combination of established markers, immunefluorescence, and in situ hybridization, we ascribed anatomical identity to EC clusters assigned by Papadaz, assessed their individual transcriptional changes during disease progression, and performed Ingenuity Pathway Analysis.

Results: We identified EC clusters corresponding to afferent and efferent arterioles, glomerular and peritubular capillaries (PTC), ascending and descending vasa recta, veins and lymphatics. BTPR ob/ob mice developed progressive PTC rarefaction. Analysis of differentially expressed genes (DEGs) and pathway activity allocated most DN-associated changes to PTC and glomerular EC. Intriguingly, several consistent DEGs showed differential up- and downregulation depending on cell type and disease stage (Fig. 1). E.g., whereas glomerular EC showed DN stage-dependent activation of IGFI signaling and inflammation, IGFI signaling and cell cycle progression were inhibited in PTC-EC.

Conclusions: Using high-resolution scRNASeq, our study provides insight into the complexity and diversity of responses in different EC compartments during progression of DN, which may help pinpoint new therapeutic targets.

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**PO0660 Funding:** Role of GRP56 in Glomerular Endothelial Cell Injury in Diabetic Kidney Disease: Basic - I
PO0662

Transcriptomic Alterations of Angiogenesis Activity in Human Mesenchymal Stromal/Stem Cells in Diabetic Kidney Disease

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Background: Therapeutic interventions that optimize angiogenic activities may reduce rates of end-stage kidney failure and extremity amputations in individuals with diabetic kidney disease (DKD). Autologous mesenchymal stromal cells (MSCs) infusion is a promising novel treatment, but DKD-related factors, including hyperglycemia and uremia, might alter MSC angiogenic repair capacity.

Methods: To explore MSC angiogenic dysregulation in DKD, we characterized the transcriptome of adipose tissue-derived MSC obtained from DKD subjects (DKD-MSC) compared to age-matched controls without diabetes or kidney impairment. Next-generation RNA sequencing (RNA-seq) was performed to identify in MSCs differentially expressed (DE; adjusted p<0.05, |log2 fold change| >1) mRNA and miRNA involved in angiogenesis (GeneCards). DE miRNAs were further inspected to identify targets involving interactions with angiogenesis genes (miRWalk and Ingenuity pathway in angiogenesis (GeneCards)). DE miRNAs were aimed to target 18 unique DE mRNA targets associated with angiogenesis. Among these miRNAs resulted in pro- and anti-angiogenic regulators including miR-17-5p, let-7d-5p, miR-125a-5p and miR-30c-5p.

Conclusions: MSC from individuals with DKD may have limited angiogenic potential and reparative capacity, warranting caution in autologous MSC transplantation in DKD.

Funding: NIDDK Support, Private Foundation Support

PO0663

Contribution of Endothelial ADAM17 in a Pre-Diabetic Mouse Model

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Background: ADAM17 activates inflammatory and fibrotic processes through the shedding of various molecules such as TNF-α or TGF-β. In physiological situations, ADAM17 is expressed mainly in the distal tubular cell while, in renal damage, its expression increases throughout the kidney including the endothelium. Galectin 3 (Gal3) is a lectin that is postulated as a biomarker of kidney damage. Its overexpression in diabetic nephropathy could be a compensatory mechanism for damage induced by reactive oxygen species (ROS). To characterize, for the first time, an experimental mouse model fed with high-fat diet (HFD) with deletion of ADAM17 in endothelial cells and to describe the expression of kidney Gal3.

Methods: After 25 weeks of HFD, glyceremia, glucose tolerance, body weight, albuminuria, glomerular microscopy (PAS staining) and Gal3 (immunohistochemistry) were analyzed in 15 wildtype (WT) mice and 15 endothelial ADAM17-KO mice.

Results: HFD mice had higher glucose levels, glucose intolerance, and higher body weight compared to standard diet (SD) mice. Moreover, HFD increased albumin/creatinine ratio in WT mice compared to ADAM17-KO mice. At the glomerular level, WT mice with HFD had bigger glomerular size and mesangial matrix expansion. In contrast, the deletion of ADAM17 prevented the increase in glomerular size and decreased the mesangial area and index. Gal3 increased its expression in ADAM17-KO mice on both SD and HFD mice (see table).

Conclusions: The deletion of ADAM17 in endothelium prevents the appearance of glomerular hyperthrophy, expansion of the mesangial matrix, albuminuria and increases the expression of Galactin-3 in the renal cortex. The increase in the expression of Gal3-3 could be a compensatory mechanism for the lack of activation of the EGFR/TNF pathway in the endothelium ADAM17-KO model.

Funding: Clinical Revenue Support
Identification of Cell-Specific Transcriptomic Changes and Cross-Talk in Diabetic Mice with Podocyte-Specific Induction of KLF6 Using Single Nuclei RNA Sequencing

Background: Krippel-Like Factor 6 (KLF6), a zinc finger transcription factor, is a key regulator of cytochrome c oxidase assembly in the podocytes. We previously reported that podocyte-specific loss of KLF6 exacerbates diabetic kidney disease (DKD). However, the role of podocyte-specific induction of human KLF6 in DKD remains unexplored.

Methods: A combination of unilateral nephrectomy and streptozotocin (UNx-STZ) was utilized to induce DKD in mice. Using the “Tie-1” system, mice with podocyte-specific induction of human KLF6 (KLF6(PODTA)) were generated by crossing NPHS2-rtTA mice with trans-8KLF6 mice and fed with doxycycline-containing diet. UNx-STZ-NPHS2-rtTA and SHAM UNx-veh mice served as diabetic and non-diabetic controls, respectively. Single nuclei (sn)RNA-seq libraries were prepared from kidney cortex using the 10X Chromium System. Raw sequencing data was aligned to mouse pre-rnRNA reference genome using Cell Ranger. Quality control, dimensionality reduction and clustering were performed using the R-package, Seurat.

Results: 23 clusters were generated using unsupervised clustering analysis. Enrichment and pathway analyses showed a downregulation of injury-related pathways such as inflammatory and interleukin signaling in the UNx-STZ-treated KLF6(PODTA) group across the podocyte, endothelial cell, mesangial cell, and proximal tubular clusters, compared to the UNx-STZ-treated NPHS2-rtTA group. Conversely, metabolic pathways such as oxidative phosphorylation and fatty acid metabolism were upregulated. A cross-reference of the differentially expressed genes (DEGs) in the podocyte cluster of the UNx-STZ-treated KLF6(PODTA) group with a KLF6 ChIP-seq data set revealed the presence of putative KLF6 binding sites in the regulatory regions of several DEGs. A unique proximal tubule (PT) cluster with distinctive gene expression signature was identified in the KLF6(PODTA) group, suggesting an intercellular communication between podocytes and the PT cells in the KLF6(PODTA) group that mediates the progression of DKD.

Conclusions: SEqRNA-seq demonstrates potential mechanisms by which podocyte-specific induction of KLF6 attenuates the progression of DKD.

Funding: NIDDK Support
**PO0669**

**The Role of Cytoskeleton-Associated Protein 4 in the Glomerulus and Diabetic Kidney Disease**

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**Background:** Cytoskeleton-associated protein 4 (CKAP4) was first discovered in the cytoskeleton (CKD) where it links the cytoskeleton to the endoplasmic reticulum (ER). It can also be located in the cell membrane and function as a receptor. CKAP4 has been shown to be involved in various physiological events besides its function in the ER, including cell proliferation and migration. In this study, we explored the function of CKAP4 in the glomerulus and its role in chronic kidney disease (CKD).

**Methods:** Glomerular CKAP4 gene expression was evaluated in different CKD cohorts. The expression of CKAP4 in human glomeruli was investigated via immunofluorescence and western blot. The CKAP4 homolog in zebra fish was knocked down in vitro and proteinuria and morphology were analyzed. shRNA was used to KD CKAP4 in human podocyte and mesangial cells in vitro. Changes in protein expression was analyzed via mass spectrometry and western blot, and the morphology of the actin cytoskeleton via immunofluorescence.

**Results:** While the human CKD cohort revealed that CKAP4 was down regulated in glomeruli from patients with diabetic kidney disease (DKD), but not in the other diseases investigated. CKAP4 was expressed by all glomerular cells, but not in lesser extent in endothelial cells. KD of the zebra fish CKAP4 homolog rendered the fish proteinuric and led to podocyte effacement. KD of CKAP4 in human podocytes and mesangial cells led to loss of actin stress fibers in both cell types. In addition, the expression of several growth factor receptors was affected, with a prominent loss of PDGF receptors in the mesangial cells reducing their proliferative response to PDGF.

**Conclusions:** Our results from the in vitro and in vivo experiments show that reduced expression of CKAP4 leads to glomerular dysfunction and changes in the actin cytoskeleton. In podocytes, this is known to cause foot process effacement which we observed. Less is known about how dysregulation of the actin cytoskeleton affects the mesangial cells, but we found that mesangial cells with CKAP4 KD down regulated their actin cytoskeleton to the extent of PDGF receptors, and had a reduced proliferative capacity. Patients with DKD have a low expression of CKAP4, we suggest that CKAP4 regulation can be a part of the disease development and progression.

**Funding:** Private Foundation Support, Government Support - Non-U.S.-

**PO0670**

**Store-Operated Ca2+ Entry Contributed to High Glucose-Induced Podocyte Injury**

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**Background:** Diabetic Nephropathy is one of the major microvascular complications of diabetes and the most common cause of end stage renal disease. Hyperglycemia is a known pathogenic stimulus for onset and progression of diabetic nephropathy. Podocyte injury is one of early features of the disease. However, the mechanism of the diabetes-induced podocyte injury is not fully understood. Store operated Ca2+ entry (SOCE) has multiple functions in both excitable and non-excitable cells. This ubiquitous Ca2+ signaling includes two key components, Orai1 (a plasma membrane protein mediating SOCE) and STIM1 (an ER membrane protein sensing Ca2+ level in the ER lumen). Previous studies have demonstrated that alterations in SOCE are involved in cell dysfunction in many cell types. However, whether and how SOCE contributes to podocyte injury in diabetes remains unknown. The current study was aimed to determine that enhanced SOCE in human diabetic kidney disease (HG)-induced podocyte injury by upregulating calpain activity.

**Methods:** All experiments were performed using cultured human podocytes. Western blot was conducted to estimate Orai1, STIM1 and nephrin protein abundance. Calpain activity was analyzed via substrate cleavage. Confocal microscopy was used to visualize podocyte actin arrangement. Calpain activity was determined by calpain activity assay kits.

**Results:** HG (25mM) treatment significantly increased Orai1, but not STIM1 protein abundance for time periods ranging from 2 to 12 hours. The HG-induced Orai1 response was dose dependent. Ca2+ imaging experiment showed that HG treatment for 12 hours increased SOCE. In addition, HG treatment significantly decreased nephrin (a podocyte marker) protein abundance and resulted in cytoskeleton rearrangement by formation of cortical F-actin. Both HG responses were significantly blunted by BTP2 (4 µM), an SOCE inhibitor. Furthermore, we found that activation of SOCE by stimulation with 1mM Ca2+ increased calpain activity which was abolished by BTP2. Intradialysis, BTP2 blunted the increased calpain activity induced by HG treatment. Moreover, calpeptin (a calpain inhibitor) attenuated the HG-induced reduction of nephrin protein abundance.

**Conclusions:** The present study suggests that enhanced SOCE contributes to HG-induced podocyte injury by increasing calpain activity.

**Funding:** NIDDK Support

**PO0671**

**HDAC6 Inhibition with CAY10603 Alleviates Renal Fibrosis Against Pyroptosis in Tubular Injury**

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**Background:** The essential role of tubular damage has been highlighted during the progression of chronic kidney diseases (CKD), included diabetic nephropathy (DN), but the treatment options are still limited.

**Methods:** We interrogated the connectivity Map (CMap) with tubular transcriptomic profiles of biopsy-proven DN to identify a drug to reverse the regulated genes in tubulointerstitial component of DN. The effects of potential drug were validated in vitro STZ-induced early and late stage diabetic CD1-1 male mice, as well as in non-diabetic mice with adenine-induced lupus-induced nephropathy (LN) and diabetic kidney injury (DKI).

**Results:** CAY10603, a specific inhibitor of histone deacetylase 6 (HDAC6), was identified as a drug to reverse the signature in both early- and late-stage DN. In patients with DN and mice with DKD, renal tubular expression of HDAC6 was significantly upregulated. In vivo, 5mg/kg dosage of CAY10603 significantly ameliorated tubular injury and tubulointerstitial fibrosis, reduced tubulointerstitial α-SMA and collagen I expression, and infiltration of F4/80+ macrophages in both early and late stage of diabetic kidney disease. In addition, CAY10603 also conferred renoprotection in non-diabetic mice including adenine-induced CKD and LPS-induced septic kidney injury. Mechanically, in vitro HK-2 cells, HDAC6 inhibition with CAY10603 regulated NLRP3 activation and membrane repair upstream and downstream of GSDMD.

**Conclusions:** Collectively, CAY10603 exhibited therapeutic potential against pyroptosis in tubular injury of CKD.

**Funding:** Government Support - Non-U.S.-

**PO0672**

**FRMD3/Protein 4.1O Increases Hippo Signaling in a Glucose-Dependent Manner**

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**Background:** FRMD3 is as a candidate gene for diabetic nephropathy and encodes for protein 4.1O. Different splice variants 207, 204, 201 are expressed in the kidney cortex. Previous data show that protein 4.1O links the actin cytoskeleton to the ER and can potentially affect the cytoskeleton. In podocytes, this is known to cause foot process effacement which we observed. Less is known about how dysregulation of the actin cytoskeleton affects the mesangial cells, but we found that mesangial cells with KD of protein 4.1O down regulated their actin cytoskeleton, to the extent of PDGF receptors, and had a reduced proliferative capacity. Patients with DKD have a low expression of protein 4.1O. We suggest that protein 4.1O regulation can be a part of the disease development and progression.

**Methods:** Human kidney biopsy samples from healthy and diabetic patients were stained for protein 4.1O with immunohistochemistry. HEK293T cells were stimulated with low (5mmol/l) or high (25 mmol/l) glucose and an osmotic control (mannitol). RNA was isolated and PCR performed. HEK293T cells expressed protein 4.1O 207, 204, 201 or the control vector. Cells were stimulated with low, high glucose or mannitol. After cell lysis, western blot was performed for phospho-YAP 397 and actin. Co-immunoprecipitation was performed under high, low and osmotic control conditions.

**Results:** Protein 4.1O expression is detected in healthy human glomeruli. In diabetic patients with CKD stage 3b to 5 and high proteinuria protein 4.1O expression is increased in podocytes. High glucose leads to enhanced transcription of FRMD3. Under high glucose condition, protein 4.1O 207 and 201 significantly increase YAP phosphorylation. However, protein 4.1O 204 (lacking a c-terminal domain) does not increase YAP phosphorylation under high glucose condition. Functionally, protein 4.1O 207 and 201 interaction is increased under high glucose conditions.

**Conclusions:** Expression of protein 4.1O is increased in human diabetic kidney disease and under high glucose conditions. Hippo Signaling is activated under high glucose conditions if protein 4.1O 207 and 201, but not 204, is expressed. The lacking cytoskeleton domain in protein 4.1O 201 may play the essential role in controlling Hippo signaling under high glucose conditions. Identifying the underlying pathomechanism for glucose-dependent regulation of the Hippo pathway by different splice variants of protein 4.1O will help to understand its molecular function in diabetic nephropathy.
**PO0673**

**Human Proximal Tubular Cells in a 3D In Vitro Culture as a Model for Exploring Diabetic Lesions**  
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**Background:** We have previously demonstrated the beneficial effect of ADAM17 deletion on human proximal tubular kidney cells (HKC-8) in 3D in vitro spheroids incubated with high glucose resembling the human kidney diabetic environment. Galectin-3 (Gal-3) is a pro-fibrotic protein and modulates the activity of fibroblasts and macrophages in chronically inflamed organs through activation of the TGF-β/Smad3 pathway and it is postulated as regulator of cardiac oxidative stress which can facilitate the development of fibrosis. Also, Dynamin related protein 1 (DRP-1) is a key regulator of the mitochondrial fission and ATP production under stress condition. As ADAM17 has been associated with TGF-β modulation during renal fibrosis, we wanted to evaluate the effect of ADAM17 deletion on Gal-3, Fibronectin and DRP-1 in HKC-8 spheroids incubated under high glucose conditions.

**Methods:** ADAM17 deletion of renal tubular cells was performed using the CRISPR/Cas9 technology. HKC-8 cells grew inside an RGD-functionalized dextran hydrogel to obtain 3D spheroids. 13 days post-seeding, the spheroids were incubated with 35mM of D-glucose (HG), 5mM of D-glucose (LG) or 35mM of mannitol as osmotic control for 72h. Immunofluorescence for Gal-3, pDRP-1 and Fibronectin was performed.

**Results:** HG increased the expression of fibronectin and pDRP-1 and tends to increase Gal-3 in wild-type (WT) spheroids. Interestingly, ADAM17 deletion decreased fibronectin expression in spheroids incubated with HG as compared to WT spheroids. Moreover, ADAM17 deletion abrogates the effect of HG on Gal-3 expression (see table and images, scale bar 50µm). The osmotic control, mannitol, did not affect the expression of the analyzed proteins.

**Conclusions:** ADAM17 blockade protects against fibrosis by decreasing fibronectin and Gal-3 and modulated the mitochondrial dynamic in human kidney tubular spheroids under high glucose conditions.

**PO0674**

**Animal Models Cannot Well Reflect the Transcriptomic Changes of Human Diabetic Nephropathy: A Comparative Study**  
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**Background:** Various mouse models have been developed and widely applied in investigating the pathogenesis of DN. Whether the models share the same underlying molecular changes with human DN is poorly understood. To this end, we performed a systematic analysis of the transcriptomes of the kidney tissues from patients with DN and various mouse models. To our knowledge, this is the largest analysis on this topic.

**Methods:** This study included the bioinformatic analysis and in vivo validation. We comprehensively analyzed the genome-wide mRNA expression of kidney tissues collected from patients with biopsy-proven DN and widely used animal models (n=60). The bioinformatics workflow is shown in figure 1. Then, the expression levels of interested genes were further validated.

**Results:** The transcriptomic profiles of all the animal models had poor correlation with those of patients with DN. However, we observed a much better correlation within species, regardless of the disease stages or modeling methods. In the GSVA analysis, we found the animal models shared similar pathological processes but could not well reflect the real circumstances in human DN. In enrichment analysis, we found the animal models shared the same pathways such as the accumulation of extracellular matrix and MAPK signaling with human DN. However, these models can not well mimic pathways such as cytokine signaling, vitamin D metabolism and SLC transporter disorders.

**Conclusions:** We found mouse models can not well reflect the transcriptomic changes of human DN in many aspects. We also provided a useful dataset to facilitate the translational research of DN.

**Funding:** Government Support - Non-U.S.
PO0675
Integrative Transcriptome Analysis Reveals Involvement of Spermato-genesis-Related Genes in Diabetic Nephropathy
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Background: Cell heterogeneity has impeded the accurate interpretation of the bulk transcriptome data from patients with diabetic nephropathy (DN). We performed an analysis by integrating bulk and single-cell transcriptome datasets to uncover novel mechanism leading to DN, especially in the podocytes.

Methods: Microdissected glomeruli and tubules transcriptome datasets were selected from Gene Expression Omnibus (GEO). Then the consistency between datasets was evaluated. The analysis of bulk dataset and single-nucleus RNA dataset was integrated to reveal the cell type-specific responses to DN. The candidate genes were validated in kidney tissues from DN patients and diabetic mice.

Results: We compared 4 glomerular and 4 tubular datasets and found considerable discrepancies among datasets regarding the differentially expressed genes (DEGs), involved signaling pathways and the hallmark enrichment profiles. Deconvolution of the bulk data revealed that the variations in cell-type proportion contributed greatly to this discrepancy. Integrative analysis uncovered that the dysregulation of spermato-genesis-related genes, including TEKT2 and PIAS2 was involved in development of DN. Importantly, the mRNA level of TEKT2 was negatively correlated with the mRNA levels of nephrin (r=-0.66, p<0.0001) and podocin (r=-0.85, p<0.0001) in human diabetic glomeruli. Immunostaining confirmed that the expression of TEKT2 and PIAS2 were up-regulated in podocytes of DN patients and diabetic mice.

Conclusions: The integrative strategy can help to us efficiently to the publicly available transcriptomics resources. Using this approach, we identified TEKT2 and PIAS2, two spermato-genesis-related genes involved in the pathogenesis of DN.

PO0676
Understanding Genetic Mechanisms of Diabetic Nephropathy at the Single-Cell Level
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Background: Diabetic nephropathy (DN) is a leading cause of end-stage kidney disease worldwide. Susceptibility to DN is inherited but genetic determinants have not been clearly defined. We have previously described a mouse model combining Akita-Rem transgene (AR) that exhibits human DN features including albuminuria, glomerulosclerosis, and genetic predisposition. Susceptible (S) 129 strain AR mice develop overt DN whereas resistant (R) C57BL/6 AR mice are largely free of kidney damage.

Methods: We performed single-cell sequencing of glomerular cells obtained from the wildtype (WT) and AR mice from both S and R strains at 10 weeks of age before overt pathological abnormalities are present in S mice.

Results: A total of 60,082 cells were sequenced from the four conditions. Within the main glomerular cell lineages: podocytes, mesangial and endothelial cells, there were distinct functional clusters corresponding to the S and R strains (see figure). Within the S but not R strain, well-defined cell clusters derived from AR and WT were identifiable within podocytes and mesangial cells, while in other cell types, the impact of strain was much greater than diabetes and renin-angiotensin activation in driving differential gene expression. Gene networks defining the strain differences have potential functional relevance in the development of glomerular diseases. For example, in podocytes, gene networks related to cytoskeleton are activated in the R strain, whereas the S strain shows upregulated oxidative stress responses. A number of candidate genes identified in human DN and other inherited nephropathies are also differentially expressed on the S and R backgrounds.

Conclusions: Single-cell sequencing analysis of glomerular cells from a DN mouse model has identified cell-specific transcriptomic profiles linked to genetic susceptibility and resistance to DN, suggesting causal mechanisms. Substantial overlap with pathways and candidate genes linked to human DN suggest that this model can be useful for understanding genetic pathophysiology of DN in humans.

Funding: Government Support - Non-U.S.

PO0677
Altered Cellular Signaling Pathways Identified by Proteomics and Phosphor-Proteomics in a Rat Model of Diabetic Kidney Disease
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Background: Alterations of cellular signaling are associated with onset and deterioration of various types of disorders, which could be the targets for new drug development and discovery. Currently, post-translational protein modification and glycosylation are identified by comprehensive proteomic analyses. Since diabetic kidney disease (DKD) is the leading cause of chronic end stage renal disease, exploring novel signaling pathways involved in the initiation and progression of DKD may have therapeutic potential. In the present study, we probing renal tissue in a DKD rat model for altered signaling cascades using proteomics and phospho-proteomics analyses.

Methods: The animal model of type 2 diabetes mellitus. Spontaneously Diabetic Torii Fatty (SDT Fatty) rats were uninephrectomized at 9 weeks of age, and then from 10 weeks of age, 0.3% NaCl was added to drinking water to exacerbate DKD progression for additional 5 weeks (Group A) or 10 weeks (Group B). After the treatment period, blood was collected for biological measurements and kidney tissue was obtained for holography and proteomics and phospho-proteomics analyses.

Results: In SDT Fatty rats, the stage of DKD was classified as ‘early’ (Group A) or ‘advanced’ (Group B) by SUN levels and expansion of mesangial matrix and glomerular sclerosis observed by PAS staining. 25 signaling cascades including the PPAR signaling pathway were activated at early stage DKD, and 41 cascades including the proximal tubule bicarborane reclamation cascade were activated at advanced stage DKD, detected by proteomics analysis in the KEGG database (P<0.05). Further, 33 annotation clusters including the ‘serpin family’ as serine protease inhibitors and the ‘s100 family’ as RAGE ligands were newly detected by functional annotation clustering determination (P<0.05). In addition, five cascades including pathways of ‘microRNA in cancer’ indicated by Crk, Hnpmp and Marks at early stage and two cascades including ‘RNA transport’ indicated by Csc3, EdGbp and Eif5c at advanced stage were detected by phospho-proteomics analysis in KEGG database (P<0.05).

Conclusions: These findings demonstrate that several groups of known and new signaling cascades may have important roles for the initiation and/or progression of DKD.

Funding: Government Support - Non-U.S.

PO0678
NETosis Contributes to the Pathogenesis of Diabetic Kidney Disease: A Proposed Mechanistic Pathway
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Background: Diabetic kidney disease (DKD) is one of the most debilitating complications of diabetes. Considerable research has focused on the key role of NADPH oxidases (NOXs) in DKD. Of note, our group has demonstrated the role of mTOR signaling pathway in mediating NOX-derived reactive oxygen species (ROS) production in DKD. Inflammation and an overactive immune response are known to be major risk factors for the development and progression of DKD. Recently, NETosis, a novel neutrophil-specific cell death process, was described to be associated with inflammation and diabetes. However, the effect of NETosis on DKD remains uninvestigated. Interestingly, increasing evidence highlights a pivotal role for the mTORC1 pathway and NOXs in regulating NETosis. Herein, we hypothesize that hyperglycemia activates the mTORC1-NOX signaling pathway, leading to excess neutrophil extracellular traps (NETs) formation and eventual kidney injury.

Methods: Control mice, mice treated with phosphor 12-myristate 13-acetate (PMA) to induce NETosis, and mice models of type 1 and type 2 diabetes treated either with Cl-aminide to inhibit NETosis or with Cl-aminide’s vehicle were used. Functional, histological, and molecular parameters of the kidneys were determined. Human transcriptomics datasets from GEO were further used for validation.

Results: Our data show that increased NETs formation mediates renal dysfunction and histopathological alterations associated with DKD. Of note, treatment with PMA mimicked diabetes-associated renal injury, as assessed by UAE, UACR, BUN and serum
cystatin C, and induced glomerular hypertrophy, glomerulosclerosis, extracellular matrix expansion, and tubulointerstitial damage. Treatment with EMPA restored renal function and decreased induced glomerular podocytopathy and injury. Increased NETs formation in diabetes was paralleled by an increase in NOX-dependent ROS production and mTOR signaling pathway activation. Our findings were further confirmed in transcriptomic analysis of remnant kidneys, and positive correlation between NETs and DKD was observed. Querying protein-protein interaction databases also revealed an association between NETs markers, mTOR signaling proteins, and NOXs.

**Conclusions:** To our knowledge, this study is the first to describe the role of NETosis in T2D, identifying NETosis as one of the final mechanistic drivers of DKD.

**Funding:** Private Foundation Support, Clinical Research Support.

**PO0679**

**Alteration of Autophagy-Related Protein 5 (ATG5) Levels and Atg5-Dependent Degradation of Unnecessary Intracellular Components in Diabetic Nephropathy**

G. G. N. N. Alkhansa, S. A. A. Eid

**Methods:** Levels of autophagy key components ATG5 and LC3B were analyzed in both human model and murine tissues. One hundred and twenty human subjects were divided into four groups: Healthy (control), diabetic without complications, diabetic nephropathy, and diabetic retinopathy. Additionally, we used kidneys from diabetic mice model (WT healthy mice and DM mice). Lysate derived from human peripheral blood mononuclear cells, and murine renal cortex lysates were subjected to western blot analyses of ATG5 and LC3B and immunohistochemical analysis was performed on mice renal tissues.

**Results:** Western blot and immunohistochemical analysis demonstrate that ATG5 protein levels were significantly decreased in DM, DN and DR patients (0.59±0.07; 0.67±0.06; 0.72±0.06 A.U. units, respectively), vs. healthy controls (0.96±0.16 A.U. units), and in DN mice compared to healthy mice (0.65±0.04; 1.15±0.13 A.U. units, respectively). Quantification of staining area (%) of ATG5 mice tissue expression also decreased in DN vs. healthy mice (4.42±1.088%; 10.87±1.011% respectively), LC3B levels and expression correlates with ATG5 results: significant reduction in peripheral blood mononuclear cells diabetic patients (with or without complications) vs. healthy controls (4.42±1.088% vs. 10.87±1.011%), LC3B levels were lower in DN vs. healthy mice (0.60±0.03; 0.68±0.07 A.U. units). Renal LC3B staining quantification revealed significant reduction in DN vs. healthy mice (1.70±0.23%; 8.5±1.17%).

**Conclusions:** We conclude that ATG5, as well as LC3B, are down regulated in diabetic patients with or without complications. This diminution contributes to deficiencies in the autophagy process. Our observations show a novel association between autophagy-related protein 5 (ATG5) and diabetic kidney and retinal diseases, with ATG5 as a candidate protein for diabetic nephropathy and retinopathy.

**PO0680**

**The Emerging Role of the mTORC2/Rictor Signaling Complex in Autophagy Dysregulation-Associated Diabetic Kidney Disease**


**Background:** Podocyte injury has been implicated in the pathogenesis of many renal diseases, including diabetic kidney disease (DKD). Dysregulation of podocyte autophagy has been positively correlated with podocyte loss and progression of proteinuria in patients with diabetes. Yet, the exact mechanisms behind diabetes-induced autophagy dysregulation remain to be elucidated. Various signaling pathways including the mTORC1 complex, involved implicated in autophagy regulation. However, the role of mTORC2 in autophagy and its interaction with key mechanistic pathways involved in DKD, including the ROS-producing enzymes, are still unknown. Herein, we investigated the role of mTORC2, its crosstalk with the NADPH oxidases 4 (NADPH4), the ROS-mediated autophagy, and the possible link to podocyte integrity in animal models of type 1 and type 2 diabetes.

**Methods:** Type1 diabetes was induced in mice by streptozotocin (STZ) injections, and type 2 diabetes was initiated by a ‘western’ diet followed by low-dose STZ injections. Mice were divided into control, diabetic, and diabetic treated with a selective mTORC2 inhibitor (JR-AB2-011). Functional, pathological, and biochemical studies were performed.

**Results:** Diabetes-induced podocyte injury is reflected by alterations of the slit diaphragm, paralleled by podocyte depletion as assessed by decreased WT1 staining and accompanied by autophagy dysregulation. The effect of autophagy was further highlighted in control mice treated with the autophagy inhibitor hydroxychloroquine, that mirrored the effect of diabetes on functional, phenotypic, histological, and molecular changes in the kidney. These observations were concomitant with an observed activation of the mTORC2/Rictor protein expression and increased levels of superoxide generation through Nox4. Of interest, these results were paralleled by activation of the mTORC1/p70S6K pathway. Moreover, specific inhibition of mTORC2 curbed the homeostatic function of the kidneys and restored the histological and phenotypical changes, consistent with regulating the Nox4/mTORC1 signaling axis. More importantly, JR treatment regulated diabetes-induced autophagy protein dysregulation (Bclin, Atg3, and LC3).

**Conclusions:** Our data suggest that targeting mTORC2 signaling could be a potential therapeutic target for DKD.

**Funding:** Private Foundation Support, Clinical Research Support.
expression of ATG5 were 6.83±0.52%, 2.59±0.54% and 6.29±0.74% for the C57, DM and DM+EMPA, respectively (P<0.001 vs. DM for both) and LC3B were 9.60±2.14%, 3.19±0.66% and 7.39±1.74% in the C57, DM mice and DM+EMPA, respectively (P<0.001 between all groups).

Conclusions: 1. EMPA Treatment induces glucosuria and body weight reduction in diabetic mice model. 2. Chronic Hyperglycemia down regulates the expression of LC3 & ATG5, the two main proteins in the autophagy process. 3. Treatment EMPA for 12 weeks reduce the the expression of these proteins in the kidney 4. EMPA can be first line treatment in type II DM patients to slow the progression of DN.

PO0683
Ferroptosis Is Involved in the Process of Diabetic Kidney Disease
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Background: Diabetic kidney disease (DKD) is a major public health problem that threatens human health and causes substantial economic burden. DKD is accompanied by accumulation of ROS and iron in the kidney, a hallmark of ferroptosis. Ferroptosis is a condition that causes cell death by accumulation of lipid reactive oxygen species (ROS), in an iron-dependent mechanism that is different from apoptosis, necroptosis and autophagy. That ferroptosis is involved in DKD has been shown recently, but its role is still unknown.

Methods: We induced diabetic kidney disease in 8-week-old male rats with streptozotocin (STZ) and treated with ferroptosis inhibitor Fer-1 to analyze the degree of renal injury and the related indexes of ferroptosis.

Results: 1. Diabetic renal injury involves ferroptosis. Accumulation of iron was also confirmed by Pannus blue staining and presented morphological changes linked to ferroptosis in DKD group: reduced mitochondrial volume, ruptured mitochondrial membrane and missing mitochondrial cristae. 2. Blocking ferroptosis can alleviate renal injury and the related indexes of ferroptosis.

Conclusions: Ferroptosis is involved in the process of diabetic kidney disease. Markers of renal tubular injury α-1-microglobulin and N-acetyl-β-D-glucosaminidase measured in urine.

PO0684
Effect of Lisinopril and Pioglitazone in a Mouse Model of Diabetic Kidney Disease
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Background: Diabetic nephropathy affects up to one third of all diabetes mellitus patients, and is the major cause of end stage renal disease. The current study evaluated the unipercutomized (UNx) obese and diabetic db/db mouse as a model of diabetic kidney disease (DKD), benchmarking a glycemic control agent (Pioglitazone) and an angiogenesis-converting enzyme inhibitor (Lisinopril) to affect kidney structure and function.

Methods: Female lean control mice (Db+/−, 2 kidneys), sham operated obese mice (db/db, 2 kidneys), and UNx db/db mice (1 kidney) were grouped based on body weight, blood pressure, glucose and albumin/creatinine ratio (UACR). Inclusion criteria were defined as blood glucose >350mg/dl and UACR >250mg/mg. Following grouping, animals were provided a diet admixture of Pioglitazone (169mg/Kg diet) or Lisinopril (0.1mg/mL) in drinking water. Compounds were administered for 8 weeks, during which body weight, food intake, water intake and blood glucose was measured.

Results: Control UNx-db/db animals showed progressive decline in renal function (UACR: 497±62mg/mg at baseline to 1054±159mg/mg at 8weeks), whereas sham operated animals remained near baseline levels (284±40mg/mg). Pioglitazone treated mice had significantly lower UACR than control UNx-db/db after 2 weeks whereas lisinopril treated animals had significantly lower UACR after 4 weeks of treatment, primarily by limiting the progression of UACR increase. Increased mesangial matrix deposition in the glomeruli was the primary lesson observed (high incidence and high severity); tubular and interstitial structural findings were very limited; little to no fibrosis was observed. Pioglitazone and lisinopril both showed a comparable effect in decreasing the severity of mesangial matrix deposition.

Conclusions: Hence, the UNx-db/db animal model of diabetic kidney disease is a powerful model of renal function decline and limited histopathological damage which responds to both anti-diabetic and anti-hypertensive control agents, and is a valuable model for the assessment of new therapeutic targets for DKD.

Funding: Commercial Support - Janssen Research & Development

PO0685
miR299a-5p Is a Novel Mediator of Fibrosis in Diabetic Kidney Disease
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Background: Diabetic kidney disease (DKD) is the leading cause of kidney failure in North America, characterized by glomerular accumulation of extracellular matrix (ECM) proteins. High glucose (HG) induction of glomerular mesangial cell (MC) profibrotic responses, mediated by the cytokines TGFβ1 and activins, plays a central role in its pathogenesis. We recently showed that TGFβ1 upregulation of microRNA (miR)299a-5p promotes its profibrotic responses in MC. Here we studied the role of this miR in DKD.

Methods: Primary mouse MC were treated with HG at 30 mM. miR299a-5p was detected by qPCR or ISH. miR overexpression and inhibition plasmids were transfected by electroporation. TGFβ1 and activin signaling was assessed by activity of their downstream mediator Smad3 using the CAGA reporter. ECM production was assessed using immunoblotting and activity of the COL1α1 promoter luciferase reporter.

Results: HG increased the expression of miR299a-5p in MC. This was also increased in type 1 Akita diabetic kidneys in both glomeruli and tubules, as assessed by ISH. In MC, miR299a-5p overexpression increased Smad3 activation and COL1α1 promoter activity. Conversely, miR299a-5p inhibition attenuated HG-induced COL1α1 promoter and Smad3 activation, as well as upregulation of ECM proteins. miR299a-5p is predicted to target the activin inhibitor follistatin (FST). This was similarly seen with miR299a-5p overexpression. CR-1 or FST treatment individually attenuated the increased COL1α1 promoter and Smad3 activity seen with miR299a-5p overexpression, and together showed an additive inhibitory effect.

Conclusions: These data support an important role for miR299a-5p in regulation of the profibrotic response to HG. Through suppression of two important anti-fibrotic proteins, CR-1 and FST, miR299a-5p potentiates the action of TGFβ1 family profibrotic cytokines. Future studies will determine whether inhibition of this miR can attenuate DKD.

Funding: Government Support - Non-U.S.

PO0686
Abstract Withdrawn

PO0687
The Nonsteroidal Mineralocorticoid Receptor Antagonist Finerenone Improves Left Ventricular Function in Preclinical Diabetic CKD
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Background: The steroidal MR antagonist (MRA) spironolactone and eplerenone reduce mortality in patients with heart failure with reduced ejection fraction (HFrEF) but their use in patients with CKD is not indicated due to the associated risk of hyperkalemia. Finerenone is a non-steroidal MRA which recently reduced the composite kidney and cardiovascular outcomes in the phase III study FIDELIO in CKD patients with T2D. Purpose: To test whether finerenone improves renal and cardiac function in preclinical CKD rat models with T2D.
Methods: 12 weeks old male Zucker Diabetic rats (ZSF1) were used as model of diabetic nephropathy administration of 10 mg/kg po., GFR (transcutaneous FITC-filtrin) and cardiac LV function/hemodynamics (LV catheterization) and LV tissue perfusion (MRI) were assessed in vivo at the age of 24 weeks.

Results: 24-week old ZSF1 rats showed classical signs of CKD, with reduced GFR (1.44±0.11 ml/min/100g body weight for non-diabetic rats vs 1.04±0.16 ml/min/100g body weight for ZSF1, p<0.05) This was associated with LV diastolic dysfunction, illustrated by increased LV end-diastolic pressure (LVEDP; 5.5±0.4 vs 8.0±0.5 mmHg, p<0.05) and LV end-systolic pressure-volume relation (LVEDPVR; 1.0±0.23 vs. 5.6±0.54 mmHg/relative volume unit, p<0.05) without significant changes in LV end-systolic pressure (LVESV; 173±10 vs 197±55 mmHg) or LV end-systolic pressure-volume relation (LVESVPR; 3.7±2.4 vs 28.2±1.09 mmHg/relative volume unit, p<0.05). LV perfusion was reduced (5.2±1.37 vs 4.1±0.21 ml/min/100g tissue, p<0.05). Finerenone treatment did not impact GFR in ZSF1 rats (0.93±0.17 ml/min/100g body weight) but reduced significantly LVEDP (5.72±0.37 vs 4.11±0.34 mmHg, p<0.05) and LV end-systolic pressure-volume relation (LVEDPVR; 2.73±0.33 vs 2.40 mmHg/relative volume unit, p<0.05). Finerenone increased LV tissue perfusion (6.90±0.34 ml/min/g LV tissue).

Conclusions: Finerenone treatment improves CKD related LV diastolic function in diabetic CKD rats, independently from changes in GFR.

Funding: Commercial Support - Bayer Grant

P00688
Development and Benchmarking of a Non-Human Primate Model of Diabetic Kidney Disease
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Background: Diabetic Kidney Disease (DKD) is the largest cause of end stage renal disease and is responsible for 40% of new patients that require dialysis. To test novel therapies for DKD, we sought to develop a non-human primate (NHP) model of DKD that would be more representative of the etiology of human disease than genetically modified mouse models and support human dose prediction and biomarker development.

Methods: Cynomolgus monkeys were fed a high fat/cholesterol diet for 5.1±2.5 (mean±SD) years and became obese (9.1±1.6 kg), hyperglycemic (267±78 mg/dL), hypertensive (systolic blood pressure [SBP] 141±111 mmHg), and maculaobuminuric (urine albumin/creatinine ratio [UACR] 562±346 mg/g). The responsiveness of the monkeys to pharmacological intervention was benchmarked using irbesartan, an angiotensin receptor antagonist (ARB), which is approved by FDA for DKD. Animals were orally dosed daily for 8 weeks with either vehicle (n=8) or irbesartan (n=14, 3 mg/kg).

Results: Exposures 24-hours after dosing were 165±111 ng/mL, similar to exposure in humans with therapeutic doses. Identification of n2-positive cell types and scoring was performed by a trained pathologist. Protein expression was compared with RNA expression in srnRNAseq datasets from human DKD kidneys and kidneys from db/db mice.

Results: All species showed strong staining in the medulla, but significant differences were noted in the cortical n2 expression between humans and other species. Mainly mesangial, endothelial and distal tubular staining was seen in human kidney. Podocytes were negative while proximal tubules stained weakly. Consistent with IHC data, strong n2 expression in human distal tubules and weaker expression in proximal tubules and glomerular cell types is seen in srnRNAseq data. In contrast, mice showed mainly podocyte and endothelial staining. Mesangial cells and mouse proximal tubules were negative for n2, and distal tubules in the cortex stained weakly. Rat kidneys were negative for glomerular n2 expression with medium to strong positivity in the distal tubules of the cortex. Finally, cynomolgus monkeys showed o2 expression in all glomerular cell types; podocytes, endothelial and mesangial, weak staining in proximal and medium to strong staining in distal tubules. Decreased o2 glomerular staining was observed in DKD kidneys compared to normal kidneys.

Conclusions: Differentiation of n2 expression pattern must be considered when extrapolating function from lower to higher species.

Funding: Commercial Support - Jansen

P00691
The HIV Protease Inhibitor Darunavir Protects Against Diabetic Kidney Injury in Mice and Alters Stress Granule-Associated Signaling
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Background: Despite the success of antiretroviral therapy (ART) in improving mortality, persons living with HIV (PLWH) still have increased risk of death and kidney disease and diabetes mellitus are important contributors to this excess mortality. Previously we reported that exposure to the HIV protease inhibitor darunavir (DRV) prevents kidney injury via mechanisms that are independent of HIV protease but by the mechanisms by which DRV protects against renal injury remain unclear. Studies in our lab found that DRV binds to several stress granule (SG) associated proteins, including G3BP1. G3BP1 is a membraneless organelle composed of translationally arrested mRNAs and ribonucleoproteins and have important roles in stress and injury responses.

Methods: Diabetes was induced in 9-week-old NOD-/- C57BL/6 mice by administration of 50 mg/kg of streptozocin (STZ) 14 weeks later, mice were treated with either DRV (100mg/kg) or control by daily oral gavage for 4 weeks. Urinary albumin-to-creatinine ratio (UACR) assay, immunofluorescence (IF) microscopy, western blotting and real-time PCR were performed according to routine protocols in our laboratory. For in vitro studies, human proximal tubular cells (HPTb) at 40-60% confluence were transfected with Accell siRNA for G3BP1 in Accell Delivery Media.

Results: STZ induced severe hyperglycemia and kidney injury in NOD-/- mice, which resulted in marked increase in UACR. DRV treatment markedly reduced UACR, attenuated tubulointerstitial fibrosis as detected by type 1 collagen and fibrinogen, and prevented loss of podocytic synaptopodin and endothelial cell G3BP1 expression in glomeruli as detected by IF. IF studies also demonstrated that G3BP1 and phosphorylation of Stat3,
Src, and Erk were increased in the kidneys of diabetic eNOS-/- mice and these changes were reduced by DRV treatment. To directly test the role of G3BP1 in promoting Stat3. Src, and Erk phosphorylation, we used siRNA to knock down G3BP1 expression in human tubular cells, which reduced phosphorylation of Stat3, Src, and Erk.

**Conclusions:** These data suggest that DRV prevents diabetes-induced kidney injury in mice in part, via interactions with the SG protein G3BP1. Additional studies are needed to further delineate the effects of targeting SG function upon diabetic kidney injury.

**Funding:** NIDDK Support

**PO0692**

**The Role of Intestinal Flora in Cinnamaldehyde Alleviating Early Proteinuria in Diabetic Nephropathy**

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**Background:** Intestinal dysbiosis played a crucial role in chronic inflammation of diabetic nephropathy (DN). Cinnamaldehyde (CIN) is a traditional natural food additive from a Chinese herb, recognized as antioxidant and anti-inflammatory medicine recently. This study was to observe the effects of CIN on renal injury and intestinal flora in DN.

**Methods:** A total of four groups of rats included DN group induced by streptozotocin (70mg/kg), treated with CIN (DNC), control (NC), and NC treated with CIN (NCN). CIN was given daily for 8 weeks. Blood glucose, bodyweight, 24h urinary volume (24HV), protein (24HP), the pathologies changes of kidney, and the protein expression of Megalin, Fibronectin, TGF-β were measured. We also sequenced 16S rDNA of the intestinal flora of the rats.

**Results:** Compared with DNC, DN showed significant improvement with lower 24HV, 24HP, Fibronectin, TGF-β, and increased Megalin. Simpson’s diversity index of the intestinal flora significantly decreased in the DNC group. PCoA (Fig. A) showed different patterns of clustering between the 4 groups (p<0.01). At genera, compared with NC, g__Lactobacillus decreases significantly in DN, but recovered in DNC, and was also confirmed as significant biomarkers by LEfSe (Fig. B). Besides g__Lactobacillus, there were 12 other differentially enriched genera in DNC, such as g__Alloprevotella, and g__Oscillospira. At species, 3 species decreased in DN and recovered in DNC, including s_Bacteroides_maxisilenis, s_Oscillibacter_sp_ER4, and s_Lachnospiraceae_bacterium_A2. They were anti-inflammatory probiotics that produce short-chain fatty acids. The abundance of 6 genera correlated well with 24HP (p<0.05, Fig. C). Tax4Fun (Fig. D) showed significantly different enriched functional categories.

**Conclusions:** Cinnamaldehyde could alleviate renal injury in DN, which was associated with the recovery of the reduced intestinal g__Lactobacillus.

**PO0693**

**Hypercglycemia-Induced Mitochondrial Dysfunction in Kidney and Brain Are Protected by β-Hydroxybutyrate Treatment**

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**Background:** The immediate effects of hyperglycemia on mitochondrial and organ dysfunction are poorly understood. Acute hyperglycemia could reveal key initiating mechanisms of diabetic kidney disease. Acute hyperglycemia exposures as occurs with poorly controlled diabetes. The potential protective benefit of ketone bodies on mitochondrial function across organs during hyperglycemia has also not been well characterized. Here, we evaluated effects of hyperglycemia and β-hydroxybutyrate (BHB) on ATP production in the mouse using a novel in vivo brain imaging approach in combination with MALDI-MSI.

**Methods:** GFAP-gal4 transgenic mice were used to test the effect of BHB on brain luciferin-luciferase bioluminescence using a Xenogen IVIS spectrum live-imaging system. Transgenic dual-glo mice expressed the luciferase in astrocytes under the gfap promoter. MALDI-MSI analysis was used to detect the acute impact of BHB on small molecule metabolites in the kidneys and brains of C57BL/6J mice. For in vivo experiments, mice were fasted, either 2.5 g/kg of BHB, 2 g/kg of glucose, or NaCl vehicle control (control). The timing effect of 20 mM BHB on mitochondria function and glycolysis in HK2 cells, in fresh mice kidney, and in brain tissue using pH and OCR measurements with the Agilent Seahorse instrument.

**Results:** We found reduced levels of ATP in both brain and kidney tissue slices of mice acutely treated with 25 mM glucose with MALDI-MSI. BHB treatments increased ATP levels in the brain and kidney tissues and cells. Acute glucose exposure in HK2 cells reduced OCR and increased ECAR, which was blocked by BHB treatment. However, brain bioluminescence was significantly decreased when mice were injected with 25 mM glucose (4 minutes after luciferin injections), consistent with a loss in ATP production. In contrast BHB injections increased bioluminescence and blocked the loss of signal in the presence of high glucose.

**Conclusions:** These data indicate that acute glucose exposure reduces ATP production in the kidney and brain, and that BHB can reverse this effect. Together, these studies suggest the acute detrimental effects of hyperglycemia on metabolism and mitochondrial dysfunction can be reversed with ketone bodies treatment.

**Funding:** Private Foundation Support

**PO0694**

**Dysfunction of the Renal Tubular Circadian Clock Leads to Enhanced Renal Gluconeogenesis and Exacerbated Hyperglycemia in Diabetic Mice**

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**Background:** The circadian rhythms define all biological process cycling with a periodicity of about 24 hours. They are believed to be an evolutionary adaptation that allows biological functions to anticipate variations of environmental conditions imposed by external rhythm. These rhythms are driven by the circadian clock, a molecular system of interconnecting loops present in virtually each cell of the body. Disturbance of the circadian rhythms or its misalignment with external environment is a risk factor for development of numerous diseases, such as depression, obesity, diabetes or cancers. However, the pathophysiological role of intrinsic renal circadian clocks in the diabetic kidney remains unknown.

**Methods:** To address this question, we used mice with streptozotocin-induced type 1 diabetes, and carrying Bmal1 deletion either in the podocytes (pcko mice) or in whole renal tubular cells (ecko mice).

**Results:** Although diabetic pcko mice did not show any additional alterations compared to diabetic Control mice, diabetic ecko mice showed exacerbated hyperglycemia, increased fractional excretion of glucose, enhanced polyuria and a more severe renal hypertrophy as compared to diabetic Control mice. Interestingly, renal gluconeogenic pathway was enhanced in diabetic ecko mice, as demonstrated by increased protein and mRNA expressions of key enzymes. Moreover, deep sequencing transcriptome and functional analysis of diabetic ecko mice showed alterations in several mechanisms affecting the gluconeogenic pathway.

**Conclusions:** Altogether, our data demonstrate that disturbance of renal tubular circadian clock enhances gluconeogenesis in proximal tubule, leading to the aggravation of the hyperglycemia of diabetic mice. These results highlight importance of circadian behaviour in diabetic patients.

**Funding:** Other NIH Support - Swiss National Science Foundation (SNSF)

**PO0695**

**Disregulation of Thiosulfate Thiotransferase Pathway Contributes to Tubulointerstitial Injury of Diabetic Nephropathy**

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**Background:** Tubulointerstitial injury plays an important role in the progression of diabetic nephropathy (DN), and its severity is closely related to the prognosis of DN. Thiolsulfate thiotransferase (TST) is a key enzyme that mediates protein S-sulfhydration and maintains mitochondrial metabolic homeostasis. This study aimed to investigate the role of TST in tubulointerstitial injury of DN and to explore its potential mechanisms.

**Methods:** Sodium thiocyanate (STC)-treated diabetic mice, adeno-associated virus with TST overexpression transduced diabetic mice, and cell culture model of HK-2 cells transfected by lentivirus with TST overexpression were used for experiments. The protein S-sulfhydration of very-long-chain acyl-CoA dehydrogenase (VLCAD) was checked by Western blotting and mass spectrometry analysis. Tubular mitochondrial fatty acid β oxidation (FAO) was checked by 1C labeling combined with mass spectrometry and Seahorse assay. Epithelial mesenchymal transition (EMT) related molecules of tubular epithelial cells was checked by immunofluorescence staining and Western blotting.

**Results:** Our results showed that the expression of TST was decreased in kidneys of diabetic mice and in high glucose-stimulated HK-2 cells, which was significantly correlated with decreased E-cadherin and increased protein expression of collagen I, fibronectin, and α-SMA. Furthermore, the down-regulation of TST expression led to the FAO dysfunction in kidneys of diabetic mice and in high glucose-stimulated HK-cells. On the contrary, STS treatment or overexpression of TST alleviated albuminuria and tubulointerstitial injury. The expression of collagen I, fibronectin, and α-SMA in TST transduced diabetic mice or HK-2 cells were significantly decreased, while E-cadherin expression was increased. Further analysis showed that pharmacological inhibition of TST significantly impaired the expression of E-cadherin and increased the expression of fibronectin and α-SMA.
Diabetic Kidney Disease: Basic - II

PO0696
CYP450: Protagonists in the Story of Diabetic Kidney Disease

Background: Diabetic kidney disease (DKD) is a grave complication and a major contributor to mortality in patients with diabetes. Cytochrome P450 (CYPs) epoxide genases metabolize arachidonic acid into the vasoactive and renal-active HETEs and EETs. Our group, among others, advanced the discovery implicating CYPs and their metabolites in the pathogenesis of DKD by regulating reactive oxygen species. Of interest, CYPs encoding genes possess different polymorphisms which alter the expression of these key enzymes, affecting the prognosis of patients with DKD. Noteworthy, the CYPs polymorphisms and their correlation with the production of 20-HETE and EETs in DKD remain poorly investigated. In the same spirit, extensive research has highlighted the role of different miRNAs in DKD. To our knowledge, the regulatory effect of miRNAs on the expression of different CYPs in DKD is not yet established. In this study, we aim to elucidate the role of CYPs polymorphism, their metabolites, and miRNAs regulating their expression in the disease onset and progression of DKD.

Methods: Blood and tissues were collected from patients with type 2 diabetes (T2D) with or without clinical manifestation of DKD. Levels of 20-HETE and EETs were assessed in the urine samples of the patients alongside with the renal CYPs enzymatic activities in human kidney biopsies. Besides, miRNA analysis was performed on the plasma collected from these patients to study CYP enzymatic regulation using the TargetScan online tool.

Results: Our data show that the circulating levels of 11,12-EETs were decreased in patients with DKD when compared to T2D patients with no clinical signs of DKD, concomitant with an increase in the 20-HETE levels. Our results show that in patients with DKD, the expression of miRNA was altered ultimately leading to the downregulation of CYP2B6, CYP4A11 and CYP4F8 enzymes. Furthermore, patients with DKD carry CYP polymorph with the minor allele frequency resulting in an alteration in their enzymatic activity and subsequently increasing 20-HETE, decreasing DPA production and concomitant with a positive correlation with the expression of the corresponding CYPs in human kidney biopsies.

Conclusions: This study yields crucial findings about novel genetic and epigenetic pathways involved in DKD and identifies biomarkers related to CYP pathways that could be of diagnostic, prognostic, and therapeutic value.

Funding: Private Foundation Support, Clinical Revenue Support

PO0697
Metabolic Images Using Fluorescence Lifetime Imaging Reveals Metabolic Alteration in Proximal Tubular Epithelial Cells in Type 2 Diabetes
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Background: Although there is a massive metabolic alteration of the kidney in diabetes, it is difficult to detect and measure the single-cell nicotinamide adenine dinucleotide hydrogen (NADH), flavin adenine dinucleotide (FAD) production, and redox potential in particular groups of tubular epithelial cells (PTCs) as the most labile mitochondrial and affected cells under high glucose environments. We investigated this study to evaluate quantitative PTECs-specific metabolic images in the diabetic kidney using fluorescence lifetime imaging (FLIM).

Methods: Kidney sections of 20 week-old db/db and db/m mice were used for FLIM. FLIM images are analyzed using the phasor approach. The FLIM image and phasor plot representing FLIM data in vector space were measured through Leica TCS SP8 SMD and LAS-X software. The NADH, FAD, and ATP levels in diabetic kidneys were measured using LC-MS analysis by Q-trap 5500.

Results: NADH and FAD located at the different subcellular levels in PTECs. The NADH phasor analysis of PTECs revealed a right-shifted trend towards shorter lifetimes from the db/m to the db/db, while there was no significant alteration of FAD between the two groups. It could be indicative of an increase in the NADH-to-FAD ratio that alters metabolic flux. In addition, the levels of NADH in diabetic kidneys were significantly increased than db/m, while the levels of FAD were reduced in diabetic kidneys. Finally, ATP level decreased in the diabetic kidney compared to db/m.

Conclusions: A new method of FLIM in PTECs is a normal approach to characterize and monitor metabolism in diabetic kidneys. Quantitative metabolic imaging using FLIM enables to measure and analyze metabolic alteration with spatial information.

Funding: Veterans Affairs Support

PO0698
Female Protection Against Diabetes-Induced Kidney Injury Is Eliminated in Kidney Tubule-Specific AMPK Gamma-2 Knockout Mice
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Background: Reduction in renal AMPK activity is associated with obesity- and diabetes-induced kidney injury which is ameliorated by AMPK stimulation in male mice. Female mice resist obesity-induced kidney injury; this protection is abolished in kidney tubule specific c1 and c2 KO female mice. We tested if interruption of AMPK activity abolishes renal protection against diabetes in AMPK c2 KO female mice. We also tested if diabetes worsens kidney injury in AMPK c2 KO male mice.

Methods: 3-4 month-old tubule-specific AMPK gamma-2 KO male and female mice (n = 6-9 per group) were employed. To generate diabetic animal model, the mice were placed on high fat diet (HFD) for one month, then they received streptozotocin (STZ) 50mg/kg body weight by IP daily for 5 days. After 1 month STZ injection, urine was collected for analyzing urinary KIM-1 and ACR.

Results: Renal cortical expression of AMPK c2 mRNA as well as protein was reduced in AMPK c2 KO mice. There were no changes in body weight and random blood glucose level between control and AMPK c2 KO male and female mice at the baseline. Body weight gain in control and AMPK c2 KO mice in both genders was increased by HFD compared to normal diet fed groups. Random blood glucose level was increased in HFD and STZ-treated control and AMPK c2 KO mice in both genders. As expected control female mice resisted HFD and STZ-induced kidney injury, whereas urinary KIM-1 excretion and albuminuria were induced in AMPK c2 KO female mice. Urinary KIM-1 excretion and albuminuria were induced by diabetes in control and c2 KO male mice with no statistical difference between two groups.

Conclusions: Renal protection against diabetes is abolished in kidney tubule specific AMPK c2 KO female mice. Therefore, regulation of AMPK, as well as its activity contributes to the protective mechanism against diabetes in female mice, and it could be used for a therapeutic target of diabetes.

PO0699
Mitochondrial Fission and Fusion Dynamics Are Regulated by Multiple Pathways in Renal Proximal Tubule Cells Treated with High Glucose
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Background: In type 2 diabetes, hyperglycemia leads to proximal tubular dysfunction, which is accompanied by altered mitochondrial homeostasis. We previously demonstrated that in renal proximal tubule cells (RPTC) grown in high glucose, as well as male and female db/db mice, mitochondrial dynamics were altered. Phosphorylation of the mitochondrial fission protein Drp1 increased and the mitochondrial fusion protein Mfn1 decreased. Studies have shown that Drp1 is activated by the RhoA/ROCK1 signaling cascade in the presence of high glucose, leading to increased mitochondrial fission. Conversely, Mfn1 can be activated by MEK/ERK signaling. However, these pathways have not been investigated in the proximal tubule. Therefore, we determined the signaling pathways responsible for altered Drp1 phosphorylation and Mfn1 expression in RPTC.

Methods: Primary cultures of RPTC were grown in the presence of high glucose (17mM), mannitol (17mM) or no glucose for 96hr and were co-treated with either Rhoa (CCG-1423), ROCK1 (Y-27632) or MEK 1/2 (GSK 1120212) inhibitors 24 hr prior harvesting. Cells were subjected to GTPassay assays to measure Drp1, Rhoa and Mfn1 activity and maximal mitochondrial respiration was measured using Seahorse XF96e analyzer.

Results: RPTC treated with glucose for 96hr exhibited an increase in Rhoa and pDrp1 at 96 hr. This increase corresponded with an increase in GTP-bound Rhoa and Drp1. Co-treatment with CCP-1423 or Y-27632 prevented the glucose-induced increase in Rhoa and Drp1, respectively. Inhibition of Rhoa and ROCK1 restored maximal mitochondrial respiration. Co-treatment with GSK 1120212 prevented the glucose-induced decrease in Mfn1.

Conclusions: Together, these results demonstrate that treatment of RPTC with glucose increases Rhoa and Drp1 activity and maximal respiration. Pharmacological inhibition of Rhoa and ROCK1 prevented increased activity of Rhoa and Drp1 and restored respiration, indicating that the Rhoa/ROCK1/Drp1 signaling pathway is necessary. In contrast, treatment with GSK-1120212 prevented the increase in mitochondrial fission and respiration in high glucose in RPTC. In contrast, we show that inhibition of the MEK/ERK signaling cascade prevents the decrease in Mfn1 observed in the presence of high glucose. These data indicate that the alteration of mitochondrial dynamics in high glucose in RPTC, is regulated by two independent signaling pathways.

Funding: Veterans Affairs Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author. 250
PO0700
Medications Targeting the Activation of Tubular Fatty Acid Oxidation Enhance the Renoprotective Effects of Roux-en-Y Gastric Bypass Surgery
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Background: Roux-en-Y gastric bypass surgery (RYGB) improves biochemical and histological parameters of diabetic kidney disease (DKD). Targeted adjunct medical therapy may enhance renoprotection following RYGB.

Methods: The effects of RYGB (n=10) and RYGB plus fenofibrate 100mg/kg, metformin 300mg/kg, ramipril 1mg/kg, and rosuvastatin 10mg/kg (RYGB-FMRR; n=9) on metabolic control and histological and ultrastructural indices of renal injury were compared after 8 weeks of treatment in the Zucker Diabetic Sprague Dawley (ZSDS) rat model of DKD. Sham-operated ZSD rats (n=9) and healthy Sprague Dawley rats (n=6) served as controls. Renal cortical transcriptomic (RNA-sequencing) and urinary metabolicomic (1H-NMR spectroscopy) responses were profiled and integrated. Omic correlates of improvements in structural and ultrastructural indices of renal injury were defined using a molecular morphometric approach.

Results: RYGB-FMRR was superior to RYG alone with respect to metabolic control, albuminuria, and histological and ultrastructural indices of glomerular injury. RYGB-FMRR reversed DKD-associated changes in mitochondrial morphology in the proximal tubule to a greater extent than RYGB. Attenuation of transcriptomic pathway activation of pro-fibrotic responses was greater after RYGB-FMRR than RYGB. Transcriptional induction of PPARα-regulated genes, expressed in the proximal tubule, mediated activation of tubular FAO in a rat model of DKD. Sham-operated ZDSD rats (n=9) and healthy Sprague Dawley rats (n=6) served as controls. Attenuation of transcriptomic pathway correlates of improvements in structural and ultrastructural indices of renal injury were defined using a molecular morphometric approach.

Conclusions: The renoprotective effects of RYGB can be enhanced through the deployment of medications targeting PPARα-mediated activation of tubular FAO responses.

Funding: Government Support - Non-U.S.

PO0701
Polyamine Catabolism Is Enhanced in Streptozotocin-Treated Mice and in Cultured Proximal Tubule Cells Exposed to High Glucose Levels: A Possible Role in Tubular Injury in Diabetic Nephropathy
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Background: Polyamines are indispensable to cell growth and survival. Their catabolism mediates cellular injury by induction of DNA and mitochondrial damage, activation of the endoplasmic reticulum stress/unfolded protein response (ERS/UPR) pathway, and innate immunity. Studies indicate that mitochondrial dysfunction, innate immune response and ERS/UPR are important mediators of tubular injury in diabetic nephropathy. We posit that polyamine catabolism is activated in diabetes mellitus and plays an important role in tubular injury.

Methods: The expression of polyamine catabolic enzymes was examined in streptozotocin (STZ)-induced diabetes in mice and HK-2 proximal tubule cells exposed to high glucose (30mM) levels. The expression levels of SAT1 and SMOX were determined by northern and western blot analyses. Nephron segment expression and localization of SAT1 and SMOX in STZ-treated mice was determined by immunohistochemistry and immunofluorescence microscopy.

Results: Expression of SAT1 and SMOX were elevated in the kidneys of STZ-treated mice compared to their vehicle-treated counterparts. Immunohistochemical and immunofluorescence microscopic studies revealed that SAT1 and SMOX expression are increased in the proximal tubule, distal convoluted tubule and collecting duct epithelial cells. In vitro studies using HK-2 cells demonstrated that the expression of both SAT1 and SMOX increases in response to 30mM glucose exposure to 30mM glucose. Based on these studies and their known injurious effects, we propose that SAT1 and SMOX play a significant role in the mediation of renal injury in diabetes mellitus likely through the induction of oxidative injury, mitochondrial damage, elevated ERS/UPR and activation of innate immune responses.

Funding: Veterans Affairs Support, Public Foundation Support

PO0702
An Interplay of Glucose, IL-1β, and PDGF-B Trigger cPLA2 Activation, Prostaglandin Secretion, and Proliferation in Human Mesangial Cells
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Background: Diabetic kidney disease (DKD) is commonly thought to be originated from diabetic hyperglycemia. DKD development is driven by early glomerular hemodynamic changes and characterized by progressive expansion of the mesangium. A connection between these findings is yet to be elucidated. We speculate that, after hyperglycemia priming, autocrine inflammatory and proliferative stimuli alter mesangial lipid metabolism activating the secretion of vasodilator hormones. Subsequently, this affects glomerular functions. Phospholipase cPLA2 was identified as the central enzyme of the metabolic cascade.

Methods: Human mesangial cells were stimulated with Glucose (30 mM), IL-1β (1 nM), PDGF-B (25 ng/ml). Their synergic counter activation was investigated by western blots and qPCR. Lipidomics was used to analyze lipid variations. Cox-2 induction and prostaglandin secretion were measured via western blot and ELISA. Activation of cPLA2, upstream of Cox-2, was studied using western blot, qPCR, activity assays. ELISA, migration, and proliferation assays were used to evaluate cPLA2 inhibition. Data were validated using the Nephroseq database.

Results: After stimulation with Glucose, NLRP3 and pro-IL-1β were upregulated. IL-1β stimulation increased PDGF-B mRNA levels. In turn, PDGF-B stimulation increased NLRP3 and pro-IL-1β protein levels. Lipidomics analysis after IL-1β and PDGF-B stimulations showed an increase of sphingosine 1 phosphate, a known activator of Cox-2. Cox-2 was induced and prostaglandins secreted accordingly. cPLA2 releases arachidonic acid, the substrate of Cox-2. cPLA2 was upregulated at gene and protein level and activated by phosphorylation. Upregulation of the pathway was confirmed in silico in DKD patients. Since cPLA2 reaction is the rate-limiting step in prostaglandin synthesis, its inhibition with AACCOCF3 was studied. Inhibition of cPLA2 reduced migration, proliferation, secretion of prostaglandins in cells treated with IL-1β and PDGF-B.

Conclusions: External stimuli (hyperglycemia from the diabetic environment) and glomerular inflammatory and proliferative stimuli prime DKD early events. The upregulation of cPLA2 was found to be critical in these events. cPLA2 inhibition reduced mesangial secretion of prostaglandins, proliferation, and migration, making it a potential target for therapy.

Funding: Private Foundation Support, Government Support - Non-U.S.
Suppression of Endoplasmic Reticulum-Associated Degradation Process by Intraglomerular Cross-Talk Between Podocytes and Mesangial Cells Causes Podocyte Injury in Diabetic Kidney Disease

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Background: Mesangial lesion and podocyte injury are essential for the progression of diabetic kidney disease (DKD). Although crosstalk between mesangial cells (MCs) and podocytes is recently suggested by single nucleas RNA-sequence analyses, its molecular mechanisms and role on disease progression still remain elusive.

Methods: We evaluated the ER stress responses of podocytes stimulated with mesangial cell culture supernatant (MC-sup) under high-glucose condition (HG) in vitro. Then, the effects of an ER-associated protein degradation (ERAD) inhibitor eeyarestatin I (EeI) in cultured podocytes and glomeruli of db/db (type 2 diabetes) mice were also examined by western blotting, immunofluorescence and TUNEL staining. Furthermore, we evaluated the effects of ERAD inhibitor on nephrin phosphorylation of podocytes by flowcytometric analysis and western blotting.

Results: In vitro experiments revealed the suppression of the ER-associated degradation (ERAD) pathway and induction of apoptosis in podocytes that were stimulated with the supernatant of mesangial cells cultured in high-glucose conditions. In diabetic mice, ERAD inhibition resulted in exacerbated albuminuria, increased apoptosis in podocytes, and reduced nephrin expression associated with the downregulation of ERAD-related biomolecules. Flowcytometry analysis of podocytes isolated from db/db (a transcription factor known to be expressed in macrophages and podocytes)-GFP knock-in mice revealed that ERAD inhibition resulted in decreased nephrin phosphorylation. Decreased nephrin phosphorylation was also confirmed in in vivo experiments.

Conclusions: ERAD has been reported to be important for avoiding ER stress and cellular damages. Our findings suggest that an intraglomerular crosstalk between MCs and podocytes inhibit physiological ERAD processes and result in decreased phosphorylation of nephrin in podocytes, which thereby lead to podocyte injury under diabetic conditions. Therapeutic intervention of the ERAD pathway through the crosstalk between these cells is potentially a novel strategy for DKD.

PO0705
DPP4 Inhibitors Ameliorate Endoplasmic Reticulum Stress in Diabetic Kidney Disease Through Upregulation of SIRT1

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Background: Endoplasmic Reticulum (ER) stress plays vital roles in the progression of diabetic kidney disease (DKD), and Dipeptidyl peptidase-4 (DPP4) inhibitors are widely used antihyperglycemic agents. Further exerting renal beneficial effects in DKD, but the precise mechanism underlying the disruption of these processes remains unclear. We examined whether SIRT1/STAT3 pathway regulated ER stress in the progression of DKD.

Methods: In vivo, male DBA/2J mice were injected by streptozotocin to form diabetic mice models, then sitaglipin (Sita) was gavaged to inhibit DPP4. We collected and analyzed kidney samples, urine and serum. In vitro, human HK-2 cells were exposed to human serum albumin (HSA), then regulated DPP4, SIRT1 with inhibitors, siRNAs and mutant miRNAs. Outcome measures included ER stress, expression of GRP78, CHOP, phosphorylation of PERK (p-PERK), cleaved caspase3 (c-CASP3), whereas Sita effectively attenuated these disorders. Meanwhile, Inhibited DPP4 increased the expression of SIRT1 both in vivo and in vitro, which has a protective effect on diabetic ER homeostasis, whereas decreased SIRT1 accentuated ER stress. Moreover, partly through elevated SIRT1, Sita regulated mitochondrial STAT3 and phosphorylation of STAT3 at ser727, which is required for STAT3 to import into mitochondria. Our work found that the inhibition of DPP4 ameliorated ER stress in DKD partly through SIRT1/STAT3 signaling pathway.

Conclusions: The results suggested a novel mechanism links the DPP4 enzyme to ER stress during tubular injury in DKD and highlight that SIRT1/STAT3 pathway may become a potential target for managing DKD.

Funding: Government Support - Non-U.S.

PO0706
Wnt5a-Ca2+ Non-Canonical Pathway Mediates Mitochondrial Dysfunction in the Progression of Diabetic Nephropathy via Mitochondrial Calcium Uniporoter

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Background: Mitochondrial abnormalities play crucial roles in diabetic tubular injury progression. Abnormal expression of Wnt5a has been detected in many metabolic diseases. However, the association of Wnt5a and mitochondrial dysfunction in diabetic nephropathy (DN) progression remains unknown.

Methods: Diabetic DBA/2J mice induced by streptozotocin were assigned to amlopidine (5mg/kg/d) and losartan (10mg/kg/d) for eight weeks. The expression of Wnt5a, mitochondrial dynamics associated proteins (Dpn1 and Mfn2), mitochondrial calcium uniporoter (MCU) were examined through Western blot and immunohistochemistry in kidney of STZ-induced diabetic and high glucose stimulated HK-2 cells. In vitro, Wnt5a overexpression induced the Ca2+ influx and aggravated mitochondrial fusion-fission disorder. After amlopidine treatment, this Wnt5a-Ca2+ pathway was restored, mitochondrial dynamics and morphological changes were recovered. Additionally, increase of MCU was also observed in the mitochondrial of tubular cells in DN, suggesting a possible link between Wnt5a-Ca2+ pathway and mitochondrial dysfunction.

Conclusions: Our study presented that Wnt5a-Ca2+ signaling pathway might be involved in mitochondrial dysfunction in the progression of DN, and MCU was possibly recognized as the important link during the regulation.

PO0707
The Potential Roles of NAD(P)H-Quinone Oxidoreductase 1 in the Development of Diabetic Nephropathy and Actin Polymerization

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Background: Diabetic nephropathy (DN) is a major complication of diabetes mellitus. NAD(P)H-quinone oxidoreductase 1 (NQO1) is an antioxidant enzyme that has been involved in the progression of several kidney injuries. However, the roles of NQO1 in DN are still unclear. We investigated the effects of NQO1 deficiency in streptozotocin (STZ)-induced DN mice.

Methods: Wild-type (WT) and NQO1 KO male mice on C57BL/6J genetic background were used. For the diabetic nephropathy model, STZ was dissolved in citrate buffer (0.1 M; pH 4.5) and prepared immediately before use. Aga-matched 8-week-old WT and NKO male mice were administered STZ (50 mg/kg body weight, intraperitoneal injection) after 4 h fasting, for five consecutive days. ACR were measured. Renal histology and molecular evaluation were done.

Conclusions: NQO1 is upregulated in the glomerulus and podocytes under hyperglycemic conditions. NQO1 knockout (NKO) mice showed more severe changes in blood glucose and body weight than WT mice after STZ treatment. Furthermore, STZ-mediated pathological parameters including glomerular injury, blood urea nitrogen levels, and foot process width were more severe in NKO mice than WT mice. Importantly, urine albumin-to-creatinine ratio (ACR) was higher in healthy, non-treated NKO mice than WT mice. ACR response to STZ or LPS was dramatically increased in the urine of NKO mice compared to vehicle controls, while it maintained a normal range following treatment of WT mice. More importantly, we found that NQO1 can stimulate actin polymerization in an in vitro biochemical assay without directly the accumulation on F-actin.

Conclusions: NQO1 has an important role against the development of DN pathogenesis and is a novel contributor in actin reorganization via stimulating actin polymerization.

PO0708
The Renoprotective Effects of the Soluble Guanylate Cyclase (sGC) Activator Runcaciguat Are Associated with Distinct Changes in Renal Gene Expression Profiles

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Background: Chronic kidney disease (CKD) progression is associated with impaired NO-sGC-cGMP-signaling, low cGMP production and increased oxidative stress. Oxidative stress modifies the native sGC to oxidized, heme-free apo-sGC which cannot be activated by NO anymore. Runcaciguat is a novel potent and selective sGC activator that binds and activates heme-free sGC independently of NO and, therefore, restores cGMP signaling. In the ZSF-1 rat CKD-model, runcaciguat displays renoprotective effects (pronounced decrease in proteinuria and lowering of HbA1c and triglycerides). To understand the underlying mode of action of the renoprotective and metabolic effects of runcaciguat, we investigated the renal gene expression profile.

Methods: The renal expression profile of genes affected by 3mg/kg/day runcaciguat in obese ZSF1 rats treated between 16 to 27 weeks of age was analyzed with a microarray (all known rat genes) and compared to gene expression changes of lean relative to obese ZSF1 rats aged 14 to 26 weeks to show deregulation over the course of the disease progression.

Results: With the selected deregulation thresholds, 45 and 82 genes were expressed at higher and lower levels after runcaciguat treatment, respectively. Thresholds were set at 1.6-fold differences between vehicle and treatment group with p<0.05. Most of the genes decreased by runcaciguat also showed decrease expression in lean vs. obese ZSF1 rat kidney, suggesting that runcaciguat converts the kidney expression profile of obese ZSF1 rats partly to the lean pattern. Of these genes, three encode proteins involved in fibrosis (e.g. collagen), inflammation (e.g. cytokines), and degeneration/regeneration (e.g. cell cycle progression genes, lipocalin 2) which is supported by the Ingenuity pathway analysis (IPA).
PO0709
Exogenous Hydrogen Sulfide Protects Kidneys of Diabetic Mice from Oxidative Injuries
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Background: Exogenous hydrogen sulfide (H2S) protects kidneys from diabetic injuries in animal models. In order to explore its mechanisms, we determined the effects of H2S donor on renal reactive oxygen species (ROS) related enzymes in diabetic mice.

Methods: Male C57Bl/6J mice (8 weeks old) were intraperitoneally injected with STZ at 50mg/kg/day for 6 days. GYY4137 (20 mg/kg/day in 6 ml of drinking water, GYY+DM group, n=5) or vehicle (6 ml of drinking water, DM group, n=4) were fed the mice 2 weeks after the initial STZ injection when blood glucose remained high relative to background mice. The 2 groups of diabetic mice were injected with long-acting insulin (10U/kg) weekly at week 3.

Results: GYY4137 ameliorated albuminuria and hyperglycemia at weeks 8 & 10. Serum insulin and creatinine were similar in the diabetic mice. Renal morphological structures (HE, Masson, PAS) were improved by GYY4137 at week 10 when the mice were sacrificed. Renal nitrotyrosine (protein oxidative injury marker) was decreased along with the decrease of laminin (early fibrosis marker) in GYY+DM mice relative to DM mice (western blotting). NOX2, NOX4 were lower but NOS1, HO2, PON1, PON2 were higher in GYY+DM than those in DM group. NOX2, NOX3, NOX1, HO1, SOD1-3 and COX1 were similar between groups. The levels of mRNA were not in agreement with the changes in proteins with all enzymes but HO2.

Conclusions: Our findings suggest that exogenous H2S may decrease ROS production and increase ROS cleavage in kidney via the affected enzymes, thus improve the renal oxidative damage in diabetic nephropathy.

PO0710
Downregulation of Ehhadh and Tubular Dysfunction in Diabetic Nephropathy
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Background: As a peroxisomal protein, enoyl-CoA hydratase and 3-hydroxyacyl-CoA dehydrogenase (Ehhadh) catalyzes the second and third committed steps in the peroxisomal beta-oxidation pathway. Ehhadh also interacts with catalase and peroxisomal biogenesis factor 5 (PEX5), which decomposes hydrogen peroxide and regulates peroxisomal biogenesis, respectively. Previously we detected reduced tubular Ehhadh expression in human and mouse diabetic nephropathy. This study aims to investigate the potential impact of Ehhadh on peroxisomal/mitochondria functional change in response to high glucose in vitro.

Methods: Primary cultured proximal tubular epithelial cells (PTC) were exposed to high glucose, mannitol or control medium. Ehhadh subcellular localization and peroxisome quantitation (area per cell) were analyzed by confocal microscopy. Ehhadh, catalase, PEX5, ACOX1, Hsd17b4, scp2, ACA1, andHO2 were measured by qPCR. Peroxidase activity and oxidative stress were also analyzed.

Results: Ehhadh transcription and protein were significantly downregulated in PTC under high glucose conditions. Ehhadh was localized mostly to peroxisomes and rarely in mitochondria. Key enzymes for beta-oxidation in peroxisomes (ACOX1, Hsd17b4, scp2 and ACA1) and mitochondrial (HO2) were not changed under high glucose conditions. Catalase transcription and peroxisome activity were reduced in high glucose vs control. PEX5 was also reduced, but peroxisome quantitation was increased 39.6% under high glucose conditions. Oxidative stress was also increased 7.6% in high glucose vs control.

Conclusions: Ehhadh downregulation is associated with reduced peroxidase activity, increased peroxisomal biogenesis and oxidative stress in PTC. Whether altering Ehhadh can impact such dysfunction awaits further study.

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PO0711
Oxidative Stress on the Kidney and Heart of Rats with Diabetic Nephropathy Treated with Esclun
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Background: Diabetes mellitus is a chronic disease which progresses with complications such as diabetic nephropathy (DN) and diabetic cardiomyopathy. Esclun (ESC) and its metabolite, esculcin, are coumarin derivatives, belonging to the Oleaceae family, found also in some more known species in the southern hemisphere, such as the pink lemon (Citrus limon). ESC has been related to antioxidant (AO), anti-inflammatory and anti-apoptotic actions. The aim of the present study was to verify the role of oxidative stress (OS) on the kidney and the heart of rats with DN, and the ESC effect on them.

Methods: We used adult male Wistar rats (N=20). Ethics Committee # 3511260318. Normal rats (CTR) or with blood glucose>200mg/dl. diabetic (DM, treated with streptozotocin 60 mg/kg, IV, single dose), received ESC (50 mg/kg, via gavage, for 8 weeks). After this period, we collected blood, 24-hr urine, the kidney and heart of these animals. The organs were homogenized for TBARS (OS marker) and Western blotting of OS and apoptosis markers.

Results: Renal function assessed by urea and creatinine was reduced in DM x CTR. Proteinuria and TBARS increased in plasma and urine in DM rats, with a reduction in DM+ESC group (p<0.05). In DM heart, there were no alterations in TBARS; glutathione, a pro-oxidant, was elevated. In the heart, Nrf-2, responsible for the transcription of several AO, was elevated in the DM, both in its cytoplasmic form and in its active, phosphorylated form. Catalase, an enzymatic AO, and caspase-3 were elevated in DM (p< 0.05).

Conclusions: ESC protected the diabetic kidneys reducing proteinuria and OS. Unlike the kidney, the hearts of DM did not present OS, although glutathione and apoptosis were not significantly changed. Nrf-2 and catalase, suggests that at this early stage of DN, they are still able to protect the cardiocvascular tissue against OS. We believe that the monitoring of this disease evolution can better clarify the role of Redox balance/ imbalance in the heart of diabetic rats. This would be very useful in the approach of prevention and treatment of cardiomyopathy, including the possible use of esculin, with its important antioxidant, anti-inflammatory and anti-apoptotic effects, as an adjuvant therapy.

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PO0712
Targeting Nox with Pan-Nox Inhibitor in Aging Diabetic Kidney
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Background: Aging process is a risk factor for altered glucose metabolism and insulin resistance. Moreover, diabetes with serious complications has been steadily increasing in older patients. Chronic inflammation and increased oxidative stress are commonly shared features of aging and diabetes mellitus. Therefore, we investigated the effect of pan-nox inhibitor on aging diabetic mice.

Methods: Diabetes was induced by intraperitoneal injection of streptozotocin at a 50mg/kg/day for 5 days in 52-week-old week C57BL/6J mice. An orally active pan-nox inhibitor from Aptabio was administered by oral gavage at a dose of 60mg/kg/day for 12 weeks in aging mice and diabetes induced aging mice. We used adult male Wistar rats (N=20), Ethics Committee # 3511260318. Normal rats (CTR) or with blood glucose>200mg/dl, diabetic (DM, treated with streptozotocin 60 mg/kg, IV, single dose), received ESC (50 mg/kg, via gavage, for 8 weeks). After this period, we collected blood, 24-hr urine, the kidney and heart of these animals. The organs were homogenized for TBARS (OS marker) and Western blotting of OS and apoptosis markers.

Results: NOX inhibition significantly improved insulin resistance in both aging and diabetic aging mice. Additionally, fasting glucose and HBA1c level were significantly improved with Nox inhibition in diabetic aging group. Interestingly, oxidative stress measured by 8-isoprostane was significantly increased in both aging and diabetic mice. Pan-nox inhibitor significantly reduced plasma 8-isoprostane level in aging group, and urinary 8-isoprostane level in diabetic group. In diabetic aging condition, there was trend to decrease in urinary albumin and nephrin excretion with nox inhibition. Simply aging did not significantly altered PAI-1 and collagen IV expressions in the kidney compared to diabetic condition. However, nox 1 and 4 expressions was as well as increased in aging mice and. It is important to note, however, that the increase in AO proteins such as Nrf2 and catalase, suggests that at this early stage of DN, they are still able to protect the cardiocvascular tissue against OS. We believe that the monitoring of this disease evolution can better clarify the role of Redox balance/ imbalance in the heart of diabetic rats. This would be very useful in the approach of prevention and treatment of cardiomyopathy, including the possible use of esculin, with its important antioxidant, anti-inflammatory and anti-apoptotic effects, as an adjuvant therapy.

Funding: Government Support - Non-U.S.
NOX5 Promotes Diabetic Kidney Disease by Modulating Redox-Sensitive Pathways
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Background: Enhanced level of reactive oxygen species (ROS) in diabetes is considered a major contributor in aggravating renal injury. We aimed to examine the role of pro-oxidant enzyme NOX5 and associated redox-sensitive pathways in diabetic kidney disease (DKD).

Methods: We examined the expression of NOX5 and associated redox-sensitive factors including NOX4, thioredoxin-interacting protein (TXNIP), a transcription factor, EGR1 (early growth response 1) and a protein kinase, PKC-α as well as ROS production in human kidney biopsies and in human renal cell lines as well as in human kidney organoids. We also assessed the effect of NOX5 expression independent of NOX4 in Nox5 transgenic mice in the presence or absence of diabetes.

Results: NOX5 was expressed in human and rat renal organoids in association with upregulation of ROS-sensitive factors including EGR1, PKC-α and TXNIP. We also observed upregulation of human NOX5 and TXNIP in renal organoids exposed to high glucose. Silencing of NOX5 attenuated high glucose induced gene expression of markers of fibrosis and inflammation as well as downregulation of EGR1, PKC-α and TXNIP. Our data also suggest that Nox5 is upstream of Nox4 and that Nox5 inhibition also downregulates Nox4, but not vice versa. In vivo, overexpression of Nox5 independent of NOX4 pathways demonstrated an increase in albuminuria, renal fibrosis and inflammation in association with upregulation of EGR1, PKC-α, TXNIP and enhanced ROS production in comparison to diabetic mice not expressing Nox5.

Conclusions: These findings suggest that NOX5 plays a key pathogenic role in renal inflammation and fibrosis, thereby providing impetus for the development of NOX5 specific inhibitor to combat DKD.

PO0714
Hyperpolarized MRI Detection of Dapagliflozin Effect on Gluconeogenesis in Live Animals: Proof of Principle
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Background: SGLT2 inhibitors including dapagliflozin (dapa) ameliorate hyperglycemia by inducing glucosuria but also induce gluconeogenesis (GNG), thus blunting efficacy. The lack of insight into the relative contributions of kidney and liver to GNG in different states is due in large part to limitations in the technology to separately assess liver and kidney GNG in live animals. Our study exploits a powerful technology, Hyperpolarized Magnetic Resonance Imaging (HP-MRI), which can detect metabolic conversions non-invasively in specific organs in animals and humans, in real-time, in vivo. Notably, the chemicals based on stable isotopes of carbon (13-C) have been used for multiple diagnostic uses in humans, for example in monitoring metabolism in cancers.

Methods: Metabolic features of healthy WT (male, age ~12 weeks) rats were studied in vivo using hyperpolarized (HP) 13C magnetic resonance imaging (MRI) is based on ~50,000-fold nuclear magnetic resonance (NMR) signal enhancements of 13C-labeled substrates. We used a dissolution dynamic nuclear polarization (DNP) to account for potential metabolic effects of injection of pyruvate, we also performed [1-13C]pyruvate tolerance tests (PTT).

Results: We successfully detected the conversion of [1-13C]pyruvate to [1-13C]lacate and [1-13C]alanine in the liver and kidneys of rats. We found that Intravenously injected HP[1-13C]pyruvate was rapidly metabolized to [1-13C]lacate and [1-13C]alanine in the liver and kidneys of rats. The PTT data show that there is a clear trend toward an increase in blood glucose following [1-13C]pyruvate injection. Dapa increased glycosuria, as expected. Furthermore, an effect of dapa was on the conversion of [1-13C]pyruvate to [1-13C]lacate and [1-13C]alanine in the kidney but not the liver. This effect, however, was variable and appeared to be influenced by baseline GNG in the rats.

Conclusions: We establish here for the first time that HP-MRI technology can detect SGLT2 effects on metabolism in live rats, and can distinguish metabolic markers of GNG in kidney vs. liver in this context. Although the methodology requires further development to be useful as a consistent marker of SGLT2 effects on GNG, it could be useful in humans both for characterizing sub-categories of T2DM and detecting risk factors for SGLT2 resistance and/or side effects.

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PO0715
Investigation of the Renoprotective Effect of SGLT-2 Inhibitors Focused on Glomerular Hyperfiltration and Oxidative Stress in Mice with Diabetic Kidney Disease
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Background: In recent clinical trials, sodium-glucose cotransporter 2 (SGLT2) inhibitors slowed the progression of DKD compared with placebo. One of the main mechanisms for the renoprotective effect of SGLT2 inhibitors in DKD is the improvement of hyperglycemia, although it has previously been demonstrated that the underproduction of A1 receptor pathway played a pivotal role in the tubulo-glomerular feedback system in type 1 diabetic model mice (Circulation, 2019). We also reported that increased glomerular oxidative stress was involved in the progression of animal model in DKD (Diabetologia, 2010). Loss of tetrahydrobiopterin (BH4), which is a cofactor of eNOS, causes uncoupling of endothelial nitric oxide (NO) synthase (eNOS), resulting in increased superoxide production in DKD (AJP Resp, 2005; JASN, 2013). In this study, we explored the renal protective effects of SGLT2 inhibition, with a focus on glomerular hemodynamics and glomerular oxidative stress.

Methods: We used db/db mice as a model for type 2 diabetes. Mice were treated with canagliflozin (CANA; 10mg/kg) for 8 weeks. We evaluated the change of single nephron glomerular filtration rate (SNGFR) and glomerular permeability of albumin using in vivo multiphoton microscopy imaging. Glomerular reactive oxygen species (ROS) and NO production were evaluated by ex vivo study. Low temperature-sulfate-polyacrylamide gel electrophoresis was performed for detection of eNOS uncoupling. In addition, tomato lectin staining was carried out to observe the vascular endothelial damage.

Results: Glomerular hyperfiltration and urinary albumin excretion in db/db mice was attenuated by CANA treatment. Accelerated ROS production and diminished bioavailable NO caused by eNOS uncoupling in glomeruli were observed in db/db mice. CANA suppressed eNOS uncoupling and improved ROS/NO imbalance via maintenance of BH4. CANA inhibited degradation of endothelial surface layer due to increased glomerular oxidative stress.

Conclusions: SGLT2 inhibitor restore glomerular hyperfiltration in DKD. Simultaneously, intraglomerular ROS/NO imbalance via eNOS uncoupling was improved by SGLT2 inhibitor.

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PO0716
Empagliflozin (SGLT-2 Inhibitor) Ameliorates Early Features of Diabetic Retinopathy and Nephropathy in Type 2 Diabetic Mice Model via the Klotho Protein
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Background: The diabetic nephropathy (DN) and diabetic retinopathy (DR) are the most common serious vascular complications of diabetes Chronic hyperglycemia in DM triggers different processes that lead to Diabetic Retinopathy (DR) and Nephropathy (DN) development. α-Klotho (KL) is an anti-aging gene encoding a protein with multiple pleiotropic effects, involved in suppression oxidative stress and inflammation processes. Empagliflozin (EMPA) is a KLOTHO agonist. This study aimed to evaluate the protective effect of Empagliflozin (EMPA) on the expression of KL on diabetic kidney disease (DKD). We used db/db mice as a model for type 2 DM with and without EMPA treatment.

Methods: BTBR mice with ob/ob leptin-deficiency develops severe type II DM with DN and DR. 8-week-old male mice were randomly divided into three groups: C57BL/6J WT Type, BTBR ob/ob vehicle and BTBR ob/ob treated with EMPA. Mice were sacrificed after 13 weeks of treatment. Mice retinas were removed and fixed by immersion in 2% paraformaldehyde overnight at 4°C. After PBS rinses eyes were immersed in increased concentrations of sucrose-PBS solutions at 4°C and finally frozen in O.C.T. Cryostat sections (16 µm) were incubated overnight at 4°C with primary anti-KL antibody, then for 1 h with secondary antibody. We assessed immunohisto-fluorescence intensity of each experimental group, using an Olympus BX53 fluorescent microscope, and identical exposure for each image. Finally, the data is presented as percent area of the formalin layer (FL) expressing the Klotho protein over the basement membrane and the positive signal to KL. Concomitantly, kidneys were removed and subjected to similar immunostaining for the KL protein.

Results: KL expression in the IPL (ganglionic cells) was 48.3±2.7% in control mice, 11.9±2.3% in C57BL/6J WT Type, BTBR ob/ob vehicle and BTBR ob/ob treated with EMPA (P<0.005 vs. untreated treated DM mice). In control mice KL expression was 6.8% of the renal tissue area, expression was attenuated in the DM mice occupying 0.065 %, in DM mice treated with EMPA, the KL expression reached 4%.

Conclusions: The data suggested that KL protein can play a potential protective factor against retinopathy and nephropathy in DM mice. Early therapy with EMPA that targets the early pathogenicity of DR and DN, is wildly needed to prevent the onset & slow the progression of those pathologies to to vision loss and dialysis, respectively.

PO0717
SGLT2 Inhibition Ameliorates Tubular Injury with Metabolic Suppression in Very Early Phase of Diet-Induced Diabetic Kidney Disease
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Background: Therapies that target the sodium glucose cotransporter 2 (SGLT2) are known to have pleiotropic effects via both metabolic and hemodynamic effects, however, mechanisms promoting renal protection are incompletely known. Here, we investigated the mechanism of reno-protective effects of SGLT2 inhibition in diabetic kidney disease (DKD), focusing on kidney metabolism.

Methods: 10-week-old male SGLT2 mutant (Sweet Pee) and wildtype (WT) mice, fed with normal or high fat diet (HFD, 60% calories from fat) for eight weeks, were analyzed. Weekly changes in body weight, food intake, insulin and glucose tolerance were determined. Renal injury was evaluated by transdermal measurement of GFR, urinary ejection fraction and glomerular hyperfiltration indexes.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: Similar degree of HFD-induced obesity occurred in both SGLT2 mutant and WT mice while compensatory hyperphagia was observed only in mutant mice. HFD led to elevation of post-prandial blood glucose level, glucose intolerance and insulin resistance. Increases in postprandial blood glucose and glycogen intolerance were blunted in SGLT2 mutant mice. Although changes of GFR and urinary albumin excretion were not observed, KIM1 and NGAL expression were upregulated by HFD feeding, indicating that the kidney responds to early phase of DKD. KIM1 and NGAL upregulation was abrogated in SGLT2 mutant mice. Furthermore, HFD feeding induced apoptosis in the cortex of WT mice, but not in SGLT2 mutants. Kidney/body weight ratio was decreased by HFD in WT but increased in SGLT2 mutant mice, suggesting metabolic differences in the kidney. Genes related to glycolysis (PGK and PKM), TCA cycle (IDH2) and fatty acid oxidation (CPT1a, CPT2, PPARα and PGC1α) were suppressed in SGLT2 mutant vs WT HFD groups.

Conclusions: SGLT2 inhibition ameliorates tubular injury associated with renal hypertrophy and metabolic suppression in very early phase of diet-induced DKD.

Funding: NIDDK Support

PO0718
mTORC2 Is Essential for Sodium-Glucose Cotransporter 2

Background: The role of mammalian target of rapamycin (mTOR) complexes mTORC1 and mTORC2 in renal tubule ion transport has been well characterized. We and others have shown that mTORC2 is a key regulatory kinase for serum and glucocorticoid kinase 1 (SGK1) target and that its activity is required for epithelial Na⁺ channel (ENaC)-dependent sodium reabsorption in the aldosterone-sensitive distal nephron (ASDN). Also, we and others have shown that mTORC2 activity is required in proximal tubule cells (RPTCs) in diabetes, which was prevented by the inhibition of sodium-glucose co-transporter 2 (SGLT2), and that mTORC1 KO in mice causes a Fanconi’s syndrome-like phenotype. However, the roles of mTORC2 in the regulation of RPTCs, particularly as it pertains to glucose reabsorption remain obscure. In this study we explore the relationship between mTORC2 and SGLT2 in CRISPR-modified HEK-293T cells and in mice, using patch clamp and membrane expression studies.

Methods: We used CRISPR-Cas9 to generate Sin1 (an essential component of mTORC2) KO HEK-293T cells, which were compared with wild-type control cells. The cells were transiently transfected with SGLT2. We recorded in WT HEK-293T cells the Dapa-sensitive SGLT2 sodium current. We used an inducible Cre-Lox system (Pax8-Lox) to KO Rictor (another key component of mTORC2) in mice. Dopaglibose-sensitive whole-cell SGLT2 sodium current was measured in the microdissected proximal tubules and HEK-293T cells

Results: Strikingly, in mTORC2-knockout HEK-293T cells the Dapa-sensitive SGLT2 sodium current was significantly reduced versus WT HEK-293T cells. In mice, mTORC2 KO caused glycosuria without hyperglycemia, and patch-clamp studies showed decreased glucose-induced, dopaglibose-inhibited Na⁺ current.

Conclusions: Knockout of mTORC2 in the HEK-293T cells or in mice inhibits SGLT2 sodium-current. Our study delineates the essential role of mTORC2 in SGLT2 function. These observations explain the broad role of SGLT2 inhibition therapy and variable resistance to their effects.

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PO0719
MAP17 and D-AKAP2, Two Major Scaffolder Proteins, Are Upregulated in Experimental Diabetic Nephropathy in Response to Empagliflozin on Top of RAS Blockade
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Background: Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have proven to delay diabetic nephropathy (DN) progression on top of the standard of care renin-angiotensin-aldosterone (RAS) blockade. This protective effect was mostly attributed to improvement in renal hemodynamics although direct effects on the kidney cannot be ruled out. Further, the molecular mechanisms underlying the synergic effect of SGLT2i and RAS blockers are unknown.

Methods: 12 weeks old diabetic db/db mice were given emagliflozin (10mg/Kg/day), ramipril (8 mg/Kg/day) or the combination of both drugs during 8 weeks. Mice treated db/db and db/m mice were used as controls. Serum glucose, blood pressure, GFR and albuminuria were measured at baseline and at the end of study. At the end of the experiment, mice were euthanized and the kidneys were saved to perform a differential high-throughput proteomic analysis by mass spectrometry using isobaric tandem mass tags (TMT labelling).

Results: Vehicle db/db mice showed increased glycaemia during the whole experiment. Empagliflozin normalized blood glucose. Ramipril treatment decreased blood pressure. Diabetic vehicle mice showed inceint DN, mesangial expansion and albuminuria were significantly increased when compared to their non-diabetic littermates. All the treatments reduced mesangial expansion and albuminuria. The differential gene expression analysis revealed a clear role of mTORC2 in SGLT2i therapy. mTORC2 KO caused glycosuria without hyperglycemia, and patch-clamp studies showed a decreased whole-cell SGLT2 sodium current. We used an inducible Cre-Lox system (Pax8-Cre-Lox) to KO Rictor (another key component of mTORC2) in mice. Dopaglibose-sensitive whole-cell SGLT2 sodium current was measured in the microdissected proximal tubules and HEK-293T cells.

Conclusions: Knockout of mTORC2 in the HEK-293T cells or in mice inhibits SGLT2 sodium-current. Our study delineates the essential role of mTORC2 in SGLT2 function. These observations explain the broad role of SGLT2 inhibition therapy and variable resistance to their effects.

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PO0720
Added Benefit of SGLT2 Inhibitor with ACE Inhibition in a Mouse Model of Severe Diabetic Nephropathy
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Background: The clinical success of sodium glucose cotransporter 2 inhibitor (SGLT2i) for the treatment of diabetic kidney disease (DKD) has ushered in a new phase in the discovery and development of novel drugs for DKD. As the development of SGLT2i did not follow the traditional drug discovery paradigm exemplified by testing efficacy in a relevant preclinical model, here we present the evaluation of combinatorial use of SGLT2i and standard of care in the hypertensive Renin AAV db/db uninephrectomized mouse model of severe DKD.

Methods: Severe DKD was established by AAV mediated hepatic overexpression of renin in uninephrectomized db/db mice. Mice were treated with Lisinopril (ACEi) in drinking water and SGLT2i (JNJ39933673) in diet, at a dose of 5 mpk for 8 weeks. Study groups included untreated DKD control (N=11), Lisinopril treated (N=11), Lisinopril + SGLT2i treated (N=11) and LacZ AAV control (N=10).

Results: SGLT2i significantly reduced blood glucose levels upon treatment inception (Day-3 vs. Day 4; 465.1±33.1 vs. 258.7±24.8; mean ± sem, mg/dl, p=0.001). ACEi reduced systolic blood pressure by 21 mm of Hg within 2 weeks of treatment (p=0.02), which was further reduced by 20 mm of Hg by SGLT2i co-treatment on week 7 (p=0.03). While ACEi treatment alone reduced UACR by 15% to 35% below baseline, dual treatment with SGLT2i led to a reduction of UACR by 49% to 67% during the 8 weeks treatment phase (p<0.05), leaving a residual albuminuria of 556±1 µg/mg. Plasma creatinine doubled during the study period and was blunted only after ACEi+SGLT2i (No treatment vs. ACEi+SGLT2i: 0.3±0.06 vs. 0.24±0.02; mean ± sem, mg/dl, p<0.05). Histological analysis revealed additive benefits of ACEi+SGLT2i, in measures of glomerular, vascular and tubulointerstitial lesions. Reduced plasma levels of sTnFlr reflected therapeutic benefits of SGLT2i on top of ACEi.

Conclusions: Our study demonstrates the possibility of testing combinatorial therapies in this translational preclinical model of severe DKD. Residual benefits in ACEi+SGLT2i animals should enable testing of novel agents in this model on this new standard of care for CKD.

Funding: Commercial Support - Janssen R&D

PO0721
Assessment of Candidate Renal Protective Drug-Induced Biomarkers in Diabetic Kidney Disease Using Targeted Proteomic Profiling
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Background: The sodium-glucose cotransporter 2 inhibitor (SGLT2i) emagliflozin slows the progression of kidney function decline in type 2 diabetes in addition to lowering blood glucose levels. However, the underlying molecular mechanisms of SGLT2i for these protective effects are not yet completely understood. We assessed non-invasive biomarkers associated with emagliflozin or enalapril treatment in a rat model of diabetic kidney disease (DKD).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

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Methods: Obese diabetic and hypertensive ZSF1 rats were treated with vehicle, enalapril (10 mg/kg/d, p.o.), or empagliflozin (30 mg/kg/d, p.o.) for 8 weeks. Along with phenotypic parameters, Olink Mouse Experimtal panel was used to simultaneously detect the levels of 92 proteins in plasma and urine samples using the proximity extension assay.

Results: Compared to vehicle and enalapril, empagliflozin reduced blood glucose, HbA1c, and urinary albumin excretion while increasing HDL levels in ZSF1 rats. Empagliflozin significantly affected the levels of 16 proteins in plasma samples. Lower plasma concentrations after empagliflozin-treatment were detected for Nectin3, tenasin-C, glial cell line-derived neurotrophic factor, and erythropoietin. In urine, we found increased levels of a select group of proteins (p < 0.05) compared to vehicle. Treatment with empagliflozin resulted in a complete correction of albuminuria, one of the hallmarks of diabetic nephropathy. Of these, compared with enalapril, empagliflozin restored the levels of dihydropyridine reductase and dimethylarginine dimethylaminohydrolase 1, proteins known for their role in decreasing ROS activity and oxidative stress. Eight plasma proteins and one urinary protein were found to be differentially expressed after enalapril treatment. Plasma tenasin-C was the only protein associated with both enalapril and empagliflozin treatment.

Conclusions: We identified biomarkers that are associated with SGLT2i and ACEi treatment. Our results may additionally provide mechanistic insights into the beneficial effects of these classes of drugs. Translation and validation of these preclinical findings in human patient samples is the proposed next step. This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 113974. This Joint Undertaking receives support from the European Union’s Horizon 2020 research and innovation programme and EFPIA with JDRF.

Funding: Commercial Support - Pharmaceuticals, Bayer AG, Wuppertal Germany

PO0722

Elucidation of Glomerular Hemodynamic Changes by SGLT-2 Inhibitors and ARBs in a Type 2 Diabetic Animal Model Using In Vivo Imaging

Yoshihisa Kadoya, Kengo Haddock, Ali B. Jensen, Susan Francis, Ulrich Lindberg, Susan Haddock, Sir Peter Mansfield Magnetic Resonance Imaging Centre School of Physics and Astronomy, University of Nottingham, Ulrik Asmar, Oliver Ulrik Lindberg, Susan Francis, Ali B. Jensen.1

Background: In recent clinical trials have shown that SGLT2 inhibitor (SGLT2i) inhibits the progression of diabetic kidney disease (DKD). We established the method for measuring single-nephron GFR (SNGFR) in mice by in vivo imaging and found that the adenosine / adenosine A1 receptor (A1AR) pathway in type 1 diabetic animal model (Kidokoro K et al. Circulation 2019). The mechanism of development of GH and improvement of GH by SGLT2i is considered to be different in type 1 and type 2 DKD. However, the detailed regulatory mechanism of GFR has not been elucidated in type 2 DKD. We conducted experiments to elucidate the glomerular hemodynamic changes in type 2 diabetic animal model, using SGLT2i alone and in combination with RAAS inhibitors.

Methods: Zucker Lenz (ZL) and Zucker Diabetic Fatty (ZDF) rats were used. Multi photon microscopy was used to evaluate SNGFR, afferent arteriole (AA) and efferent arteriole (EA). The change in AA, EA, and SNGFR were observed every 30 minutes after SGLT2i administration. Furthermore, we investigated the involvement of the adenosine / A1AR pathway in type 2 diabetic animals using an A1AR antagonist (A1ARant). We made a SGLT2i + ARB combination group and measured AA, EA, and glomerular volume.

Results: ZDF showed a significant increase in blood glucose and urinary protein levels compared to ZL. SNGFR, AA, and EA were significantly increased in ZDF compared to ZL indicating GH. SGLT2i administration resulted in correction of AA hyperfiltration and inhibition of GH. The inhibitory effect on hyperfiltration by SGLT2i was abolished by the coadministration of A1ARant. There was no significant change about blood pressure, but urinary protein excretion was significantly suppressed by ARB treatment. In ZDF, Glomerular volume was significantly increased, while there were no significant changes in AA and EA. SGLT2i ameliorated abnormal expansion of AA also in the presence of ARB, and no change in EA.

Conclusions: Our results showed that the regulation of AA vascular tone by the adenosine / A1AR pathway and GFR was involved in the GH in type 2 DKD.

Funding: Commercial Support - TAISH PHARMACEUTICAL CO., LTD.

PO0723

GLP-1’s Effect on Renal Perfusion and Oxygenation Measured with Quantitative MRE: A Potential Renoprotective Pathway in the Human GLP-1-Renal Axis

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Background: GLP-1 receptor agonism has shown significant beneficial cardiovascular effects that may be related to renoprotection. In the human kidney, a high GLP-1 extraction and its natriuretic effect are fully dependent on the GLP-1 receptor and associated with suppression of angiotensin II. Preclinical data showed that angiotensin II constricts vasa recta vessels and decreases renal blood flow. The current study was designed to test the hypothesis that GLP-1 increases renal medullary perfusion.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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2/3 nephrectomy (n=7; Nx) or 5/6 Nx (n=4). Rats recovered for 4 weeks, then underwent insulin tolerance testing (ITT; 0.75 U/kg i.v.) before and after alkali (2 weeks 0.1M NaHCO3) and acid loading (1 week 0.1M NH4Cl) in the drinking water. Male Zucker obese rats (10 wks) underwent 5/6 Nx (n=4) and were also given 4 weeks of recovery before being placed on 0.1M NH4Cl for 4 days.

Results: In Nx SD rats, 0.1M NaHCO3 did not produce metabolic alkalosis (Table 1) or reduce insulin sensitivity (P0.67). 0.1M NH4Cl in Nx SD rats produced a mild metabolic acidosis (Table 1). However, this did not alter the response to insulin (P0.56). 0.1M NH4Cl produced a severe metabolic acidosis in Zucker rats with 5/6 Nx (Table 1). Again, however, this was not associated with an impaired insulin response. Rather, following NH4Cl loading, Zucker rats had a greater response to insulin (P0.01). Unexpectedly, we observed a negative relationship between the magnitude of change in blood glucose (inverse area under the curve) and plasma pH (r20.27, P0.003) and plasma HCO3- (r20.33, P=0.0098) in remnant kidney rats.

Conclusions: These data demonstrate that metabolic acidosis does not impair insulin sensitivity in rats. Our data suggest that the direct effects of metabolic acidosis are unlikely to underlie significant impairments in insulin sensitivity in CKD.

Funding: Other NIH Support - P01HL134604 (to PMO), R21AI150723 (to PMO)

Table 1.

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Blood Glucose (mg/dL)</th>
<th>Plasma pH</th>
<th>Plasma HCO3- (mEq/L)</th>
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<td>0% NH4Cl</td>
<td>200 ± 10</td>
<td>7.4 ± 0.1</td>
<td>24 ± 2</td>
</tr>
<tr>
<td>100% NH4Cl</td>
<td>240 ± 20</td>
<td>7.1 ± 0.2</td>
<td>20 ± 1</td>
</tr>
</tbody>
</table>

Figure 1.

PO0726 Understanding Mechanisms Underlying Diabetic Kidney Disease Using Integrative Transcriptome and Proteome Profiling of Insulin-Resistant Hepa1c1c7 Cells

Abigail C. Lay,1 Van Du T. Tran,2 Florence Mehli,2 Dmytro Kryvokhyzha,3 Virginie M. Betin,4 Marieangela C. Wilson,1 Kate J. Heesom,1 Richard Coward,1 BEAT-DKD consortium1 University of Bristol, Bristol, United Kingdom, 2Swiss Institute of Bioinformatics, Lausanne, Switzerland, 3Lunds Universitet, Lund, Sweden.

Background: One of the strongest metabolic features of diabetic kidney disease (DDK), in both type 1 and type 2 diabetes, is insulin resistance and it is increasingly clear that disruptions to renal cellular insulin responses can drive DDK development. The present study aims to generate a comprehensive network of molecular changes occurring in the kidney in response to insulin resistance using cell models.

Methods: Conditionally immortalised human podocytes (Pod), glomerular endothelial cells (GEC), mesangial cells (MC) and proximal tubular cells (PTC) were studied. A diabetic, insulin resistant, environment was established using a combination of TNFα, IL-6, high glucose and high insulin. The cellular proteome and transcriptome were studied simultaneously using Tandem-Mass-tagged mass spectrometry and RNA sequencing. To explore the changes occurring in insulin resistance, integrated transcriptome and proteome data were analysed using univariate and multivariate statistical models and gene set enrichment analysis (GSEA) was performed to identify significantly regulated cellular processes.

Results: Initial results revealed that exposure to a diabetic environment induced differential insulin resistance between human kidney cell lines. Differential expression analysis of both transcriptome and proteome found that insulin resistance was the most pronounced effect on expression in Pod and PTC and highlighted 45 consistently regulated genes/proteins. GSEA identified consistent increases in the inflammatory response, ER stress and glycoprotein metabolism and a consistent decrease in hippo signalling across all insulin resistant cells. In contrast, mitochondrial-related signatures were significantly reduced at the protein level in Pod and PTC but increased in GEC. Investigation of these gene/protein signatures in human DDK cohorts is currently ongoing.

Conclusions: By performing integrated omics profiling on renal cell models, we identified conserved and cell-specific changes occurring in insulin resistance. Integration with human cohort data will highlight conserved pathways and the utility of cell models in pre-clinical investigations, aiding the identification of molecular processes underlying the development and progression of DDK.

PO0727 Insulin Resistance Is Associated with Decreased Renal Insulin Receptor Beta in Aged D4 Null Mice

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Background: Insulin resistance is a major concern in metabolic disorders related to diabetes.

Methods: In order to explore the hypothesis that D4 dopamine receptor (D4R) increases carbohydrate by insulin sensitivity through its activation of insulin receptor beta (IR-beta), we demonstrated the functional role of D4R in the prevention of insulin resistance by studying D4r null (D4r-/-) mice and wild-type (D4r+/+) littermates.

Results: We found that D4r-/- mice (14 mos) had increased fasting blood glucose regardless of sex but their urines were negative for glucose and ketones, suggesting that the mice fed normal salt/normol fat diet were pre-diabetic. Serum insulin levels were increased in male D4r-/- mice but not altered in female D4r-/- mice after an 8 hr fast indicating that these mice have resistance or sensitivity to endogenous insulin. The aged male and female D4r-/- mice had similar body weights, fasting serum total and free cholesterol, triglycerides, to their age and sex -matched D4r+/+ littermates, suggesting that the old D4r-/- mice were not obese and had no dyslipidemia. Relative to D4r+/+ littermates (100±7%, n=6), D4r-/- mice had decreased IR-beta (19±4%, n=4) but normal protein expressions of IR-alpha, insulin degrading enzyme, insulin substrate 1, sodium glucose transporter 2 and glucose transporters in renal cortex homogenates, indicating that the decreased protein expression of IR-beta contributed to the insulin resistance in the aged D4r-/- mice. D4r-/- mice had decreased phosphorylated IR-beta at Tyr1631&1345, Tyr1162. Renal expression of insulin receptor beta was located in mouse renal glomerulii and tubules and co-localized n the apical membrane with NCC in the distal convoluted tubules in cortex and NKCC2 in the thick ascending limbs of loop of Henle in the outer medulla. D4R and IR-beta were co-immunoprecipitated in immortalized mouse renal distal convoluted tubule cells and the co-immunoprecipitation was increased by D4R agonist and not altered by D4R antagonist.

Conclusions: Our results suggest that disruption of D4R may play an important role in the insulin resistance via interactions with IR-beta in kidney.

Funding: Other NIH Support - P01HL134604 (to PMO), R21AI150723 (to PMO)

PO0728 Renal Mass Reduction Enhances the Blood Glucose Response to Exogenous Insulin in Rats

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Background: The effect of chronic kidney disease (CKD) on responses to exogenous insulin is complex and may vary depending on the level of underlying insulin resistance. The kidneys play an important role in the catabolism of insulin, and progression of CKD in rats with diabetes mellitus is often associated with reducing insulin needs. Conversely, impairments in insulin sensitivity are observed in CKD patients absent diabetes, indicating that CKD itself may drive insulin resistance.

Methods: To clarify the roles of CKD and underlying insulin resistance on the response to exogenous insulin, in the current study we investigated the effect of graded renal mass reduction on the blood glucose response to insulin to healthy Sprague Dawley (SD) and insulin resistant Zucker obese rats. Male SD (12 wks) and Zucker obese (10 wks) rats underwent either sham (n=6 SD, 3 Zucker), 2/3 nephrectomy (n=7 SD; Nx), or 5/6 Nx (n=8 SD, 4 Zucker). Rats recovered for 4 weeks, then underwent insulin tolerance testing (ITT; 0.75 U/kg i.v.).

Results: There was a graded response in the blood glucose curves for SD rats (Plevel0.0001; Fig 1A) with sham rats having the smallest blood glucose response to insulin. 5/6 Nx rats had the greatest response to insulin. Similarly, the blood glucose response to insulin was about 5x greater for Zucker 5/6 Nx rats than for sham rats (Plevel0.0019; Fig 1B). There were no significant differences in plasma insulin levels during the ITT between NX and sham SD rats, while sham Zucker rats had greater plasma insulin levels than Nx rats (P0.0001).

Conclusions: These data indicate that renal mass reduction increases the response to exogenous insulin independent of the level of underlying insulin resistance, and that this is not mediated by an increased half-life of circulating insulin. Further investigation into the factors that contribute to the insulin responses in CKD may identify novel targets for the treatment of insulin resistance.

Funding: Other NIH Support - P01HL134604 (to PMO), R21AI150723 (to PMO)

PO0729 The Essential Role of Intact Mitochondrial Substrate Balance in Preventing Renal Injury

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Background: Alterations in mitochondrial function are linked to the development of chronic/diabetic kidney diseases. Proximal tubular cells (PTCs) are highly energy demanding, covering this metabolic need mostly from mitochondrial fatty acid oxidation is suggested, but not entirely clear whether derailingments in mitochondrial metabolism and function are forerunners of tubular damage. In our previous studies we modeled mitochondrial substrate overload - an important aspect of metabolic disease - by creating proximal tubule cell models of insulin resistance. The enzyme carnitine acetyl-transferase (CrAT) in the PTC. These studies revealed that mitochondrial substrate overload in proximal tubules causes tubular injury and secondary glomerulosclerosis.

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PO0730
Speinx-Basin Galanin Receptor 2 Agonist (NS200) Improves Diabetic Nephropathy in Type 2 Diabetes
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Background: Spexin is a novel neuropeptide having an emerging role in metabolic diseases such as obesity and diabetes and involved in energy homeostasis and food intake. Spexin-galamin receptor 2 agonist (NS200) has anti-apoptotic action and anxiolytic effect. The aim of this study is to investigate the effect of NS200 on insulin resistance and diabetic nephropathy in type 2 diabetic animal.

Methods: 8 to 10 week old db/db and db/db mice were treated with NS200 for 12 weeks. NS200 was administered by intraperitoneal injection at a dose of 1.0 mg/kg/day as reported in the previous study.

Results: There were no changes in body weight, food and water intake, urinary volume, fasting glucose level and HbA1c level by NS200 treatment in diabetic mice. Insulin tolerance test and glucose tolerance test were also unchanged by treatment. NS200 lowered systolic blood pressure. Interestingly, NS200 improved urinary albumin excretion significantly in diabetic mice. Renal histology showed reduced glomerulosclerosis and tubulointerstitial fibrosis in treatment groups. Renal TGFβI and IV collagen expressions were decreased in NS200 treated group, whereas PAI-1 and F4/80 expression were increased in treatment group. Insulin signaling pathway such as PI3K, p-AKT, and p-ERK protein expression were significantly suppressed by treatment in diabetic nephropathy. Despite there were no beneficial effects in basal metabolic parameters and insulin resistance, NS200 treatment in diabetic mice showed renoprotective effects in urinary albumin excretion and renal structural changes.

Conclusions: Our results provide the evidence that spexin-basin galanin receptor 2 agonist by NS200 has renoprotective effect in diabetic nephropathy. These findings support the mechanism via its inhibition of renal insulin signaling pathway therefore provide a considerable promise as a new agent in diabetic nephropathy.

PO0731
Cell Sex and Sex Hormones Regulate Kidney Metabolism of Glucose and Glutamine: Implications for Diabetic Kidney Disease
Sergi Clotet Freixas,1 Olga Zaslawer,1 Chiara Pastrello,1 Max Kotlyar,1 Catriona M. McEvoy,1 Sofia Farkona,1 Aninda D. Saha,1 Alexander Boshart,1 Allison Ditt,1 Brandy A. Wicklow,1 Tom D. Blydt-Hansen,3 James W. Scholey,2 Hannes L. Rost,2 Ana Konvalinka,1 University Health Network, Toronto, ON, Canada; 1The University of British Columbia Department of Pediatrics, Winnipeg, MB, Canada; 2University of Manitoba Department of Pediatrics and Child Health, Winnipeg, MB, Canada; 3The University of Toronto, Toronto, ON, Canada.

Background: Diabetic kidney disease (DKD) is the major cause of end-stage kidney disease. Male sex is a risk factor for DKD, but the reasons for this predilection are unclear. We demonstrated that androgens accentuate DKD in vivo, and increase enzymes involved in glucose and glutamine metabolism, in male prximal tubular epithelial cells (PTECs). We aimed to determine the effect of cell sex and sex hormones on kidney metabolism.

Methods: Male and female PTECs were stimulated with control, dihydrotestosterone (DHT), or estradiol. Sex differences in key metabolites were validated in diabetic mice, and in type 2 diabetic patients and their age- and weight-matched healthy controls (n=180, cCARE cohort).

Results: Male PTECs showed significantly higher glycolysis, oxygen consumption (OCR), glucose consumption, oxidative stress, and apoptosis, compared to female PTECs, especially in the presence of DHT. Higher OCR in male PTECs was further enhanced in the presence of glucose and glutamine, but not observed in the presence of pyruvate, suggesting a shift in metabolic substrates. Male PTECs showed a decline in OCR and ATP production over time, and increased lactate production. Male PTECs had significantly higher intracellular levels of TCA cycle metabolites (glutamate, citrate, malate, aspartate) and glutathione metabolites. In turn, female cells had higher levels of pyruvate. In vivo, male sex was associated with increased circulating levels of glucose, lactate, and glutamate in healthy and diabetic mice. Male sex was also independently associated with increased serum levels of glumetate, succinate, fumarate, and 9 metabolites of the glutathione cycle, in healthy and diabetic individuals.

Conclusions: This is the first study to demonstrate that the kidney metabolism of glucose and glutamine is modulated by cell sex and sex hormones. Male sex was linked to increased oxidative stress, cell injury, glucose- and glutamate-related enzymes, lactate secretion, and levels of TCA cycle and glutathione metabolites. Our key findings provide a basis for further investigation of sex-specific metabolic measures of DKD in diabetic individuals. Our work has uncovered physiological sex differences that are important for DKD and may lead to new therapeutic paradigms based on patient sex.
Conclusions: Proteins identified by LC-MS/MS from glomerular cross-sections successfully distinguished kidney biopsies with DN from normal kidneys. Moreover, a set of differentially expressed proteins were identified, most of which were previously suggested to play a role in the development of DN, which further emphasizes the applicability of LC-MS/MS as a diagnostic tool.

Funding: Private Foundation Support, Government Support - Non-U.S.

PO0734
The Extracellular Matrix Signaling Molecule Endotrophin Is Associated with Diabetic Complications in Type 1 Diabetes
Alexandra L. Muller,1,2 Daniel Guldager Kring Rasmussen,1 Nina H. Tougaard,1 Pernille F. Rønn,3 Federica Genovese,1 Morten A. Karstrup,1 Tine Hansen,2 Peter Rossing,2,3,1 Nordic Bioscience, Herlev, Denmark; 2Steno Diabetes Center Copenhagen, Gentofte, Denmark; 3University of Copenhagen, Copenhagen, Denmark.

Background: Persons with diabetes have a high risk of late complications related to both the micro- and macrovascular circulation. Early intervention targeting several risk factors is implemented, but tools to predict complications before clinical manifestations are still lacking. The PRO-C6 assay reflects collagen (COL) type VI formation and factors is implemented, but tools to predict complications before clinical manifestations are still lacking. The PRO-C6 assay reflects collagen (COL) type VI formation and are involved in gene regulation and play important roles in the pathogenesis of various renal diseases, including diabetic kidney disease (DKD). lncRNA signatures associated with DKD, however, have not been fully established. The objective of this study was to determine the whole blood lncRNA signature that is associated with increased risk of DKD progression.

Methods: Eighty-eight lncRNAs that were previously reported to be related to DKD were measured by quantitative PCR (qPCR) in RNA from whole blood (PAXgene RNA tubes) in 22 patients with type 1 diabetes and chronic kidney disease (12 of whom progressed to ESKD during 7-10 years of follow-up). GAPDH was used for sample normalization. We assessed declining kidney function as eGFR slope (mL/min/1.73m²/year).

Results: Seventy-two of the 88 lncRNAs were detectable in more than half of the samples included in this study (n>11). Using Pearson's test, eGFR slope was found to be significantly correlated with lncRNAs H19 (r=0.56, P=0.0073) and CRNDE (r=-0.42, P=0.05). H19 and CRNDE were not correlated with HbA1c (r=-0.15, P=0.32 and r=-0.15, P=0.52 respectively), suggesting that these lncRNAs are associated with progression of DKD mediated by distinct pathways(s) independent of hyperglycemic condition

Conclusions: We investigated plasma lncRNA profiles associated with declining kidney function in patients with diabetes. Although we need to confirm the results in an independent validation panel, our findings suggest that H19 and CRNDE are associated with declining kidney function and have potential to serve as circulating biomarkers for progression of DKD.

Funding: Commercial Support - Novo Nordisk

PO0736
Long Non-Coding RNA Profiles and Declining Kidney Function in Patients with Diabetes and CKD
Eichihiro Satake,1 Hiroki Kobayashi,2 Zaipul I Md Dom,1 Kristina V. O’Neil,1 Bozena Krolewski,1 Marcus G. Pezzolesi,1 Andrzej S. Krolewski,1 Joslin Diabetes Center, Boston, MA; 2University of Utah, Salt Lake City, UT.

Background: Long non-coding RNAs (lncRNAs) are endogenous molecules that are involved in gene regulation and play important roles in the pathogenesis of various renal diseases, including diabetic kidney disease (DKD). lncRNA signatures associated with DKD, however, have not been fully established. The objective of this study was to determine the whole blood lncRNA signature that is associated with increased risk of DKD progression.

Methods: Eighty-eight lncRNAs that were previously reported to be related to DKD were measured by quantitative PCR (qPCR) in RNA from whole blood (PAXgene RNA tubes) in 57 youth with T1DM, 59 with T2DM, and 44 healthy control subjects. The UCSD progression.

Results: Urinary sphingolipids are elevated in youth with diabetes and correlate with eGFR and albuminuria. Urinary sphingolipids may therefore represent an early marker of DKD.

Funding: Commercial Support - Novo Nordisk

PO0735
Urinary Sphingolipids in Youth-Onset Diabetes
Edward Nehus,1 Mark Mitsuves,2 1Marshall University, Huntington, WV; 2Cincinnati Children’s Hospital Medical Center, Cincinnati, OH.

Background: Sphingolipid metabolism is altered in diabetes has been implicated as a mediator of diabetic kidney disease (DKD). The purpose of this study was to evaluate urinary sphingolipids as an early marker of kidney injury in youth with type 1 (T1) and type 2 diabetes (T2DM).

Methods: A comprehensive panel of urinary sphingolipids, including sphingomyelin (SM), glucosylceramide (GC), ceramide (Cer), and lactosylceramide (LC) species, was performed in patients with youth-onset diabetes from the Treatment Options for Diabetes in Youth (TODAY) cohort. Sphingolipid levels, normalized to urine creatinine, were compared in 57 youth with T1DM, 59 with T2DM, and 44 healthy control subjects. The association of sphingolipids with early markers of DKD (albumin-to-creatinine ratio [ACR] and estimated glomerular filtration rate [eGFR]) was evaluated.

Results: Median age (IQR) of youth with diabetes was 22.2 years (19.9, 23.6) and the median duration of diabetes was 9.3 (8.5, 10.2) years. Urinary sphingolipid concentrations in youth with and without DKD (ACR ≥ 30) were significantly elevated compared to healthy subjects (all p<0.001). There were no significant differences between youth with type 1 and type 2 diabetes. All sphingolipid species were positively correlated with eGFR (all p < 0.001) and negatively with albumin-to-creatinine ratio (p < 0.001 for SM, Cer, GC; p = 0.0015 for LC). In multivariable analysis that adjusted for BMI and HbA1c, all urinary sphingolipid species remained significantly associated with eGFR (all p < 0.01). SM, GC, and Cer species remained independently associated with ACR (all p < 0.05).

Conclusions: Urinary sphingolipids are elevated in youth with diabetes and correlate with eGFR and albuminuria. Urinary sphingolipids may therefore represent an early marker of DKD.

Funding: Commercial Support - Novo Nordisk
A Comparison of PromarkerD to Standard-of-Care Tests for Predicting Renal Decline in Type 2 Diabetes

Kirsten E. Peters,1,2 Scott D. Bringans,1 Wendy A. Davis,3 Richard Lipscombe,1 Timothy Davis.2 PromarkerD moderate and PromarkerD remained significantly associated with the 1° outcome after adjusting for eGFR decline ≥30% in participants with baseline eGFR <60 mL/min/1.73 m². Logistic regression was used to compare the association of i) PromarkerD, ii) eGFR, iii) ACR, and iv) eGFR-ACR, with outcomes during 4 years of follow-up. Model performance was assessed by the ROC area under the curve (AUC).

Results: At baseline, participants (mean age 65 years, 54% males, median diabetes duration 7 years) had mean eGFR 82 mL/min/1.73 m², geometric mean ACR 26 mg/g and were classified by PromarkerD as low (65%), moderate (13%) or high risk (24%) for renal decline. During 4.2 yrs of follow-up, 107 (13%) participants reached the 1° endpoint. PromarkerD had significantly greater predictive performance (AUC=0.88) compared to eGFR (0.82), ACR (0.63) and eGFR-ACR (0.82) (all p<0.001). Higher PromarkerD scores had a stronger association with the 1° outcome (odds ratio (OR) 5.26, 95% CI 2.99–9.22) per standard deviation (SD) increase compared to lower eGFR and a higher ACR (OR=2.63 (2.13-3.23) and 1.21 (1.04-1.40) per 1 SD increase, respectively). PromarkerD remained significantly associated with the 1° outcome after adjusting for eGFR and ACR (OR=2.78 (2.19-3.53) per 1 SD increase). PromarkerD moderate and high risk groups were highly prognostic for the 1° outcome (OR 8.11 and 21.34 versus low risk, respectively; both p<0.001).

Conclusions: PromarkerD outperformed the standard of care tests eGFR and ACR for predicting future renal decline in T2D.

Funding: Commercial Support - Proteomics International

A three-dimensional representation of the relationships between IL-9, MPs, and ACR.

Human Kidney Proteomics Identifies Biomarkers Associated with Kidney Function in Patients with Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) is the most common cause of chronic kidney disease (CKD) and end stage kidney disease, worldwide. However, the pathogenic mechanisms of poorly understood. While RNA sequencing emerged as an important tool to understand gene expression changes, protein level changes are poorly understood. SOMAson is an emerging method that can robustly measure the level of thousands of proteins.

Methods: We have performed unbiased SOMAscan proteomics and quantified the amount of 1317 proteins in 24 snap frozen kidney tissues collected from nephrectomies. Our samples included 10 control healthy samples, 10 from subjects with overt DKD (CKD stage 3a), and 14 from subjects with late DKD (CKD stages 3b or 4). Demographic and clinical characteristics of the subjects were collected.

Results: The mean of age was 61 ± 16 and 65 % of the subjects were male. The median glomerular filtration rate (eGFR) was 108 (33) in control, 54 (5) in overt DKD, and 32 (28) in late DKD. We identified 279 proteins showing differences at overt DKD samples, and 381 proteins in late DKD samples compared to controls. Gene ontology analysis indicated enrichment for immune system and metabolic processes. The protein level of matrix metalloproteinase-7 (MMP-7) showed the strongest differences between control and DKD. Linear regression, adjusted for key co-variates identified 96 proteins those levels correlated with eGFR. We observed a moderate correlation between transcript and protein levels (r = 0.43, p > 2.2e-16).

Conclusions: SOMAson proteomics identified important changes in protein expression in overt and late DKD, these could serve as important biomarkers or therapeutic targets.

Funding: NIDDK Support

Diabetes Mellitus Associates with Differences in the Metabolome of Patients with CKD

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Background: Diabetic Mellitus (DM), the most common cause of chronic kidney disease (CKD), is associated with increased risk of death, cardiovascular disease, and kidney failure, even if the DM is well-controlled. We hypothesized that significant differences exist in the metabolome of CKD patients with well-controlled DM versus CKD without DM. We performed unbiased SOMAscan proteomics and quantified the amount of 1317 proteins in 24 snap frozen kidney tissues collected from nephrectomies. Our samples included 10 control healthy samples, 10 from subjects with overt CKD (CKD stage 3a), and 14 from subjects with late CKD (CKD stages 3b or 4). Demographic and clinical characteristics of the subjects were collected.

Methods: We have performed unbiased SOMAscan proteomics and quantified the amount of 1317 proteins in 24 snap frozen kidney tissues collected from nephrectomies. Our samples included 10 control healthy samples, 10 from subjects with overt CKD (CKD stage 3a), and 14 from subjects with late CKD (CKD stages 3b or 4). Demographic and clinical characteristics of the subjects were collected.

Results: The mean of age was 61 ± 16 and 65 % of the subjects were male. The median glomerular filtration rate (eGFR) was 108 (33) in control, 54 (5) in overt DKD, and 32 (28) in late DKD. We identified 279 proteins showing differences at overt DKD samples, and 381 proteins in late DKD samples compared to controls. Gene ontology analysis indicated enrichment for immune system and metabolic processes. The protein level of matrix metalloproteinase-7 (MMP-7) showed the strongest differences between control and DKD. Linear regression, adjusted for key co-variates identified 96 proteins those levels correlated with eGFR. We observed a moderate correlation between transcript and protein levels (r = 0.43, p > 2.2e-16).

Conclusions: SOMAson proteomics identified important changes in protein expression in overt and late CKD, these could serve as important biomarkers or therapeutic targets.

Funding: NIDDK Support

Diabetes Mellitus Associates with Differences in the Metabolome of Patients with CKD

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Background: Diabetic Mellitus (DM), the most common cause of chronic kidney disease (CKD), is associated with increased risk of death, cardiovascular disease, and kidney failure, even if the DM is well-controlled. We hypothesized that significant differences exist in the metabolome of CKD patients with well-controlled DM as compared to CKD patients without DM. Unpaired t-tests were performed to compare metabolites between the 2 groups and Spearman correlation was utilized to evaluate the potential correlation between the metabolites and measures of kidney function. MetaboAnalyt (V5.09) was utilized to identify metabolic pathways that differed between those with or without DM.

Results: In the subjects with CKD and DM, the mean(SD) hemoglobin A1c was 7.1(1.8) vs 5.5(1.4) in those with CKD but without DM. Of the 90 metabolites detected by GC-MS, 17 differential metabolites were significantly altered in the CKD with DM vs CKD without DM groups (p < 10). MetaboAnalyt indicated galactose metabolism, glycerolipid metabolism, starch and sucrose metabolism, fructose and mannose degradation, and fatty acid biosynthesis are the top differential pathways between both groups. In those with CKD and DM, citrate correlated with estimated glomerular filtration rate (r=0.42, p=0.031) and homocysteine and glyceral correlated with ACR (r=-0.42, p=0.048 and r=-0.42, p=0.044, respectively).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: We have identified significant differences in the metabolome of CKD patients with well-controlled DM compared to those without DM. Further research is needed to evaluate the potential role of these metabolic pathways and if they contribute to the high morbidity and mortality burden in CKD patients with DM.

Funding: NIDDK Support, Veterans Affairs Support

PO0741

Urinary Biomarkers and ESKD Risk in Persons with Diabetes and CKD

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Background: Tubulointerstitial damage is a feature of diabetic CKD, but correlates poorly with eGFR and albuminuria. Urine biomarkers of kidney tubule health may be independently associated with risk of ESKD in diabetic CKD.

Methods: We identified 1,145 participants from the REGARDS study with baseline eGFR≤60 mL/min/1.73m2 and diabetes. Per case-cohort design, we randomly selected a subcohort of 560. Within the subcohort there were 93 ESKD cases; we further sampled all remaining ESKD cases not included in the subcohort (N=68). These 161 ESKD cases were identified by USRDS linkage over mean follow-up of 4.3±2.7 years. In baseline urine samples, we measured biomarkers of kidney tubule injury (kidney injury molecule-1 [KIM-1]), inflammation and fibrosis (monocyte chemoattractant protein-1 [MCP-1]; chitinase-3-like protein [YKL-40]), function (alpha-1-microglobulin [α1m]; uromodulin [UMOD]), and cell repair (epidermal growth factor [EGF]). Using weighted Cox models, we calculated hazard ratios (HR) of ESKD by baseline biomarkers. LASSO regression identified a subset of biomarkers most strongly associated with ESKD.

Results: Subcohort participants had mean age 70±9 years, 47% male, 53% Black, mean eGFR=40±13 mL/min/1.73m2 and median ACR=33 (IQR 10-213) mg/g. Adjusting for baseline eGFR and albuminuria, higher KIM-1, α1m, and MCP-1 were each associated with higher ESKD risk. Strengths of association were of comparable magnitude to urinary albumin (Table). LASSO regression retained KIM-1 (HR per doubling=1.31 [1.06-1.62]) and α1m (HR per doubling=1.36 [1.08-1.70]) as most strongly associated with ESKD.

Conclusions: Among persons with eGFR≤60 mL/min/1.73m2 and diabetes, urine KIM-1 and α1m captured the influence of kidney tubule health on longitudinal risk of ESKD. These biomarkers may facilitate identification of persons with kidney disease and diabetes at greatest risk of ESKD.

Funding: NIDDK Support

Adjusted HR per doubling of individually-modeled urine biomarkers with ESKD

PO0742

The Potential Value of Urinary Extracellular Vesicles VEGF-A165b in Diagnosis of Diabetic Kidney Disease

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Background: Novel biomarkers are needed for management of diabetic kidney disease (DKD). Urinary extracellular vesicles (uEVs) were used as an ideal resource of biomarkers in kidney disease. VEGF-A165b is a angiogenic factor secreted from podocytes correlated with DKD. The study was aimed to evaluate the diagnostic value of uEVs-VEGF-A165b in DKD.

Methods: Urine samples were collected from 36 patients with T2DM and 12 controls. Subjects with T2DM were stratified into three groups according to UACR, eGFR, and T2DM duration. To isolate exosomes, 25 ml urine was ultracentrifuged to obtain exosomes. Protein was extracted from uEVs and subjected to western blot (WB) for detecting VEGF-A165b. Immunohistochemistry (IHC) staining of VEGF-A165b was performed in kidney paraffin sections from STZ-induced DM rats. ROC curve was used to evaluate the diagnostic value of uEVs-VEGF-A165b in DKD.

Results: Urinary MVs and exosomal VEGF-A165b were higher in T2DM with ACR≥300mg/g than those with ACR<30mg/g. In addition, urinary MVs and VEGF-A165b were higher in patients with ACR≥300mg/g than those with ACR<30mg/g, and exosomal VEGF-A165b levels were lower in patients with ACR<300mg/g than those with ACR≥300mg/g. Furthermore, VEGF-A165b in uEVs increased with the DM duration. VEGF-A165b in patients with duration longer than 10 years were higher than those whose duration was less than 5 years. Correlation analysis revealed eGFR was negatively correlated with urinary MVs and exosomal VEGF-A165b. ROC curve showed that AUC of urinary MVs and exosomal VEGF-A165b for the diagnosis of DKD were 0.9091 and 0.8269. IHC revealed that VEGF-A165b was elevated in renal tubules in STZ-induced DM rats.

Conclusions: A increased level of uEVs-VEGF-A165b was observed in DKD patients and was correlated with decline of eGFR. uEVs-VEGF-A165b may be used as a promising biomarker reflecting the severity of DKD and may suggest a pathological role in the development of the disease.
that lower baseline hemoglobin and HDL-c levels were independent predictors of annual decline in eGFR (OR, 0.69, 95% CI 0.53–0.89, P = 0.005; respectively). Furthermore, time-averaged hemoglobin and HDL-c levels were also independent predictors of annual decline in eGFR (OR, 0.62, 95% CI 0.46–0.82, P = 0.001; OR, 0.97, 95% CI 0.94–0.99, P = 0.007, respectively).

Conclusions: Our findings highlight the important effect of lower hemoglobin and HDL-c levels as independent predictors of rapid decline in eGFR in patients with type 2 diabetes and preserved kidney function.

PO0744
Post-Hospitalization Blood Pressure (BP) and Diabetes (DM) Control and Outcomes in Patients with Diabetic Kidney Disease (DKD)
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Background: DKD is the most common cause of ESKD in the US but because the course of progression is prolonged, research to elucidate risks and effective interventions are difficult. In a high-risk cohort with DKD, do post-hospitalization BP and DM control act as good surrogate markers for outcomes?

Methods: Using Looking Glass, Montefiore Medical Center’s clinical database, we created a cohort of patients with a first discharge in 2016 who met the following criteria: CKD stage 3b or 4 and Proteinuria >300 and <5000mg/gm. Follow up data regarding CKD outcomes up to 2 years, clinic visits, RAASi prescriptions, mean systolic BP (SBP) and HgbA1c levels within 1 year of discharge were collected. Cox proportional hazards was used in adjusted analyses, to estimate the HR of mean SBP and HgbA1c levels, both dichotomized at the 75th percentile, with ESKD incidence or death over 2 years of follow-up.

Results: A total of 572 individuals met DKD criteria and had a first discharge in 2016. The mean age for the cohort was 66.8 years (SD 11.5), 244 (42.7%) were male, 224 (39.3%) were Black, 210 (36.8%) were Hispanic and 33 (5.8%) were White. Sixty-eight percent had a readmission within 1 year of discharge with median time to readmission at 63 days (IQR 22-194). Ninety-three percent of individuals had an outpatient clinic visit and the median number of clinic visits was 30 (IQR 16-47) over 1 year, with median time from discharge to an outpatient visit of 8 days (IQR 4-18). Mean SBP was 138mmHg (SD 22.2) with 26.9% of individuals with a mean SBP >150mmHg during 1 year of follow up. Mean HgbA1c was 8.6 (SD 2.1) with 192 (33.6%) who had HgbA1c >9.7 over 1 year of follow up. Eighty-eight (15.4%) patients died and 99 (17.3%) progressed to ESKD over 2 years of follow up. In models adjusting for age, sex and race/ethnicity there was a positive association between SBP >150 (HR 1.53, 95% CI 1.12-2.09) and HgbA1c>9.7 (HR 1.58 95% CI: 1.16-2.15) and time to ESKD or death.

Conclusions: High mean BP and HgbA1c levels during 1 year post-discharge are associated with adverse outcomes in a cohort of hospitalized patients with DKD. These measures serve as useful surrogate biomarkers to study DKD interventions in a high-risk population.

PO0745
Finerenone Dose-Exposure-UACR Response Analyses of FIDELIO-DKD Phase 3 and the Effect of SGLT-2 Inhibitor Co-Medication
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Background: The mineralocorticoid receptor antagonist finerenone and sodium-glucose cotransporter 2 inhibitors (SGLT2i) have been shown to reduce albuminuria and the risk of kidney failure. The combination of these therapies holds promise to augment nephroprotection through activation of different pathways. Model-based approaches considering individual dosing and exposure and correcting for covariates can support stronger conclusions than stratification for baseline comedication. We developed the popPKPD model described the observed UACR data well, with a additive effects of SGLT2i on top of finerenone.

Methods: A total of 37296 UACR measurements in 5674 patients (549 patients with any recorded SGLT2i use) were analyzed using linear mixed-effects popPKPD modelling considering individual drug exposure. The model was used to characterize the trajectory of UACR progression over time, the exposure-response relationship of finerenone on UACR and the effect of SGLT2i.

Results: The popPKPD model described the observed UACR data well, with a proportional UACR progression over time, an indirect power model for the exposure-response relationship of finerenone and a constant effect of SGLT2i use. SGLT2i use did not modify finerenone efficacy (P=0.25) and indicated with 95% confidence that finerenone is at least 94.1% as efficacious in reducing in UACR in patients using SGLT2i compared to placebo.

Conclusions: We successfully developed a popPKPD model that adequately described the dose-exposure-response of finerenone on UACR. The results demonstrate additive effects of SGLT2i on top of finerenone.

Funding: Commercial Support - Bayer AG
Potential to be an effective tool for trial enrichment.

KidneyIntelX platform in participants in the CANVAS trial with UACR <300 mg/g and type 2 diabetes and normo- or microalbuminuria. We sought to assess the value of KidneyIntelX for future clinical trials in patients with high levels of albuminuria to increase event rates. KidneyIntelX is a composite risk score that incorporates both clinical data and plasma biomarkers.

Methods: Plasma TNFR-1, TNFR-2, and KIM-1 were measured on the Renalytix KidneyIntelX platform in participants in the CANVAS trial with UACR <300 mg/g (n=3277). A logistic regression model incorporating the 3 biomarkers and clinical variables was applied to obtain the predicted probabilities for a composite kidney outcome (doubling of eGFR, death, or kidney replacement therapy). We analyzed the effects of CANA on time to first occurrence of doubling of serum creatinine (SCr) and end-stage kidney disease (ESKD) in subgroups by baseline estimated glomerular filtration rate (eGFR; <45, 45-60, and >60 mL/min/1.73 m²), with consistent benefits observed irrespective of baseline eGFR.

Results: A total of 14,543 participants from the CANVAS Program (N = 10,142) and CREDiTE (N = 4,401) were included. Among participants with baseline eGFR measurements, 1919 (13.2%) had eGFR <45 mL/min/1.73 m², 2972 (20.4%) had eGFR 45-60 mL/min/1.73 m², and 9649 (66.3%) had eGFR >60 mL/min/1.73 m². CANA delayed the time to first doubling of SCr event and first ESKD event relative to placebo (PBO). Compared with PBO, CANA reduced the risk of doubling SCr (HR, 0.58; 95% CI, 0.55–0.87), irrespective of baseline eGFR, consistently across eGFR subgroups (interaction P = 0.78; Figure 2). Reduced risk of ESKD was also seen with CANA versus PBO (HR, 0.69; 95% CI, 0.55–0.87), irrespective of baseline eGFR (interaction P = 0.86).

Conclusions: In patients with T2DM and high CV risk or nephropathy, CANA reduced the risk of doubling of SCr and ESKD, with consistent benefits observed across baseline chronic kidney disease stage, including those with preserved eGFR >60 mL/min/1.73 m².

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
PO0749
Phase Ib Study of the Soluble Guanylate Cyclase Activator BI 685509 in Patients with Diabetic Kidney Disease
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Background: Soluble guanylate cyclase (sGC) plays a key role in the kidney nitric oxide–cyclic guanosine monophosphate (NO-cGMP) pathway. Increased albuminuria is associated with kidney function loss. The NO-independent sGC activator BI 685509 lowers albuminuria in experimental models. This Phase Ib study (NCT03165227) assessed the safety and efficacy of BI 685509 in patients with diabetic kidney disease and albuminuria.

Methods: This placebo (PBO)-controlled, multiple dose study enrolled patients with type 1 or type 2 diabetes, estimated glomerular filtration rate (eGFR) 20–75 mL/min/1.73m² and urinary albumin to creatinine ratio (UACR) 200–3500 mg/g. Patients (N=74) were randomised to three active dose groups receiving oral BI 685509 (tested doses after tolerability were BI 690517 3/10/40 mg), and urine albumin creatinine ratio (UACR) (UACR₀) and 10-h (UACR₁₀) (PBO, 3 mg QD and 3 mg QD only) urine. Results: At baseline, median eGFR was 47.0 mL/min/1.73m² and median UACR was 641.5 mg/g, although this varied between groups. Drug-related adverse events (AEs) occurred in 12 patients (16.2%; BI 685509 15.3%, PBO 20.0%); the most frequent were constipation and hyperkalaemia (both 3.7%, n=2). Treatment was only prematurely discontinued in 5 patients (9.3%; BI 690517 n=4; PBO n=1), 2 cases (3.7%)

Proportion of responders (≥20% decrease from baseline in UACR)

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PO0752
A Comparison of the Renal Composite Outcome Between Sodium-Glucose Cotransporter 2 Inhibitors and Glucagon-Like Peptide 1 Receptor Agonists in Japanese Diabetes Patients
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Conclusions: By this retrospective study, SGLT2 treatment has shown more preferable influence on the change of eGFR than GLP1Ra treatment in Japanese T2DM patients.

PO0753
Role of β2-Adrenergic Receptor Agonists in the Treatment of Diabetic Nephropathy
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Background: Diabetes is the leading cause of end stage kidney disease (ESKD) and affects podocytes. We previously showed in cells and mice that pharmacological activation of mitochondrial biogenesis by the long-acting β2-AR agonist formoterol contributes to podocyte recovery from injury.

Methods: We examined the association between COPD, in which the vast majority of patients receive β2-AR agonists, and CKD progression in a national cohort created from patient records within the Veterans Health Administration (VHA). Cohort members were defined based upon ICD-9 codes (ICD-9: 416.8, 416.9, 490.x-505.x, 506.4, 508.1, 7.0 % in GLP1Ra treated patients (p = 0.063 caliper and no replacement.

Conclusions: By this retrospective study, SGLT2 treatment has shown more preferable influence on the change of eGFR than GLP1Ra treatment in Japanese T2DM patients.

PO0754
Comparative Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Serum Electrolyte Levels in Patients with Type 2 Diabetes: A Network Meta-Analysis of Randomized Controlled Trials
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Background: Previous studies have reported that sodium-glucose co-transporter 2 (SGLT2) inhibitors (SGLT2is) affect serum electrolytes levels, especially magnesium, sodium, potassium, phosphate, and calcium. We performed two random-effects pairwise analysis and network meta-analyses to calculate the weighted mean difference (WMD) and 95% confidence intervals (CI).

Results: In total, we included 26 RCTs involving 28,943 T2D patients with 6 SGLT2is. Compared with the placebo, SGLT2is were significantly associated with elevations in serum sodium by 0.77 mmol/L (95% CI, 0.60 to 0.94 mmol/L) and serum potassium by 0.12 mmol/L (95% CI, 0.01 to 0.23 mmol/L). Our network meta-analysis showed no evidence of significantly superior efficacy of any specific SGLT2 inhibitor over the others, although dapagliflozin was associated with a larger magnitude in significant increase usage in serum magnesium associated with dapagliflozin compared with placebo (1.59 mmol/L, 95% CI 0.75 to 2.43 mmol/L). Similarly, no statistically detectable differences were evident between any two of SGLT2 inhibitors on serum levels of other electrolytes.

Conclusions: SGLT2is caused significantly increased serum magnesium and potassium levels, consistent with a class effect of SGLT2 inhibition. However, further investigation on more data for long-term efficacy and safety in T2D patients with different clinical phenotypes are needed for further investigation.

PO0755
Association of Fibrate Use with Cardiovascular Disease Mortality Across CKD Stages
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Background: Elevated serum lipids are risk factors for cardiovascular disease (CVD) in the general population and common first-line treatment includes fenofibrate for those with high triglycerides (TG) or low high-density lipoproteins (HDL). Recent studies have suggested that fibrates may be beneficial for CVD death outcomes in those with chronic kidney disease (CKD). Yet how the relationship between fibrates and early CVD death differs across CKD stages remains uncertain.

Methods: In male Veterans with adverse lipid levels (TG ≥150 mg/dL or HDL ≤40 mg/dL), initial fibrate users and non-users were matched on CKD stage, TG and HDL levels. The cohort of 233,082 patients were followed until 2014. We used inverse probability weighting in the fitting of marginal structural models to adjust for time-varying confounding and informative censoring in investigating the average direct effect of fibrate use (reference: non-use), with 24-month cardiovascular mortality. Models were stratified by CKD stage.

Results: Patients were a mean±SD age of 62±12 years, and 26% of patients had CKD or end-stage renal disease (ESRD). The median[IQR] of baseline TG and HDL were 310 [220,436], and 34 [30, 40] mg/dL, respectively. Across all baseline CKD stages, the use of fibrates was associated with lower risks in CVD death compared with non-users. These associations gradually declined across advancing CKD stages, where patients with ESRD on renal replacement therapy had the lowest observed risks (Hazard Ratio[95%CI]: 0.54[0.34, 0.87] [Figure 1].

Conclusions: Fibrates use was associated with lower CVD mortality. These risks varied across CKD stage, but those with ESRD tended to have better CVD death outcomes. Additional studies are imperative to better tailor lipid therapy and management against adverse outcomes among the late-stage CKD and ESRD patients.

Funding: Veterans Affairs Support
PO0756

Effect of CKD Stage on Myocardial Infarction Risk with Niacin Use in Male Veterans

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Background: Niacin is a lipid therapy shown to have cardio-protective effects, particularly in those with high triglyceride (TG) and low high-density lipoprotein (HDL) levels. But, in chronic kidney disease (CKD) patients who have elevated risk of cardiovascular risk and altered lipid levels, it remains unclear if CKD stage impacts these associations.

Methods: In males with worse lipid levels (TGr150 mg/dL or HDLr40 mg/dL), we matched patients with an incident niacin prescription to non-niacin users on CKD stage, TG and HDL levels. In this study of 336,178 niacin users and non-users, we evaluated the relationship of time-varying niacin use with 24-month myocardial infarction (MI) hospitalization. Cox models included adjustment for time-varying covariates and were stratified by baseline CKD stage.

Results: Patients were mean 64 years old, with a medianIQR of TG and HDL of 203[143, 297] and 34[29, 39] mg/dL, respectively. In unadjusted models, non-CKD, CKD 4/5 and end-stage renal disease (ESRD) niacin users had higher risks of a MI hospitalization, yet CKD 3A-3B patients had null risks, compared with non-users. With adjustment for case-mix variables, including comorbidities, we observed a linear relationship across baseline CKD stages, where risks progressively increased with worse stage. Non-CKD niacin users had lowest risks of 24-month MI hospitalization, while both CKD 4/5 and ESRD patients trended towards elevated risks of event. The relationships between niacin use and MI hospitalization remained the same with adjustment for laboratory and other lipids.

Conclusions: In time-varying analyses, niacin use was associated with lower risks of 24-month MI hospitalization in non-CKD and CKD 3A patients. The risks of MI hospitalization were progressively elevated with worse CKD stages. Additional studies are needed to further examine the relationship between lipid modulating therapies in the context of CKD patients.

Funding: Veterans Affairs Support

PO0757

Advantages of Metformin for the Prevention and Mitigation of Diabetic Foot Ulcer in Diabetic Kidney Disease from a Large-Scale, Real-World Cohort

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Background: Diabetic foot ulcer (DFU) and diabetic kidney disease (DKD) are diabetes-related microvascular complications strongly correlated with high morbidity and mortality. Metformin potentially confers a wound-healing advantage, although there are no well-established evidence. We first time investigated the effect of metformin on DFU among large retrospective cohort of DKD.

Methods: This retrospective cohort study enrolled DKD patients from two South Korean tertiary-referral centers. Primary outcomes were all-cause mortality and DFU events; secondary outcomes included hospitalization, amputation, composite of amputation or vascular intervention, and Wagner Grade >3. Multivariate cox analysis and Propensity score matching (PSM) was used to balance baseline intergroup differences between metformin users and metformin non-users.

Results: Among 10,832 patients (4,748 metformin non-users), the 117.5±6.9 months follow-up period, all-cause mortality rate and DFU incidence were, 37.1%, and 5.2%, respectively. Fully adjusted multivariate Cox analysis showed that metformin users had a lower all-cause mortality (adjusted hazard ratio 0.63; 95% confidence interval 0.58–0.68; p<0.001) and DFU events (0.39; 0.31–0.8; p<0.001, Table). After PSM, metformin users showed lower all-cause mortality (0.61; 0.55–0.67; p<0.001), DFU events (0.42; 0.32 –0.56; p<0.001), and secondary outcomes (hospitalization, amputation, composite of amputation or vascular intervention, and DFU with Wagner Grade >3, Table).

Conclusions: Metformin therapy in DKD patient can lower all-cause mortality, DFU incidence, and DFU progression.

Survival analysis of primary and secondary outcomes

PO0758

Gaps in CKD Awareness Among People with Type 2 Diabetes

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Background: Diabetes is one of the most common causes of chronic kidney disease (CKD) in adults, with around 1 in 3 people with diabetes also living with CKD. Clinical guidelines recommend annual screenings of urinary albumin and glomerular filtration rate for people with type 2 diabetes (T2D). Previous studies have identified low awareness, testing and diagnosis of CKD among people with T2D and their healthcare providers (HCP). By drawing comparisons to cardiovascular disease (CVD), the present study aimed to assess awareness of CKD, renoprotective diabetes therapies, and kidney health metrics among people with T2D.

Methods: In February 2021, 1021 people with T2D from the dQ&A Patient Panel responded to an online survey assessing perceptions, knowledge, HCP engagement, and lifestyle behaviors related to CKD and CVD. Respondents received $10 USD for completing the survey. Data was collected with Qualtrics, prepared with IBM SPSS, and analyzed in MarketSight.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
**Results:** Awareness of the link between T2D and CKD was lower than awareness of the risk between T2D and CVD; 57% of respondents strongly agreed that having T2D increases the risk of CKD, compared to 63% who strongly agreed that T2D increases the risk of CVD. The percentage of respondents who often consider their personal risk of CKD (19%) was also lower than for CVD (26%). Awareness of renoprotective and cardioprotective therapies was low overall. While 37% were aware that some T2D drugs are cardioprotective, only 22% were aware of renoprotective benefits. Respondents on SGLT-2 inhibitors or GLP-1 agonists were more likely to be highly aware of their cardioprotective benefits than their renoprotective benefits (52% vs. 50% for SGLT-2 users, 45% vs. 31% for GLP-1 users). Knowledge of personal metrics for renal health indicators, eGFR (38%), and uACR (26%), lagged behind knowledge of diabetes and CVD metrics: weight (100%), A1C (98%), blood pressure (94%), and cholesterol (75%). Only 41% of respondents had discussed their CKD risk with a diabetes-related HCP, but those who had were more likely to be aware of CKD risks and therapies.

**Conclusions:** This data highlights a gap between T2D patients’ awareness of CKD risks and protective therapies and those of CVD. To prevent CKD and improve outcomes, this study emphasizes the need for better patient education on CKD’s connection to T2D.

**Funding:** Commercial Support - AstraZeneca

**PO0759**

**Feature Selection and Machine Learning Model for Predicting Diabetic Kidney Disease Risk in Asians**

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**Background:** Machine learning (ML) techniques may improve disease prediction and interpretability of regression models by identifying the most relevant features in multi-dimensional data. We evaluated the ability of various ML classifiers for feature identification and improving the prediction accuracy of diabetic kidney disease (DKD).

**Methods:** We utilized longitudinal data from 1364 Chinese, Malay and Indian participants aged 40-80 years with diabetes but free of DKD who attended the baseline visit of the Singapore epidemiology of Eye Diseases Study in 2004-2011 and were followed up for 6 years (2011-2017). Incident DKD (n=162) was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m² or 25% decrease in eGFR at follow-up. We evaluated 339 features including demographic/clinical, retinal imaging, genetic and serum metabolomics profile and tested nine ML algorithms along with feature selection (gradient boosting decision tree, elastic net, random forest, support vector machine, neural network, LASSO etc.). The performance of the best ML model based on feature selection (AUC, sensitivity and specificity of 0.852, 80% and 81%, respectively) was compared to logistic regression (LR) and traditional risk factors using the area under the receiver operating characteristic curve (AUC), sensitivity and specificity.

**Results:** The best performing model was a combination of Recursive feature elimination (RFE) for variable selection and Elastic Net (EN) using 15 predictors from demographic/clinical + metabolite set with AUC, sensitivity and specificity of 0.852, 83.0% and 73.5% compared to 0.796, 83.0% and 61.8% by LR. The top-15 predictors of DKD risk included seven risk factors and eight metabolites: age, antidiabetic medication use, presence of hypertension, diabetic retinopathy, higher levels of systolic blood pressure, HbA1c, lower levels of eGFR, higher levels of triglycerides in IDL, phospholipids in chylomicrons and medium LDL, total cholesterol in chylomicrons and very small VLDL, medium LDL, cholesterol esters in very large HDL and lower levels of DHA, lactate and acetate.

**Conclusions:** ML together with feature selection improved prediction accuracy of DKD risk in the general population with diabetes and identified novel risk factors including metabolites.

**Funding:** Government Support - Non-U.S.

**PO0760**

**Risk Score to Predict CKD Among Mexican Individuals with Diabetes Mellitus**

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**Background:** The two major causes of CKD are type 2 diabetes (T2D) & hypertension, which are responsible for up to two-thirds of the cases. More than half of patients in Mexico with incident ESRD have an underlying diagnosis of T2D. Some prediction models have been developed for the purposes of screening CKD & its progression. However, their generalizability to the Mexican population is not known, & few have been validated in different populations & rarely in LMIC. We aimed to develop & validate a lab and office-based risk prediction score for CKD among Mexican patients with T2D.

**Methods:** The prospective cohort consisted of 105,310 patients enrolled in the Integral Management of Diabetes by Stages program. 18,148 patients were randomly assigned to the training group & testing sets on an 80:20 ratio. Logistic regression models were used to assess risk factors for CKD. A stepwise selection process was performed to determine the best predictive equations.
PO0762
Using Machine Learning to Predict CKD upon Type 2 Diabetes Mellitus Diagnosis
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Background: Chronic kidney disease (CKD) accounts for the majority of increased risk of mortality for diabetic patients, manifesting in approximately half of patients diagnosed with type 2 diabetes mellitus (T2DM). Although increased screening frequency can avoid missed diagnoses, this is not implemented uniformly. We developed and retrospectively validated a machine learning algorithm (MLA) to predict CKD within 5 years upon T2DM diagnosis.

Methods: Electronic health records (EHR) data of 171,201 recently diagnosed T2DM patients (age ≥18) was extracted from a proprietary database of >700 healthcare sites across the US between 2007-2020. A random forest MLA was developed to assess risk of Stage 3+ CKD (CKD 3+) in T2DM patients using EHR data collected in the year prior to T2DM diagnosis. International Classification of Diseases codes (ICD-9 and ICD-10) were used to identify T2DM and CKD 3+ patients. The MLA was tested on a hold-out test set of 42,801 patients as well as a separate external validation dataset. The Centers for Disease Control and Prevention (CDC) CKD risk score was used as a comparator. Performance of the MLA and CDC CKD risk score were assessed on the hold-out test set and the external validation dataset via area under the receiver operating characteristic curve (AUROC).

Results: On a hold-out test set and an external validation dataset, the MLA outperformed the CDC CKD risk score when analyzed for prediction of CKD 3+ in recently diagnosed T2DM patients (Fig 1).

Conclusions: This retrospective study shows that a MLA can provide timely predictions of CKD among recently-diagnosed T2DM patients. Early detection of CKD in diabetic patients may enable therapeutic interventions, lifestyle changes, prevention of progression, and reduction of dialysis dependency, as well as healthcare costs.

Figure 1. Area under receiving operating characteristic curves for the machine learning algorithm (MLA) and CDC CKD risk model (CDC) for Stage 3+ diabetic CKD predictions performed on the hold-out test set and external validation dataset.

PO0763
Contemporary CKD Incidence Rates in Diabetes by Race/Ethnicity, Sex, and Age
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Background: Diabetes is the most common cause of chronic kidney disease (CKD), yet little is known about current CKD incidence rates and demographic predictors in these patients. The study aim was to estimate CKD incidence over time in adults with diabetes treated in two large healthcare systems.

Methods: The Center for Kidney Disease Research, Education, and Hope registry data is curated from electronic health records at Providence St. Joseph Health and University of California Los Angeles Health. Age, sex, and race/ethnicity adjusted CKD incidence rates were calculated over two-year time periods covering 2014–2019. CKD was identified by ≥2 laboratory measures (estimated glomerular filtration rate <60 mL/min/1.73m^2, urine albumin/creatinine ratio ≥30 mg/g, urine protein/creatinine ratio ≥150 mg/g) a90 days apart or administrative codes. Diabetes was identified by laboratory measures (HbA1c, blood glucose), use of glucose-lowering medication, or administrative codes.

Results: The overall CKD incidence (95% CI) rate in diabetes declined from 109.1 cases/1000 person-years (106.1–112.1) in 2015–14, to 102.2 cases/1000 person-years (101.7–106.8) in 2016–17, to 96.0 cases/1000 person-years (93.5–98.5) in 2018–19 (p<0.001 for trend, Figure). CKD incidence only declined in Whites over these time periods. CKD incidence rates were lowest in Whites and Asians and highest in American Indians/Alaska Natives (AI/AN) and Native Hawaiians/Pacific Islanders (NHIPI). CKD incidence rates were higher in men than women and increased with age.

Conclusions: CKD incidence has recently declined in patients with diabetes overall, and specifically among Whites. AI/AN and NHIPI patients with diabetes had the highest rates of CKD incidence. Studies of targeted strategies in high-risk populations will be important to prevent CKD.

Funding: Other U.S. Government Support

PO0764
Renal Oxygenation, Perfusion, and Blood Flow in Type 1 Diabetes with Albuminuria Compared with Healthy Controls
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Background: The mechanisms behind the progression of diabetic kidney disease in type 1 diabetes (T1D) are poorly understood. We aimed to evaluate the renal oxygenation, perfusion and blood flow using magnetic resonance imaging (MRI) in persons with T1D and albuminuria and in healthy controls (CONs).

Methods: Cross-sectional study in 15 persons with T1D and albuminuria compared with 15 CONs. MRI (3 Tesla Philips Scanner) was used to assess renal R^2 (a low value corresponds to a high tissue oxygenation), renal perfusion (arterial spin labelling) and renal artery flow (phase contrast imaging). Differences in outcomes between groups and associations were adjusted for age and sex.
Results: There was no difference between groups in the mean (SD) age (T1D: 58 (14) years; CONs: 56 (15) years; p=0.82) or in the gender distribution (33% female in both groups, p<1). Participants with T1D had a mean duration of diabetes of 38 (18) years, a higher median urinary albumin creatinine ratio (UACR) (T1D: 46 (IQR 21-58) mg/g; CONs: 4 (3-5) mg/g; p<0.0001) and a lower mean estimated glomerular filtration rate (eGFR) (T1D: 73 (32) ml/min/1.73m²; CONs: 88 (15) ml/min/1.73m²; p=0.12), although not significantly for the latter. There were no significant differences between groups in renal cortical R2* (T1D: 22.2 (5.0) s⁻¹; CONs: 22.1 (2.6); p=0.02) or medullary R2* (T1D: 33.9 (6.1) s⁻¹; CONs: 37.7 (4.6); p=0.14). Renal cortical perfusion was lower in T1D than in CONs (T1D: 163 (40) ml/100g/min; CONs: 224 (49) ml/100g/min; p<0.01). There was no difference in the medullary perfusion (T1D: 43 (11) ml/100g/min; p=0.92). Renal artery blood flow was lower in T1D than in CONs (T1D: 360 (130) ml/min; CONs: 430 (113) ml/min; p=0.01). A lower renal cortical perfusion was associated with a higher UACR (p<0.01) but not with eGFR (p=0.25). A lower renal artery blood flow was associated with a higher UACR (p=0.01) and with a lower eGFR (p=0.01).

Conclusions: Renal cortical perfusion and artery blood flow were lower in persons with T1D and albuminuria than in healthy controls, confirming findings from previous studies. Impaired renal cortical perfusion and blood flow were associated with impaired renal function.

Funding: Private Foundation Support

PO0765

CKD-Associated Frailty Risk Trajectory over Time Among Patients with Newly Diagnosed Diabetes Mellitus: A Population-Based Cohort Analysis

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Background: Patients with chronic kidney disease (CKD) and diabetes mellitus (DM) are at high risk of frailty and adverse functional outcomes. CKD likely further aggravates the risk of frailty among patients with DM. However, whether the timing of CKD onset relative to incident DM affects the subsequent risk of frailty over time remains unclear.

Methods: We recruited patients with newly diagnosed DM but without frailty from a population-based cohort (n=488,458), dividing them into those without CKD throughout study period (7 years), with CKD prior to DM diagnosis, and with CKD years after incident DM. Their risk of frailty, based on a modified FrAIL scale, were examined. We used Cox proportional hazard regression to calculate CKD-associated risk of frailty, accounting for demographic, morbidity, medication, and prior hospitalization, followed by multiple regression analyses to calculate the annual probability of developing frailty starting immediately after incident DM.

Results: Among the enrolled patients with newly diagnosed DM, 80.8% (n=394,673) had no CKD throughout study period, while 3.3% (n=16,017) and 15.9% (n=77,748) had CKD prior to and after DM, respectively. Cox proportional hazard regression showed that newly diagnosed diabetic patients with CKD after DM had a significantly higher risk of developing frailty than those without CKD throughout study period (hazard ratio [HR] 1.649, 95% confidence interval [CI] 1.45 – 1.88), while those with CKD before DM had a higher but rather modest risk (HR 1.200, 95% CI 1.11 – 1.29). The annual probability of frailty occurrence was highest early during the course of DM and decreased slowly but gradually among CKD after DM group, while that of frailty remained stable throughout the study period among CKD prior to DM group (Figure).

Conclusions: The risk of CKD-related frailty exhibited temporal changes in patients with newly diagnosed DM. It would be prudent to carefully select the timing of providing frailty-oriented care in these patients.

PO0766

Understanding Patient Receptivity Towards Receipt of Prognostic Risk Score for Diabetic Kidney Disease

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Background: Few studies examined the attitudes of patients with diabetic kidney disease (DKD) on risk stratification tools. An intrinsic barrier to undertake a risk stratification test is knowledge, awareness, and desire to know the risk of kidney disease. This study aimed at exploring the baseline knowledge about kidney disease category and type 2 diabetes mellitus (T2DM) as a major contributing factor, alongside possible motivators, and the patient’s receptivity towards risk score delivery of KidneyIntelX, a novel prognostic test that assesses the risk of kidney disease progression over the next 5 years in patients with DKD stages 1-3.

Methods: In May 2021, we contacted a subset of patients with stages 1-3 DKD and T2DM at one primary care site at the Mount Sinai Health System to communicate results obtained on their KidneyIntelX test and we administered a survey. We assessed patient knowledge about the test, their receptivity, and attitude on the usefulness of the test to improve their kidney health.

Results: A subset of patients (n=37) tested with KidneyIntelX in May 2021 were successfully contacted by the APRN on the DKD Care Navigation Team at Mount Sinai and completed the post-test survey. The majority of patients (70%) were aware diabetes is a contributing factor to kidney disease. 73% were unfamiliar with the prognostic test goals, while 27% were provided with an explanation by their physician. 89% were appreciative of the post-test call, and receiving risk scores through a post-test call were helpful for all patients (60% helpful, 40% very helpful) in improving their understanding of kidney health. Additionally, all patients were motivated to implement lifestyle changes to improve kidney health, and 63% desired educational content on diabetes, kidney disease and diet (Table).

Conclusions: Dedicated phone calls from the Care Navigation Team after KidneyIntelX testing enhanced patient understanding about kidney disease and revealed substantial motivation to take appropriate actions and receive further education for their kidney health.

Funding: Commercial Support - Renalytx, Clinical Revenue Support

PO0767

Adequacy of Laboratory Monitoring of CKD for Diabetic Patients Empaneled with Primary Care

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Background: Studies have shown poor adherence to chronic kidney disease (CKD) guideline adherence in primary care, contributing to late referral to nephrology and suboptimal clinical outcomes. We sought to assess the performance of our health system in adhering to laboratory monitoring guidelines for diabetic patients with laboratory confirmed CKD.

Methods: We identified all adult patients empaneled in a regional health system who had creatinine and urinary albumin measurements between 2014-2016 excluding pregnant patients, as well as those transplanted or already on dialysis or hospice and crossed this cohort with our existing diabetic patient registry. CKD defined based on calculated GFR and CKD risk defined per the Kidney Disease Improving Global Outcomes (KDIGO) guidelines. We defined laboratory monitoring compliance as meeting the number of chronic kidney disease (DKD) criteria, 13966 (50%) were missing a measure of albuminuria, 8030 (28.7%) had moderate risk patients was adequate but the patients in the higher risk categories had worse guideline adherence. Better decision support systems are needed to improve kidney care for this high risk population.

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PO0768
Characteristics of Patients with CKD and Diabetes by Use of ACE Inhibitors or ARBs
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Background: The Center for Kidney Disease Research, Education and Hope (CURE-CKD) registry is curated from electronic health records (EHR) of >3.4 million patients with or at-risk of chronic kidney disease (CKD) at two, large healthcare systems. The study aim was to compare demographic and clinical characteristics of patients with CKD and diabetes (DM) by use of angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor II blockers (ARBs).

Methods: Demographic and clinical characteristics of adults (≥20 years) with CKD and DM (guideline-based laboratory criteria, use of glucose-lowering agents, administrative codes) were described for the time periods of 2015-17 and 2018-20. Pearson's chi-squared (categorical), Student's t-test (normal, continuous), or Mann-Whitney U (non-normal, continuous) analyses determined differences between users and non-users of ACEI or ARB defined by prescriptions in the EHR.

Results: ACEI/ARBs were used in 59% and 58% of patients with CKD and DM in 2015-17 and 2018-20, respectively. Adults >60 years old, men, and White/non-LatinX individuals more commonly used ACEIs/ARBs (Table). In both time periods estimated glomerular filtration rate (eGFR) was significantly lower and systolic blood pressure was significantly higher in ACEI/ARB users versus non-users. The urine albumin-to-creatinine ratio did not differ by ACEI/ARB use. SGLT2 inhibitors and GLP-1 receptor agonists were more commonly given to ACEi/ARB users but prescribing of these agents was rare overall.

Conclusions: ACEi/ARB use remains sub-optimal in patients with CKD and DM and differences in use were influenced by age, sex, race/ethnicity, and use of non-pharmacological interventions (exercise, nutrition, telehealth, educational, health worker, and cultural) to achieve improved glycaemic control, and reduction of clinical or infection-related mortality risk. However, it is unclear whether different HbA1c levels affect mortality risk of cause-specific deaths or not.

PO0769
Impact of Non-Pharmacological Interventions in Indigenous Populations with Diabetes Mellitus on Cardiovascular and Kidney Disease: A Scoping Review Using the RE-AIM Framework
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Background: Diabetes mellitus is a common cause of mortality from cardiovascular (CV) and kidney diseases. This scoping review utilized the RE-AIM (reach, efficacy, adoption, implementation, and maintenance) framework to assess the impact of non-pharmacological interventions on CV and kidney health outcomes (KHO) in Indigenous populations.

Methods: We searched Medline, Embase, Cochrane Library, CINAHL, Web of Science, PsycINFO and other grey literature to identify studies that used non-pharmacological interventions (exercise, nutrition, telehealth, educational, health worker, and cultural) to achieve improved glycaemic control, and reduction of clinical or laboratory markers of CV or KHO in Indigenous communities.

Results: Our search yielded 7,692 studies, from which 35 studies were selected. Culturally appropriate interventions were mostly utilized (77.1%); telehealth programs were least utilized (8.6%). Clinical and laboratory indices of CV and KHO were infrequently assessed (KHO assessed in 40%); improved kidney function was reported in 10.5% of health worker interventions. (Table 1). Reporting of items of the RE-AIM framework showed that internal validity items were more frequently reported than those of external validity: reach (60%), efficacy (52.1%), adoption (46.1%), implementation (41.9%), and maintenance (37.2%) (Table 2).

Table 1: Characteristics of patients with CKD and diabetes by use of ACE inhibitors or ARBs

Table 2: Proportion of diabetes interventions in Indigenous populations reporting the 21 items of RE-AIM framework

PO0770
Cause-Specific Death Differed Based on HbA1c Levels in Hemodialysis Patients with Diabetest
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Background: Adequate glycemic control with achieving target HbA1c is critical in hemodialysis (HD) patients with diabetes and HbA1c level is closely associated with mortality risk. However, it is unclear whether different HbA1c levels affect mortality risk of cause-specific deaths or not.

Methods: A total 24,620 maintenance HD patients with diabetes were enrolled from the electronic health record-based registry data of Korean Society of Nephrology. Plasma HbA1c level was measured at the time of the study data entry, and patients were classified into six categories according to the HbA1c level (≤5.5%, 5.6-6.5%, 6.6-7.5%, 7.6-8.5%, 8.6%-9.5%, and >9.5%). In multivariable Cox regression analysis, we examined the relationship between HbA1c level and the cause-specific death (cardiovascular, infection, non-cardiovascular, non-infection).

Results: Compared with the group with HbA1c 6.6-7.5%, the risk of all-cause mortality in each group tended to increase as HbA1c level rose; 0.99-fold (95% confidence interval [CI], 0.91-1.07) in HbA1c 5.6-6.5%, 1.08-fold (95% CI, 0.99-1.19) in HbA1c 7.6-8.5%, 95% CI, 0.99-1.19), 1.26-fold in HbA1c 8.6-9.5% (95% CI, 1.12-1.42), and 1.57-fold in HbA1c >9.5% (95% CI, 1.39-1.78). In cause-specific death analysis, cardiovascular-related mortality risk showed similar hazard ratio pattern like all-cause mortality risk the adjusted risk for each group were 0.96 (95% CI, 0.84-1.09), 1.17 (95% CI, 1.01-1.35), 1.53 (95% CI, 1.29-1.82) and 1.57-fold (95% CI, 1.30-1.91) for HbA1c 5.6-6.5%, HbA1c 7.6-8.5%, HbA1c 8.6-9.5% and HbA1c >9.5%, respectively. However, infection-related mortality risk did not significantly increase across HbA1c strata except the risk in HbA1c >9.5% group (HR, 1.71; 95% CI, 1.29-2.26). Non-cardiovascular related/non-infection related mortality risk did not increase in all six HbA1c categories.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: All-cause mortality and cause-specific mortality risk were different across groups to HbA1c levels in the patients who were undergoing HD with diabetes. Furthermore, this study showed that cardiovascular mortality risk needs to be assessed in priority than infection or non-cardiovascular related/non-infection mortality risk when HbA1c level is increased in HD patients with diabetes.

PO0771
In-Hospital Outcomes in Diabetic Ketaoidosis and Impaired Kidney Function
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Background: Diabetes Mellitus is one of the most common causes of End-Stage Renal Disease (ESRD) in the United States. In this study, we used the National Inpatient Sample (NIS) database to compare the outcomes of Diabetic Ketoacidosis (DKA) among patients with Chronic Kidney Disease (CKD) and ESRD to DKA with normal creatinine.

Methods: We performed a retrospective study using the 2016 NIS, which comprises 20% of hospital discharges for that year. We included patients aged 18 or older admitted to the hospital with a principal diagnosis of DKA. Diagnosis data were obtained by utilizing ICD 10 CM codes. A multivariate logistic regression model was used to analyze the effect of ESRD on mortality and intubation rate. Linear regression was used to analyze the impact of ESRD on length of stay. All outcomes were adjusted to age, sex, race, insurance status, Elixhauser Comorbidity index, hospital location, and characteristics.

Results: A total of 184,050 patients were included in the study, of which 12,605 had CKD and 6025 had ESRD. The mean age was 44.1 years (SD 12.8), and 51.9 % of patients were female in ESRD. The mean length of stay was 5.2 days for the ESRD group and 3.1 days for DKA with the normal creatinine group. The adjusted length of stay was 0.9-day longer (p=0.001), and the adjusted cost of hospitalization was 13,684 US dollars more expensive in the ESRD group. Adjusted Odds Ratio for mortality 1.2 (CI 0.58-2.4, p = 0.61), and intubation 0.95 (CI 0.64-1.4, p = 0.81) were not statistically significant.

Conclusions: DKA in ESRD patients was associated with increased length of stay and cost of hospitalization. Further studies looking into factors contributing to the longer length of stay in the ESRD population will help in improving outcomes and significant cost reduction in taking care of these patients.

Table 1

*Adjusted for Age, sex, race, elixhauser comorbidity index, insurance status hospital location and characteristics.

PO0772
Hypoglycemia and Glycemic Status Ascertained by Continuous Glucose Monitoring vs. Blood Glucose in a Prospective Hemodialysis Cohort

Background: In non-CKD patients, evidence shows continuous glucose monitoring (CGM) provides convenient, automated, and less invasive measurements vs. conventional self-monitoring of blood glucose, and leads to reduced hypo-/hyperglycemia and glycemic variability (hypoglycemia risk factor), as well as increased time in goal glucose range and quality of life. However, accuracy of CGM interstitial glucose vs. gold-standard blood glucose measures has not been well-studied in dialysis patients.

Methods: In 18 HD patients with diabetes hospitalized during 10/2020-5/2021, we conducted simultaneous protocolized glucose measurements using 1) Dexcom G6 CGM devices vs. 2) blood glucose levels using capillary fingertip or venous blood glucose, with the latter measured 4 times per day (before each meal and at night), plus every 30 minutes during HD. We examined the correlation of averaged CGM and blood glucose levels, and compared the prevalence of hypoglycemia detected by these methods.

Results: During the overall assessment period, Pearson and Spearman correlations for averaged CGM vs. blood glucose were 0.65 and 0.66; similar correlations were observed when stratified by HD vs. non-HD periods. A similar proportion of patients were identified as having American Diabetes Association (ADA) Level 1 Hypoglycemia (<70mg/dl) using CGM and blood glucose (33%). In contrast, a higher proportion of patients were identified as having ADA Level 2 Hypoglycemia (<54mg/dl) by CGM (33%) vs. blood glucose (11%). A similar proportion of patients were identified as having high glucose variability (≥5CV>36%) using CGM vs. blood glucose (11%).

Conclusions: In a prospective cohort of hospitalized HD patients with diabetes, CGM interstitial glucose via the Dexcom G6 remote access system showed similar correlation with blood glucose levels. Whereas CGM vs. blood glucose had similar detection of Level 1 Hypoglycemia, CGM had greater detection of Level 2 Hypoglycemia vs. conventional approaches.

Funding: Commercial Support - Dexcom, Inc.

PO0773
Effectiveness of Intradialytic Plantar Electrical Nerve Stimulation During Hemodialysis to Improve the Gait in Adults with Diabetes and Renal Failure: A Randomized Double-Blinded Controlled Trial
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Background: Impaired mobility is a persistent problem among patients undergoing hemodialysis (HD). Although exercise could be beneficial, factors such as post-dialysis fatigue, time limitation, and severe frailty to travel may result in poor adherence to conventional exercise programs. To address this gap, we are exploring an alternative therapy using intradialytic plantar electrical nerve stimulation (IPENS) provided during the routine hemodialysis process.

Methods: Participants were randomized into either an intervention group (IG: n=21, age=55±2.7 years, BMI=30.6±1.3 kg/m², female=31%) or a control group (CG: n=24, age=52±2.2 years, BMI=32.2±1.2 kg/m², female=41%). The IG received 1-hour IPENS during the routine HD process (3 sessions/week) for 12 weeks. The CG received an identical but non-functional device for the same period. Participants and therapy-providers were blinded to the group allocation. Gait performance was assessed under single-task (ST) and dual-task (DT) conditions at the baseline, 6 week, and 12-week under supervised condition. To determine the effect of intervention, we estimated Cohen’s effect size d. In addition, time effect, group, and time×group effects were estimated using general linear model.

Results: All participants in the IG tolerated the IPENS and completed all therapy sessions, indicating the feasibility. While, under DT condition, cadence (steps/min) and stride time (sec) increased significantly in both groups over the time, we observed a trend towards higher improvement in IG cohort (Cohen’s d=0.54, p=0.086 for cadence and d=0.52, p=0.09 for stride time) with a medium effect size compared to CG. We observed significant time effect on other gait parameters under ST and DT conditions with the similar trends towards group effect.

Conclusions: This pilot trial provides earlier results on IPENS therapy’s feasibility and effectiveness as an alternative therapeutic program to improve gait in HD patients. Even though, the improvement didn’t reach statistical significance in our current sample size. However, the effect size was medium, which is very promising.

Funding: Government Support - Non-U.S.

PO0774
Economic Burden Associated with CKD Progression Based on Kidney Disease: Improving Global Outcomes (KDIGO) Risk Categories in Type 2 Diabetes
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Background: CKD progression adds substantial economic burden in T2D. This study evaluated the medical costs associated with CKD progression defined by KDIGO risk categories in patients with T2D and CKD.

Methods: A prevalent cohort of adult patients with T2D and CKD who had measures using GFR and UAER indicating moderate or high KDIGO risk categories were identified from the Optum electronic health records database (Jan 2007- Dec 2019). CKD progression was defined as an increase in KDIGO risk category. Annualized costs for inpatient admissions, emergency room visits, and outpatient visits were evaluated for up to 2 years after the index date (i.e., the first record indicating CKD progression for progressed; the later of the first record indicating the patient’s risk category or two years before the end of follow-up for non-progressors).

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Results: Among 218,624 patients with baseline moderate risk, 41,986 (19%) progressed to high risk and 3,102 (1%) progressed to very high risk. Compared to non-progressors, the annual incremental costs were $5,193 for patients progressed from moderate risk to high risk, $18,168 for moderate risk to very high risk, and $15,280 for high risk to very high risk (Figure 1). Inpatient costs were the major driver of incremental costs. CKD-related medical costs contributed to 28%, 34%, 42%, and 44% of total medical costs in the 4 groups, highest in patients who progressed to very high risk.

Conclusions: Patients with T2D and CKD in KDIGO moderate or high risk categories had significantly higher medical costs when they progressed to a higher KDIGO risk category compared to those without progression. Preventing progression could bend the cost curve in patients with T2D and CKD.

Funding: Commercial Support - Bayer

PO0775
Geographic Variations in Healthcare Resource Utilization (HRU) and Costs and Their Associations with Albuminuria Testing in Patients with CKD and Type 2 Diabetes (T2D)
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Background: Albuminuria monitoring is critical for CKD management. The study evaluated the geographical urine albumin-to-creatinine ratio (UACR) monitoring patterns in the US along with the associated economic outcomes in patients with CKD and T2D.

Methods: Adult patients with T2D and CKD were identified from the Optum Clininformatics® claims data (Jan 2015-Dec 2019). HRU, healthcare costs (in 2020 USD), and percentage of patients receiving at least one UACR test were summarized by state during the one-year after T2D and CKD diagnoses. Patients who had dialysis or kidney transplantation before or during the study period were excluded.

Results: Among the 101,057 patients with T2D and CKD, the average annual healthcare costs were $23,830, and percentage of patients receiving at least one UACR test was lower in patients with T2D and CKD. Among patients with T2D and CKD, the average annual healthcare costs were $28,636 and increased with CKD severity, from $20,122 (stage I) to $28,636 (stage V). Among patients with T2D and CKD, the average annual healthcare costs were $27,230 and increased with CKD severity, from $20,122 (stage I) to $28,636 (stage V). Among patients with T2D and CKD, the average annual healthcare costs were $28,636 and increased with CKD severity, from $20,122 (stage I) to $28,636 (stage V). Among patients with T2D and CKD, the average annual healthcare costs were $28,636 and increased with CKD severity, from $20,122 (stage I) to $28,636 (stage V).

Conclusions: Patients with CKD and T2D had high HRU and healthcare costs with large variations across states. Lower UACR testing rates were associated with higher healthcare costs, lower UACR testing rates tended to have higher healthcare costs (Figure 1b). States with lower UACR testing rates were associated with higher healthcare costs (Figure 1b). States with lower UACR testing rates were associated with higher healthcare costs (Figure 1b). States with lower UACR testing rates were associated with higher healthcare costs (Figure 1b). States with lower UACR testing rates were associated with higher healthcare costs (Figure 1b).

Funding: Commercial Support - Bayer U.S. LLC

PO0776
Cardiovascular and CKD-Related Healthcare Costs for Patients with Type 2 Diabetes and CKD
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Background: Cardiovascular (CV) events and chronic kidney disease (CKD) management incur high medical costs in patients with type 2 diabetes (T2D) and CKD. This study aimed to provide reliable regression-based cost estimates of these events among patients with T2D and CKD.

Methods: This study used Optum Clininformatics® claims data from 52,599 adults with T2D and CKD identified during 2015-2019 and followed until disenrollment, death, or end of data availability. Medical costs (2020 USD) associated with CV events and CKD management were estimated using a generalized estimating equation model adjusting for age, sex, as well as CV complications and medical costs at baseline. Costs were assessed in 4-month cycles as commonly evaluated in clinical trials in this population, with acute event costs assessed in the first 4 months after the incident CV events and renal replacement therapies (RRT). Mortality costs were assessed in the last month prior to death.

Results: The estimated 4-month CKD management costs were $7,725 for stage 1 or 2, $8,928 for stage 3, $10,809 for stage 4, and $11,879 for stage 5 without RRT. The acute event costs for T2D and CKD were $87,538 and $124,271, respectively. The estimated acute event costs for dialysis and kidney transplantation were $87,538 and $124,271, respectively. The acute event costs for dialysis and kidney transplantation were $87,538 and $124,271, respectively. The acute event costs for dialysis and kidney transplantation were $87,538 and $124,271, respectively.

Conclusions: CV events and CKD management incur significant healthcare costs for patients with T2D and CKD. The cost estimates from this study may support the parametrization of economic models and help clinicians determine the cost-effectiveness of interventions.

Funding: Commercial Support - Bayer U.S. LLC

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Clinical and Histological Predictors of Renal Survival in Patients with Biopsy-Proven Diabetic Nephropathy

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Background: Diabetic nephropathy (DN) is one of the most important complications of diabetes and has become the leading cause of end stage renal disease (ESRD). However, clinical and pathological factors alone can’t reliably predict renal survival in patients with biopsy-proven DN, potentially resulting in the delayed treatment of patients at a high risk of renal failure. Therefore, this study sought to develop and validate a predictive model incorporating both clinical and pathological markers to predict renal outcomes in patients with biopsy-proven DN.

Methods: A predictive nomogram was developed based upon data pertaining to 194 patients with biopsy-proven DN. The prognostic relevance of individual clinicopathological variables was assessed through univariate and multivariate Cox regression analyses. A prognostic nomogram was then developed and validated based upon concordance (C)-index values, area under curve (AUC) and calibration curves. Internal validation was conducted through bootstrap resampling, while the clinical utility of this model was assessed via a decision curve analysis (DCA) approach.

Results: Nephrotic-range 24-hour proteinuria, late-stage chronic kidney disease (CKD stage 3-4), glomerular classification III-IV, and an IFTA score 2-3 were all identified as independent predictors of poor renal outcomes in DN patients and were incorporated into our final nomogram. Calibration curves revealed good agreement between predicted and actual 3- and 5-year renal survival in DN patients, while the C-index value for this nomogram was 0.845 (95% CI 0.826–0.864) and the 3- and 5-Year AUC were 0.933 (95% CI 0.898-0.968), 0.923 (95% CI 0.886-0.960). DCA analysis revealed that our nomogram was superior to models based solely upon clinical indicators.

Conclusions: A predictive nomogram incorporating clinical and pathological indicators was developed and validated for the prediction of renal survival outcomes in patients with biopsy-proven DN. This tool will be of value to clinicians, as it can serve as an easy-to-use and reliable tool for physicians to guide patient management based on individualized risk in order to improve patient outcomes.

Histological Diabetic Nephropathy in Autopsied Diabetic Cases with Normoalbuminuria from a Japanese Community-Based Study: The Hiyama Study

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Background: Albuminuria is a clinical indicator of diabetic nephropathy (DN). However, it is controversial whether pathological DN lesions are present in diabetic individuals with normal albuminuria. We investigated the association between albuminuria levels and the frequency of DN lesions in autopsied diabetic cases from a Japanese community.

Methods: Autopsied specimens obtained from deceased in the town of Higashima from 2002 to 2017 were used in the present study. During this period, 131 deceased individuals with diabetes underwent autopsy examinations. A total of 106 autopsied cases with diabetes mellitus (mean age 76 years, 43.4% male) who died within 6 years since the last health examination were included in the study. Urinary albumin-creatinine ratio (UACR) levels were divided into three groups: <30.0, 30.0–299.9, and ≥300.0 mg/g. The kidney specimens were evaluated with light microscopy, and were categorized into class 0–I, IIa, IIb, and III glomerular DN lesions according to the Renal Pathology Society’s criteria. A Cochrane-Armitage test was used to examine the association between the UACR levels and the presence of class IIa or higher glomerular DN lesions.

Results: In the overall cases, the frequency of class IIa or higher glomerular DN lesions was 63.2% (IIa, 36.8%; IIb, 3.8%; and III, 22.6%). Its frequencies increased significantly with higher UACR levels (P for trend = 0.02, Figure). Even in individuals with UACR of <30 mg/g, the frequency of class IIa or higher glomerular DN lesions was 51.2%.

Conclusions: The present study showed a positive association of the UACR levels with the presence of class IIa or higher glomerular DN lesions, which were also frequently found even in the normoalbuminuria range, among autopsied diabetic cases from a Japanese community.

Figure.
PO0780
Prevalence and Risk Factors Associated with Diabetic Nephropathy in Patients with Diabetes Undergoing Nephrectomy
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Background: Diabetic kidney disease (DKD) affects about 40% of patients with diabetes and is the most common cause of end-stage renal disease in the US. The prevalence of morphologic features of DKD, known as diabetic nephropathy (DN), is likely underestimated since kidney biopsies are performed when other diseases are clinically suspected. The availability of non-neoplastic kidney tissue from nephrectomies offers us the opportunity to evaluate the prevalence and risk factors associated with morphologic evidence of DKD.

Methods: A total of 198 nephrectomies of diabetic patients, where the status of the native kidney biopsy, diagnoses of diabetes and CKD but not on dialysis. Clinical, demographic, and administrative data from two large healthcare systems. Inclusion criteria consisted of a native kidney biopsy, diagnoses of diabetes and CKD but not on dialysis. Clinical investigators manually abstracted health history, laboratory data, and histological features from kidney biopsy reports. DKD was classified as: diabetic nephropathy (DN), DM mixed with nondiabetic lesions (Mixed), and nondiabetic lesions only (Other).

Results: In 523 patients with diabetes who underwent kidney biopsy in the years 2015-2017 (Table), diagnostic frequencies were DN 39.8% (n=208), Mixed 36.9% (n=193), Other 23.3% (n=122). Patients with DN were younger, displayed higher levels of albuminuria, nodular glomerulosclerosis and arteriolar hyalinosis than the Mixed group. Those with DN more commonly had diabetes duration >10 years and higher albuminuria compared to the Other group, while lesions characteristic of DN (mesangial expansion, nodular glomerulosclerosis, GBM thickening, arteriolar hyalinosis, tubular basement membrane thickening) were uncommon in Other.

Conclusions: Higher levels of albuminuria, nodular glomerulosclerosis and arteriolar hyalinosis were distinctly more common in DN compared to Mixed and Other groups, and nodular glomerulosclerosis was rarely observed in the Other group. Future work will use machine learning models of the EHR data to predict DN and select precision therapies.

PO0781
Biopsy Results in a Diverse Diabetic Cohort
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Background: Diabetes is the most common cause of kidney failure in the US. However, many of these patients never receive a biopsy, and therefore diabetic nephropathy (DN) is presumed based on clinical features. Therefore, we sought to determine the prevalence and outcomes of non-diabetic renal disease (NDRD) in a diverse cohort of diabetic patients referred for biopsy.

Methods: Patients were included if they had a biopsy performed at The Mount Sinai Hospital from 2018-2019, and if they had a hemoglobin A1c > 6.5% or diabetes was mentioned in their past medical history. Charts were excluded if no data existed after biopsy, dialysis-dependence occurred prior to biopsy, and if insufficient amounts of glomeruli were observed. Baseline characteristics including age, gender, race/ethnicity, blood pressure, creatinine, and urine protein/creatinine ratio (UPCR) were recorded. Outcomes measured were 1 year UPCR, 1 year creatinine, need for dialysis, and death.

Results: In total, 81 charts were included for analysis, of which 21 biopsies had DN alone, 26 had DN + NDRD, and 27 had NDRD alone (Figure 1A). In patients with NDRD, a broad range of pathology was seen (Figure 1B). There were no significant differences in characteristics of patients with DN alone and any NDRD (Figure 1C). There was a non-statistically significant difference in median one year creatinine and one year UPCR between patients with DN and NDRD (1.67 vs. 3.07 (p=0.1) and 2490 vs. 3540 (p=0.2)). Additionally, there was a non-statistically significant difference in death and dialysis treatment between DN and NDRD patients, 4 (14%) vs. 3 (6%) (p=0.2) and 5 patients (18%) vs. 19 (36%) (p=0.09), respectively. DN had lower odds of requiring dialysis at 1 year from biopsy OR 0.39 (95% CI 0.13-1.19).

Conclusions: In our selected diverse population of diabetic patients with kidney biopsies, the majority of patients had NDRD on pathology. While not statistically significant, DN patients had lower follow up creatinine and UPCR, and less patients on dialysis at 1 year.
Methods: Post-hoc analysis of a double-blind, cross-over trial where persons with type 2 diabetes and albuminuria received treatment with dapagliflozin (10 mg) and placebo for 12 weeks in random order. The original primary outcome was change in the urinary proteomic classifier CKD273. suPAR level was assessed in plasma samples collected at all 3 visits. Effect of dapagliflozin on suPAR level was determined using unpaired t-test for comparison between baseline and end-of-treatment for the dapagliflozin and the placebo treatment period, and paired t-test for comparison between the two treatment periods. A secondary analysis investigated the association between baseline suPAR and CKD273 using Pearson correlation.

Results: Of the 36 persons who completed study, 11% were female, mean ±SD age was 64.8 years, HbA1c 73.15 mmol/mol (8.9±1.4%), eGFR 84.1±19 ml/min/1.73m², and median (IQR) urinary albumin creatinine ratio was 154 mg/g (94-329). Median (IQR) suPAR at baseline was 3.44 ng/ml (2.49-4.35) and CKD273 score was 0.59 (0.180.77). suPAR levels after 12 weeks of dapagliflozin was -0.13 ng/ml (95% CI -0.72;0.36; p=0.50) and placebo -0.19 ng/ml (-0.71;0.33; p=0.46), mean difference 0.06 ng/ml (95% CI -0.15;0.27; p=0.57). Pearson correlation R between baseline suPAR and CKD273 score was 0.17 (95% CI -0.17;0.48; p=0.32).

Conclusions: This post-hoc analysis could not demonstrate an effect of 12 weeks of treatment with dapagliflozin on plasma suPAR level in individuals with type 2 diabetes and albuminuria. In addition, plasma suPAR was not correlated to the urinary proteomic classifier CKD273 classifier.

PO0784

Predictive Model of Non-Diabetic Nephropathy in Patients Affected by Diabetes
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Background: Between 50-60% of diabetics with renal involvement have non-diabetic nephropathy (NDN). Renal biopsy is still required for renal diagnosis that includes diabetic nephropathy (DN), NND, or mixed form. The objective of the current study is to provide a tool in the daily clinical practice through a predictive model of NND that is clue for the indication of renal biopsy.

Methods: Observational, retrospective and multicenter study of the pathological results of kidney biopsies in patients with diabetes from 2002 to 2014. A logistic regression analysis and the probability of presenting NND was calculated using a postoperative score. Cox proportional hazards models were used to evaluate metabolic acidosis as a predictor of progression from prediabetes to diabetes among patients with CKD. The incidence of diabetes was 10.8±6.8 years. 26.6% (n=221) of patients presented diabetic retinopathy, 18.8% (n=156) peripheral vasculopathy and 17.7% (n=147) ischemic heart disease. 288 patients (34.6%) presented microhematuria. 39.5% (n=329) presented DN, absence of diabetic retinopathy (OR:3.97;2.7-5.82; p<0.0001), and absence of peripheral vasculopathy (OR:1.61, 1.03-2.52, p=0.038) were identified as independent risk factors for NDN. A ROC curve with an area under the curve of 0.724 was obtained. A predictive model obtaining a score (see figure) for each variable and finally a NDN prediction score was performed. In our new score, the number increases as increased the probability of NDN.

Conclusions: In our study, around 66% of biopsied patients with diabetes presented NDN. Microhematuria, absence of diabetic retinopathy, absence of peripheral vascular disease, and older age were independent risk factors for NDN. We obtained a score that increases as increased the probability of NDN. This could be in a next future a useful tool for the clinical indication of renal biopsy in patients with diabetes and kidney disease.

PO0786

Metabolic Acidosis and the Risk of Progression to Diabetes in Patients with Prediabetes and CKD
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Background: Diabetes and metabolic acidosis are known risk factors for progression of CKD. Treatment of metabolic acidosis has been shown to reduce insulin resistance among patients with CKD and diabetes, but whether metabolic acidosis predicts progression from prediabetes to diabetes among patients with CKD is unknown.

Methods: Optum’s de-identified Integrated Claims-Clinical database of US patients (2007-2019) was queried for patients with non-dialysis CKD stages 3-5 with 2 consecutive serum bicarbonate of 12 to <22 mEq/L (metabolic acidosis) or 22 to <30 mEq/L (normal serum bicarbonate) with ≥1 year prior data and ≥2 years of post-index data or death within 2 years. Patients with prediabetes (HbA1c 5.7 to <6.5%, fasting plasma glucose 100 to <126 mg/dL, or 75 g oral glucose challenge 140–199 mg/dL) were followed for up to 11.5 years for incident diabetes identified through lab values, diagnosis, or prescriptions. Cox proportional hazards models were used to evaluate metabolic acidosis as a predictor of incident diabetes, adjusting for age, sex, race, low-income status, geocoded education and baseline BMI, eGFR, metabolic syndrome and polycystic ovary syndrome. Death was also evaluated as a competing risk.

Results: 7156/136,067 patients had evidence of prediabetes during the pre-index year. 47% (1362/292) of patients with baseline metabolic acidosis and 46% (3143/6864) with normal serum bicarbonate developed diabetes during the outcome period (P=0.8).

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Patients with metabolic acidosis developed diabetes sooner on average compared with patients who had normal serum bicarbonate (544 vs 643 days); however, baseline metabolic acidosis was not a significant predictor of time to incident diabetes in adjusted analyses (HR 1.20, 95% CI 0.96–1.50). Metabolic acidosis (HR 1.26, 95% CI 1.08–1.46), Black race (HR 1.28 [1.11–1.47]), male sex (HR 1.11 [1.01–1.21]), and higher BMI (HR 1.05 [1.02–1.08]) were associated with a higher risk of progression to diabetes. Higher baseline eGFR was associated with lower risk of progression to diabetes (HR 0.993 [0.988–0.997]).

Conclusions: In this longitudinal analysis of non-dialysis CKD stages 3-5 patients with prediabetes, metabolic acidosis was not associated with progression to diabetes.

Funding: Commercial Support - Tricida, Inc.
Disparities in Quality of Care for Dialysis Patients

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Background: An understanding of disparities in quality of care for dialysis patients may inform priorities for quality improvement and approaches for achieving greater health equity. It is also not known whether disparities have been improving or worsening or whether they vary geographically.

Methods: We used Medicare claims and CROWNWeb data to evaluate disparities based on race, ethnicity, dual eligibility, and rural-urban location. Using criteria developed by AHRQ, we identified disparities in 2019 based on a statistically significant regression-adjusted difference in a quality indicator and at least a 10% relative difference between groups. We estimated generalized linear models with clustering for patients and adjustments for age, sex, cause of ESRD, duration of ESRD, and comorbid conditions at ESRD incidence. We examined national trends in disparities from 2015-20 and variation in disparities in ESRD Networks in 2019.

Results: There is evidence of disparities in U.S. dialysis patients for a range of quality indicators in 2019 (Table), some of which relate to measures in the ESRD Quality Incentive Program. Disparities involving racial minorities and dual eligible beneficiaries accounted for 13 of 16 measured disparities nationally. These disparities largely persisted over time and were found in most ESRD Networks.

Conclusions: There are ongoing racial, socioeconomic, and rural-urban disparities among dialysis patients in a range of quality indicators. There may be valuable opportunities for quality initiatives in ESRD to improve health equity.

Funding: Other U.S. Government Support

Risk Factors and Outcomes of Gout in Dialysis Patients: A Cohort Study of the United States Renal Data System (USRDS)

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Background: Limited research exists regarding gout among dialysis-dependent end-stage renal disease patients. This study aimed to evaluate the epidemiology, risk factors, and outcomes of dialysis patients with gout.

Methods: Using 2017 USRDS data, this study identified dialysis patients ≥18 years of age with Medicare as the primary payer. Baseline characteristics and comorbid conditions for dialysis-dependent patients with gout were assessed at dialysis initiation as well as 3-months preceding their gout diagnosis and compared with non-gout dialysis patients. All-cause hospitalization and mortality risk were also estimated and compared between gout and non-gout patients.

Results: Of 275,651 dialysis patients in 2017, 41,312 (15%) had ≥1 gout claims following initiation of chronic outpatient dialysis. More than 1/3 of gout diagnoses were made during urgent or emergency care visits. Compared to non-gout patients, gout patients were more likely to be older (mean 64.5 ± 16.7 years), male (62% vs 54%), of Asian race (6.2% vs 3.7%), and obese (31.4 ± 32.0 kg/m²). Gout patients were also found to be more likely to undergo hemodialysis via central venous catheter (15% vs 13%). Compared with non-gout patients, gout patients had a higher comorbidity prevalence of diabetes (67% vs 62%), hypertension (93% vs 74%), and cardiovascular conditions (heart failure [49% vs 30%], ischemic heart disease [49% vs 30%], peripheral vascular disease [32% vs 22%], stroke [12% vs 8%], acute myocardial infarction [7% vs 3%] and angina [4% vs 2%]). Adjusted regression analysis showed that older age (OR=4.23 for 65 vs 66 years; 95% CI 4.03-4.43) and previous transplant (OR=2.37, 95% CI 2.14-2.50), and comorbid hypertension (OR=2.71, 95% CI 2.59-2.83) are the 3 most significant factors associated with gout diagnosis. In multivariate analysis, risk of hospitalization and mortality was higher by 11% (95% CI 9.2% and 95% CI 12.6%, respectively in the year after diagnosis).

Conclusions: The prevalence of gout was 15% in the US Medicare dialysis-dependent population. Gout patients had a higher comorbidity burden especially for cardiovascular conditions and higher risk of hospitalization and mortality. Future studies are needed to elucidate whether improved recognition and management of gout may reduce the risk for worse cardiovascular outcomes.

Funding: Commercial Support - Horizon Therapeutics

Racial Disparities in Staff CPR Performance Within US Dialysis Clinics: The Role of Clinic Resources and Patient Factors

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Background: Cardiac arrest occurs frequently in outpatient dialysis clinics, and immediate and prompt CPR provision improves patient outcomes. However, Black patients in dialysis clinics receive CPR from clinic staff less often compared to White patients. We examined the contribution of dialysis facility resources and patient factors to the observed racial disparity in CPR.

Methods: Retrospective cohort study linking the National Cardiac Arrest Registry to Enhance Survival (CARES) and Medicare Annual Dialysis Facility Report registries. We identified cardiac arrests occurring within US outpatient dialysis clinics via geolocation matching. Differences in facility size, quality, staffing and patient related factors were measured and compared according to patient race. Multilevel multivariable logistic regression models including these factors were constructed to examine the influence of these factors on the observed disparity in CPR rates between Black and White patients.
Results: From 2013-2017, we identified 1,554 patients experiencing cardiac arrest in dialysis clinics. Compared to White patients, Black cardiac arrest patients dialedy in larger facilities (26 vs 21 dialysis stations, p<0.001), with less RNs per station (0.29 vs 0.33, p<0.001), and facilities with lower quality scores (# citations 6.8 vs 6.3, p=0.04). Facilities treating Black patients cared for a higher proportion of patients with a history of cardiac arrest (41 vs 35%, p=0.001), HIV/Hepatitis B (5.1% vs 2.9%, p=0.001) and Medicaid enrolled patients (15% vs 11%, p<0.001). After accounting for these differences and other covariates, there was no change in the racial disparity for CPR in Black vs. White patients (OR=0.45 (95% CI 0.27-0.75). The disparity was greater among older Black patients compared to younger patients (interaction p=0.04). Other patient related and facility quality-related factors did not moderate the racial disparity in receipt of CPR.

Conclusions: The racial disparity in CPR delivery within dialysis clinics cannot be explained by differences in facility resources and quality. Reducing this disparity will require a multi-faceted approach including developing dialysis clinic-specific protocols for CPR and addressing potential implicit bias.

Funding: NIDDK Support

PO0795
Weekly Risks of Death and Hospitalization Among Incident Patients Undergoing Dialysis
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Background: During the first year of hemodialysis, risks of mortality and morbidity are elevated. However, it remains unclear when patients transition from relatively higher “incident” risk to relatively lower “prevalent” risk. We estimated trajectories of weekly risks of death and hospitalization among patients who recently initiated hemodialysis.

Methods: We analyzed data from the United States Renal Data System. The cohort included all patients who initiated outpatient hemodialysis in 2014-2017; for analysis of “incident” risk to relatively lower “prevalent” risk. We estimated trajectories of weekly incidence rates of death and hospitalization during the first 52 weeks of hemodialysis. We used joinpoint regression with a maximum of five knots to estimate best linear interpolations of incidence trajectories.

Results: The cohort included 395,233 incident patients. Risk of death peaked in week 1 to 3; high but steadily decreasing risk from week 3 to 13; moderate and gradually decreasing risk from week 13 to 30; and consistent risk from week 30 to 52. Risk of hospitalization was highest in dialysis week 1. There were four phases of risk: high but sharply decreasing risk from week 1 to 5; moderate and steadily decreasing risk from week 5 to 11; moderate and gradually decreasing risk from week 11 to 24; and consistent risk from week 24 to 52.

Conclusions: Weekly risks of death and hospitalization are highest during the first 13 to 14 weeks after initiation of outpatient hemodialysis, and gradually decline thereafter. However, risk trajectory details—including the timing of the transition from “incident” to “prevalent” status—vary among outcomes.

Funding: Commercial Support - AstraZeneca

PO0796
Shortened or Skipped Hemodialysis Sessions Attributed to Uremic Pruritus: A National Kidney Foundation Patient Survey
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Background: Hemodialysis (HD) patients are at risk for uremic pruritus, a common and bothersome condition that may make it difficult for patients to complete the prescribed HD sessions. The purpose of this study is to investigate the extent to which pruritus contributes to patients shortening or skipping HD sessions. Studies have demonstrated that shortening and skipping HD treatments increases mortality risk.

Methods: An online survey of adults (18 years and older), across the U.S. from November 11-27, 2020, was conducted using two links posted on the National Kidney Foundation Facebook page. A $5 electronic Amazon gift card incentive was offered to the first 300 respondents with a valid email address.

Results: There were 692 participants among 2604 initial responders, excluding 1,252 for partial survey completion, 516 for not having kidney disease and 144 for kidney disease without HD treatment. Demographics and clinical characteristics include mean age 38.5 years ±11.8, 46.8% under 35 years, 45.5% females, 15% Black or African American, 9% Hispanic, 9% American Indian, 3% Asian, 74.7% employed or attending school, 45.3% with 1-5 years HD vintage, 81% treated with center HD and 19% treated with home HD. This population is younger and enriched for home HD and employment compared to 2018 results from the USRDS 2020 Annual Data Report, with only 11% HD age ≤ 45 years, 2% treated with home HD and low employment prevalence. Pruritus was common with 64.0% (428/669) self-reporting itch that is at least somewhat intense on a Likert scale, including 25.7% (172/669) of patients reporting itch as very or extremely intense. Shortening or skipping an HD session because of pruritus was reported at least some of the time by 55.0% (334/601) and 50.4% (303/601) of participants, respectively. Patients reporting the itch as very or extremely intense were more likely to skip or miss HD treatments. Among the members of the HD care team, nephrologists 43.2% (299/692) were the most likely professional to be identified by patients to talk with about itchy skin.

Conclusions: This survey cohort of HD patients showed pruritus leading to skipped or shortened HD sessions occurred in about half of the patients. The results support uremic pruritus as a significant cause of skipped or shortened HD sessions for the dialysis care team to consider.

Funding: Commercial Support - Cara Therapeutics

PO0797
Association of Length of Interdialytic Interval and Patient-Reported Symptoms
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Background: Symptom burden of patients on in-center hemodialysis (HD) is high. Hospitalization and mortality is higher after the long interdialytic interval due to accumulation of fluid and electrolytes. It is unclear whether symptom burden is affected by the length of interdialytic interval.

Methods: We surveyed patients ≥18 years old, on HD for ≥30 days, and on HD three times a week at the Mount Sinai Kidney Center. Patients completed a survey about presence and severity (5 point scale) of 21 symptoms at the end of their HD treatments for 12 sessions. Symptom severity was calculated by multiplying the symptom with the severity and could range from 0 to 84, it was then summed per survey and the mean value per patient was calculated. We used negative binomial regression to determine the association of interval with symptom count.

Results: During the study period, 97 HD patients completed all surveys. The mean age was 56±14 years, 52% were female, and 52% were Black. The majority of patients reported symptoms, which ranged from a low of 8% for chest pain to 61% for fatigue (Figure 1A). More patients reported having a1 symptom after the long interdialytic interval than after the short interdialytic interval 67% vs 59%, P=0.01. Mean symptom severity was higher after the long interdialytic interval (5.8±0.5 vs. 4.7±0.5, P=0.001) (Figure 1B). Symptoms that tended to be more common after the interdialytic interval were fatigue, itching, dry mouth, bone pain, and restless legs (Figure 1C). After adjustment for age, gender, and race, the incidence rate of symptoms was 28% higher after the long interval (IRR 1.2, 95% CI 1.09-1.33).

Conclusions: Symptoms are common in patients on maintenance HD. Symptom burden is slightly higher after the long interdialytic interval than the short interdialytic interval.

Funding: NIDDK Support, Commercial Support - Renal Research Institute
PO0798

Modifiable Risk Factors Associated with Death over the Long Interval for In-Center Hemodialysis Patients

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Background: Routine thrice weekly in-center hemodialysis (HD) is associated with increased risk of death around the long interval without dialysis. We evaluated this risk and explored modifiable risk factors associated with increased risk of death.

Methods: Prevalent Medicare beneficiaries (21,331) receiving maintenance three weekly in-center HD in facilities operated by a large not-for-profit dialysis provider from 1/1/2009–12/31/2016 were included. We calculated daily death rates for an observation week (consisting of days HD-2, HD-1, HD1, HD2, HD2+2, and HD3) occurring after a week of usual outpatient care, defined by at least one outpatient treatment, with no inpatient hospital stays, exclusive of, or SNF days. HD3 represents the Monday or Tuesday following the long interval. A logistic regression model with patient random effects estimated the effect of patient characteristics, including age and treatment vintage, and treatment parameters including inter-dialytic weight gain (IDWG), >4.6% of estimated dry weight, and intra-dialytic hypotension, on the probability of dying over the long interval (HD-2, HD-1, and HD1) as compared to either dying on any other day in the week or survival.

Results: Among 2,019 deaths included in analyses, the highest death rates were observed on HD1 and HD3. Factors associated with increased odds of death over the long interval included older age, IDWG >4.6% of estimated dry weight, pre-HD SBP <120 mm Hg prior to last treatment in the observation week, and skipped treatment in the prior week (table).

Conclusions: High inter-dialytic weight gain, low pre-HD SBP, and skipped treatments during the preceding week are potentially modifiable factors associated with increased risk of death over the long interval. These factors can help identify patients who will benefit from HD prescription modification.

PO0800

Characterization of Gout in US Patients Treated with Hemodialysis (HD) and Peritoneal Dialysis (PD)

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Background: Gout occurs frequently in patients with renal disease and can lead to a significant burden on quality of life and functional status. In the US hemodialysis (HD) and peritoneal dialysis (PD) population, there has been little reported on gout prevalence, patient characteristics, and associations with outcomes.

Methods: We used data from large commercial and Medicare HMO plans including UnitedHealthcare, Aetna, and Humana to identify incident patients. We identified 233,564 patients with DD ESRD, of which 10% were incident. These patients reported 2,439,804 outpatient dialysis months in 2019. Among all patients, 28.4% did not report PB use in 2019 (26.4% among prevalent patients and 46.6% among incident patients). Among patients with any PB use, the average number of outpatient dialysis months was 10.9, of which 6.4 (60%) reported PB use. Average months with PB use were 3.8 for CAPD, 5.3 for CCPD, and 6.4 for hemodialysis.

Conclusions: We found gaps in PB use among patients receiving outpatient dialysis who were also prescribed a binder in 2019. Binder use was reported in 60% of all outpatient dialysis months for patients in our study, suggesting that PBs may have been underutilized or required only intermittently. Further studies are needed to determine the reasons for gaps in PB use and to identify opportunities for control of phosphate levels among patients with DD ESRD.

Funding: Commercial Support - Akemia Therapeutics, Inc.

PO0799

Real-World Use of Phosphate Binder Agents Among Dialysis-Dependent Patients with CKD in Medicare Fee-for-Service

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Background: Phosphate binders (PBs) are prescribed to control hyperphosphatemia among patients with chronic kidney disease. The need for phosphate intervention peaks among those with dialysis-dependent (DD) end-stage renal disease (ESRD). We used Centers for Medicare & Medicaid Services 100% Research Identifiable Files (RIF) data, representing 100% of Medicare fee-for-service beneficiaries, to characterize contemporary PB utilization among established and incident patients with DD ESRD across dialysis modalities.

Methods: We identified incident and prevalent patients with DD ESRD in the 2018-2019 RIF data, separating hemodialysis, continuous ambulatory peritoneal dialysis (CAPD), or continuous cycling peritoneal dialysis (CCPD) patients based on frequency of revenue codes. We assessed monthly PB use for calcium acetate, sevelamer carbonate, sevelamer hydrochloride and carbonate, and sucroferric oxyhydroxide. PB use was defined as a filled prescription covering >15 days in a calendar month.

Results: We identified 233,564 patients with DD ESRD, of which 10% were incident. These patients reported 2,439,804 outpatient dialysis months in 2019. Among all patients, 28.4% did not report PB use in 2019 (26.4% among prevalent patients and 46.6% among incident patients). Among patients with any PB use, the average number of outpatient dialysis months was 10.9, of which 6.4 (60%) reported PB use. Average months with PB use were 3.8 for CAPD, 5.3 for CCPD, and 6.4 for hemodialysis.

Conclusions: We found gaps in PB use among patients receiving outpatient dialysis who were also prescribed a binder in 2019. Binder use was reported in 60% of all outpatient dialysis months for patients in our study, suggesting that PBs may have been underutilized or required only intermittently. Further studies are needed to determine the reasons for gaps in PB use and to identify opportunities for control of phosphate levels among patients with DD ESRD.

Funding: Commercial Support - Akemia Therapeutics, Inc.
PO8081

**Fatigue Prevalence and Associations with Non-Diuretic Anti-Hypertensive Medications in the Maintenance Hemodialysis Population**

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**Background:** It is well known that dialysis patients suffer from fatigue post dialysis. It is possible that fatigue is exacerbated by antihypertensive medications. We hypothesized that post-dialysis fatigue (PDF) duration was positively correlated with the number of antihypertensive medications.

**Methods:** We conducted cross sectional survey and 6 month retrospective medical record chart review at three privately owned dialysis clinics in Illinois. The survey consisted of 50 questions related to fluid and blood pressure management, the validated Post-Dialysis Fatigue and Time to Recover from Dialysis Survey (PDF TIRD), and the validated National Institute of Health Patient Reported Outcomes Measurement System fatigue short form. A random mixed effect model was created through a reverse stepwise process in order to assess associations. Chi-squared analysis was performed with categorical symptom data.

**Results:** One hundred and two patients consented to the study, 96 had complete medical records with all research variables and survey values captured. The average number of dialysis sessions captured per patient was 50.0 ± 19. The average time on maintenance hemodialysis was 5.06 ± 4.93 years with a range of 0.2 to 28 years. Seventy six percent (73/96) of dialysis patients suffered from post-dialysis fatigue. Most patients (53/96) reported that their fatigue was the worst after dialysis. On average patients required 462.67 ± 655.18 minutes (7.7 ± 10.92 hrs) to recover after dialysis. In our random mixed effect model, the time required to recover post-dialysis was positively associated with the number of non-diuretic antihypertensive medications: For every anti-hypertensive medication, patients experienced an additional 210 minutes (3.5 hrs) of fatigue post dialysis fatigue.

**Conclusions:** Post-dialysis fatigue is a pervasive problem in the dialysis population that has significant consequences on patients’ quality of life. While fatigue has several important contributing factors, the number of non-diuretic blood pressure medications appear to exacerbate patient fatigue. Further investigation on the survival and quality of life benefits, including fatigue, of patients maintained on non-antihypertensive medications versus volume control strategies is needed.

PO8082

**Dialysis Adequacy and Risk of Dementia in Elderly Hemodialysis Patients**

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**Background:** Dementia is prevalent among elderly patients undergoing hemodialysis. However, the association between dialysis adequacy and the risk of dementia is uncertain.

**Methods:** A total of 10,567 patients aged ≥65 years undergoing maintenance hemodialysis who participated in a national hemodialysis quality assessment program were enrolled. The patients were classified into quartile groups based on single-pool Kt/V levels. The associations between single-pool Kt/V and the development of dementia, Alzheimer’s disease (AD), and vascular dementia (VD) were examined.

**Results:** The mean age of the patients was 72.9 years, and 43.4% were female. The median number of dialysis sessions was 1.6 ± 0.3. During a median follow-up of 45.6 (45.6–69.9) months, there were 27,6, 23.9, and 2.8 events/1000 person-years of overall dementia, AD, and VD, respectively. The incidences of overall dementia, AD, and VD were lowest in the highest single-pool Kt/V quartile group. Compared with the lowest single-pool Kt/V quartile, the risk of incident dementia, AD, and VD were significantly lower in the highest quartile (sub-distribution hazard ratio [SHR]: 0.69, 95% CI: 0.57–0.84 for AD).

**Conclusions:** Increased dialysis clearance was associated with a lower risk of developing dementia in elderly hemodialysis patients.

PO8083

**Risk of 30-Day Hospital Readmission in Patients with ESKD with and Without Autosomal Dominant Polycystic Kidney Disease**

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**Background:** Among end stage kidney disease (ESKD) patients with autosomal dominant polycystic kidney disease (ADPKD), relatively little is known about the epidemiology and risk factors for 30-day readmissions in the US. Therefore, we evaluated

**Methods:** We utilized the Nationwide Readmission Database from 2016-2018 to identify patients admitted for ESKD with and without ADPKD using ICD-10 codes. A propensity scoring method assigned to each hospitalization computed by multivariate logistic regression model to establish matched cohorts to reduce bias due to confounding covariates (age, gender, patients’ insurance type, quartile classification of median household income extrapolated from zip code, Elixhauser comorbidity index (ECI), hospital location and teaching status) between the 2 groups. We used single question on logistic regression to evaluate the association of ADPKD with 30-day hospital readmissions.

**Results:** From 2016-2018, after propensity matching, there were 11,578 index admissions for ESKD patients with ADPKD and 11,422 index admissions for ESKD patients without ADPKD. Those who had ADPKD during index admissions had fewer 30 days readmissions (12.8% vs 13.5%, p<0.001). The cost of hospitalizations and readmissions in ESKD patients with ADPKD were higher than non-ADPKD patients (Figure 1A). Patients who were readmitted were more likely to have kidney transplant, non-routine discharges, and have non-elective index admissions. Longer length of stay, Medicaid insurance, discharge to short term hospital, specialized care, home health care and against medical advice were associated with increased odds of readmission, and higher ECI score and ADPKD was associated with decreased odds of readmission (OR 0.85, 95% CI 0.8 – 0.9) (Figure 1B).

**Conclusions:** ESRD patients with ADPKD were less likely to have 30-day readmission than patients without ADPKD.
PO0805

Safety and Efficacy of Difelikefalin in Black or African American Patients on Hemodialysis with CKD-Associated Pruritus: Pooled Analysis of KALM-1 and KALM-2

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Background: Difelikefalin (DFK) is an investigational, peripheral opioid antagonist significantly reduced itch intensity in hemodialysis (HD) pts with CKD-associated pruritus (CKD-aP) in the Phase 3 KALM-1 and KALM-2 trials. People of Black or African American (AA) race were well represented in these studies. This pooled analysis reports efficacy and safety of DFK in Black or AA pts.

Methods: HD pts with moderate-to-severe CKD-aP were randomized to intravenous DFK 0.5 mcg/kg or placebo (PBO) 3 times/wk for 12 wks. The primary endpoint was the proportion of pts achieving a clinically meaningful 3-point improvement from baseline (BL) in the weekly mean of 24-hr daily Worst Itch Intensity Numerical Rating Scale (W1-NRS) scores at wk 12. Secondary endpoints included proportion of pts achieving ≥3-point improvement in W1-NRS score and change in itch-related QoL score (5-D Itch and Skindex-10) from BL to wk 12. Adverse events (AE) through wk 12 were collected.

Results: Of 851 pts randomized in KALM-1 and KALM-2, 249 (29%) pts self-identified as Black or AA (DFK: 135; PBO: 114). Mean BL WI-NRS score was 7.2 and 7.3 in the DFK and PBO groups. A greater proportion of pts who received DFK vs PBO achieved clinically meaningful improvements in itch intensity and itch-related QoL (Figure). Most common treatment-emergent AEs (≥2%) with DFK occurring at ≥1% higher incidence vs PBO were diarrhea (10.4% vs 6.2%), dizziness (10.4% vs 2.7%), vomiting (7.4% vs 4.4%), headache (5.2% vs 0.9%), and hyperkalemia (5.2% vs 2.7%). Serious AE incidence was similar between groups.

Conclusions: DFK significantly reduced pruritus intensity and improved itch-related QoL in Black or AA HD pts with moderate-to-severe CKD-aP. DFK was well tolerated with an acceptable safety profile. The safety and efficacy of DFK in Black or AA pts was similar to the overall population.

Funding: Commercial Support - Vifor Pharma

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

PO0806

Prevalence of Latent Tuberculosis Infection and Its Risk Factors in Japanese Hemodialysis Patients

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Background: The majority of active tuberculosis (TB) cases develop from latent tuberculosis infection (LTBI). Since the risk of TB in hemodialysis (HD) patients is particularly high, interferon-gamma release assay (IGRA) for LTBI screening in HD patients is considered important. However, the prevalence and characteristics of LTBI in Japanese HD patients remain obscure.

Methods: We performed an observational cross-sectional study of LTBI using IGRA QFT-IG tests in 118 HD outpatients enrolled at 3 hospitals of varying location and function.

Results: Of the 118 patients, 96 were QFT negative, 7 were QFT indeterminate, 14 were QFT positive, and 1 was QFT judgment impossible. No patient had active TB. Confirmed (QFT positive) and possible (QFT positive/indeterminate) LTBI patients totaled 14 (11.9%) and 21 (17.8%), respectively. The LTBI possible group was significantly older and had a significantly higher rate of nephrosclerosis versus the QFT negative group. The indeterminate group had a significantly longer HD period. The QFT results were not remarkably affected by other clinical data, including hospital characteristics. The possible LTBI rate increased age dependently, with higher values from 60 years of age.

Conclusions: The prevalence of LTBI is high in Japanese HD patients, especially from the age of 60 years. Older age was a significant risk factor for LTBI, with prediction difficulty using other clinical data. Extended HD may mask IGRA results. Therefore, aggressive screening for LTBI is advised in all HD patients regardless of hospital location or type, especially in patients over 60 years of age or newly commencing HD.

PO0807

Associations of Pre-Dialysis Care with Trajectories of Adverse Clinical Outcomes Among Patients Initiating Dialysis

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Background: Health care during advanced chronic kidney disease likely influences outcomes during the first year of end stage kidney disease (ESKD). We assessed associations of nephrology care, erythropoiesis-stimulating agent (ESA) therapy, and red blood cell (RBC) transfusion before hemodialysis initiation with trajectories of adverse clinical outcomes during the first year after initiation.

Methods: We analyzed United States Renal Data System data. The cohort included patients who initiated outpatient dialysis in 2014-2017 and carried Medicare coverage during the year preceding dialysis initiation. We stratified the cohort by care in that one-year interval: nephrology care (per ESRD Medical Evidence Report), ESA therapy (per Medicare claims), and RBC transfusion (per Medicare claims). In each stratum, we estimated weekly incidence of all-cause death, hospitalization, and three-point major adverse cardiac events (MACE) during the first 52 weeks of dialysis. We used jointpoint regression to estimate incidence trajectories.

Results: The cohort included 132,879 patients. Before dialysis initiation, 65% received nephrology care, 14% used an ESA, and 32% received an RBC transfusion. As shown, nephrology care and ESA therapy were associated with lower risks of adverse clinical outcomes during the first year of dialysis, whereas RBC transfusion was associated with higher risks. However, trajectories of weekly incidence during the first year were similar in all subgroups.

Conclusions: Pre-ESKD nephrology care and pre-ESKD ESA therapy were associated with lower risks of adverse clinical outcomes during the first year of dialysis, whereas RBC transfusion was associated with higher risks. Regardless of pre-ESKD care, risks were higher during the early part of the first year.

Funding: Commercial Support - AstraZeneca
PO0808
Temporary Changes in Hemodialysis Parameters in Patients Affected by COVID-19 Infection: A Visual Guide
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Background: ESKD patients on dialysis have been significantly affected by the COVID pandemic. By now, a substantial number of patients have survived the disease. We display graphically the temporary changes in dialysis parameters of patients that have survived COVID-19 infection.

Methods: All patients receiving hemodialysis at Emory dialysis centers diagnosed with COVID-19 infection between 3/1/20 to 1/31/21 who survived for at least 3 months were identified. The date of COVID-19 diagnosis was used to time-reference dialysis parameters including duration of hemodialysis, weight, ultrafiltration, mean arterial pressure pre-dialysis, hemoglobin, albumin, calcium, phosphorus, potassium, serum bicarbonate, absolute lymphocyte count and Kt/V. The temporary behavior of these parameters is presented graphically. Data manipulation, analysis and graphical display was performed using R-software and tidverse package.

Results: 96 patients were identified. 82% were African-American with a median age of 64y/o. 52% were male and 60% were diabetics. The median time on dialysis was 2.5 years. All studied parameters showed a significant deviation from baseline measurements obtained in the 60 days prior to the diagnosis of COVID-19. The parameter with the least amount of change was Kt/V. In the subsequent 2 months after diagnosis, all of the parameters studied returned to baseline except for Potassium, that remained below pre-morbid levels 2 months after the COVID-19 diagnosis. These changes are presented in Figure 1.

Conclusions: COVID-19 infection has a significant impact on hemodialysis parameters as presented in figure 1. The temporary variation of the most common parameters associated with COVID-19 infection presented in this study can be used as reference for patients, dieticians, and nephrologists caring for ESKD affected by COVID-19.

PO0809
Reducing Haemodialysis Frequency in a Satellite Unit During the COVID-19 Pandemic
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Background: People dependent on unit HD are vulnerable to COVID-19. We describe the safety and outcomes of reducing HD frequency to minimise patient exposure to the virus.

Methods: HD was reduced from thrice to twice-weekly in selected patients for 9 weeks from March 2020. Urine output, heart failure, fluid-overload, hyperkalaemia, medication and patient preference were considered. Patients were asked to restrict dietary potassium, salt and fluid. Selected patients reducing HD frequency received 10g once-weekly sodium zirconium cyclosilicate (SZC). Group 1: Continue thrice-weekly HD Group 2: Twice-weekly HD +SZC Group 3: Twice-weekly HD -SZC. Pre-HD serum potassium (sK+) and bicarbonate (sHCO 3-), systolic blood pressure (SBP) and weights were monitored. COVID-19 transmission, hospitalisation and death were recorded.

Results: Of 77 patients (mean age 70 years, 74% male), 17 continued thrice-weekly HD. 60 patients reduced to twice-weekly HD, of which 43 received SZC. There were 494 fewer HD treatments over 9 weeks. There was no significant difference in mean monthly sK+ in any group between March (pre-intervention), April and May; but 6 patients returned to thrice-weekly HD early due to hyperkalaemia or fluid-overload. SZC was increased to 10g twice-weekly in 15 patients. There was a reduction in mean monthly sHCO 3- during twice-weekly HD. No changes were made to oral or HD bicarbonate prescriptions. There was no significant difference in pre-HD weight or SBP from baseline in patients dialysing twice-weekly. Only 2 of the 14 admissions over 9 weeks were related to hyperkalaemia or fluid-overload. 5 patients tested positive for COVID-19. 2 of the 3 deaths during this period were due to COVID-19. Both were elderly males with CVD and chronic respiratory disease. 1 patient died of a MI after returning home from HD.

Conclusions: Reducing HD frequency in carefully selected patients is safe, and with strict infection control and timely COVID-19 testing, can reduce COVID-19 transmission and patient transfer to HD hubs. Dietetic review and SZC can reduce hyperkalaemia. Improved documentation of urinary output and cardiac function would optimise this approach.

PO0810
Paraoxonase 1 Gene Variants Concerning Spontaneous HCV Clearance in Hemodialysis Patients
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Background: We aim to explore associations between three PON1 SNVs (rs705379, rs854560, and rs662) and spontaneous clearance of HCV infection in uremic patients treated with maintenance HD. Epistatic interactions between tested PON1 SNVs and the IFNL4 variant rs368234815 were also investigated.

Methods: The study included 83 HD patients who spontaneously resolved HCV infection (all had known IFNL4 rs368234815 variant) and 104 subjects with persistently positive blood tests for HCV RNA (102 were successfully genotyped for IFNL4 rs368234815 variant). We genotyped PON1 by HRM method (rs662) or predesigned TaqMan SNV Genotyping Assay (rs854560, rs705379). We used a regression model including genetic and clinical data, which significantly differed patients with spontaneous HCV clearance and subjects with persistent HCV infection and could be
used as explanatory variables for HCV outcome. Epistatic interactions between tested PON1 SNVs and IFNL4 rs36824815 were analyzed by the multifactor dimensionality reduction method.

Results: PON1 rs662 GG (OR 9.94, 95% CI 1.20 – 82.7, P = 0.022) and rs584560 TT (OR 4.31, 95% CI 1.62 – 11.5, P = 0.003) genotypes were associated with a higher probability for HCV resolution than the genotypes composed of at least one more frequent allele. The most common haplotype, rs662A_rs854560A, was inversely associated with spontaneous HCV clearance. Compared to this haplotype, the rs662G_rs854560T indicated a 5.09-fold (95% CI 0.99 – 26.2, P = 0.032) higher chance for HCV resolution.

The closest to significance was the epistatic gene-gene interaction between PON1 rs662 and rs854560 variant allele homozygotes are associated with a higher frequency of spontaneous HCV clearance in HD patients in univariate analyses.

P00811
Cost-Effectiveness of Hepatitis C Virus Testing Strategies in US Hemodialysis Centers
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Background: The Centers for Disease Control and Prevention and the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend screening all patients for hepatitis C virus (HCV) infection prior to starting outpatient hemodialysis (HD), every 6 months thereafter, and every 1-3 months if a center is outbreak-detected. Yet, the cost-effectiveness of such screening frequency is not clear. We therefore sought to compare the clinical and cost-effectiveness of HCV testing strategies in US hemodialysis centers.

Methods: We parameterized the Hepatitis C Cost-Effectiveness (HCV-CE) model to reflect the US HD population, using United States Renal Data System and literature data. We simulated HCV infection, progression, treatment, and outbreaks within dialysis centers at the literature-reported frequency (approximately 1%). We competed 5 strategies to compare clinical outcomes and cost-effectiveness of screening, ranging from no testing, to all 6-monthly HD testing, each with every 3-month screening during a simulated outbreak in 1% of centers. We estimated the life expectancy, quality-adjusted life years (QALYs), total HCV infections identified and cured, liver-related deaths, costs (US$2019) and incremental cost-effectiveness ratios (ICERs). We simulated cohorts of 100 million individuals over a 20-year time horizon and across a health sector perspective.

Results: With no HCV testing or treatment, average life expectancy was 5.22 years, with 2.5 million HCV infections, 678,350 cirrhotic individuals, and 182,646 deaths from liver disease (Table 1). Screening only at HD initiation increased HCV care rates by 77% and decreased liver deaths by 79%, with an ICER of $71,533 per QALY saved compared to no screening. Increasing screening to every 2 years decreased liver-related deaths by an additional 31% with an ICER of $119,853 over screening at HD entry only. Screening annually or every 6 months was not cost-effective using a willingness to pay threshold of $100,000, even with halving baseline mortality rates or perfect linkage to care.

Conclusions: Testing for HCV in HD provides good economic value, but current CDC and KDIGO recommended intervals are not cost-effective.

Funding: NIDDK Support, Other NIH Support - NIDA, NIAID, Private Foundation Support.

Table 1: Model outcomes and incremental cost-effectiveness ratios, discounted present value of 100 million individuals over 20 years across all health sectors.

P00812
Disease Activity and Adverse Events in Patients with ANCA-Associated Vasculitis Undergoing Long-Term Dialysis: The DIAS Study
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Background: Kidney impairment of ANCA-associated vasculitides can lead to kidney failure. Patients with kidney failure may suffer from vasculitis relapses, but are also at high risk of infections and cardiovascular events, which questions the maintenance of immunosuppressive therapy.

Methods: Patients with ANCA-associated vasculitides initiating long-term dialysis between 2008-2012 in France, registered in the national REIN registry, and paired with the National Health System database, were included. We analyzed the proportion of patients in remission off-immunosuppression over time, and overall and event-free survival on dialysis (censoring for kidney transplantation). We compared the incidence of vasculitis relapses, serious infections, cardiovascular events and cancers before and after dialysis initiation.

Results: 229 patients were included: 142 with granulomatous polyangiitis (GPA) and 87 with microscopic polyangiitis (MPA). 82 patients received a kidney transplant. Mean follow-up after dialysis initiation was 4.6 ± 2.7 years. The proportion of patients in remission off-immunosuppression increased from 23% at dialysis initiation to 62% after 5 years. Overall survival rates on dialysis were 86%, 66% and 54% at 1, 3, and 5 years, respectively. Main causes of death were infections (35%) and cardiovascular events (26%), not vasculitis flares (6%). The incidence of vasculitis flares decreased from 111 to 7 episodes/100 person-year before and after dialysis initiation (p=0.05). Overall, during follow-up, 53% of patients experienced a serious infection, 52% a cardiovascular event, and 17% a vasculitis relapse.

Conclusions: The proportion of patients with ANCA-associated vasculitides in remission off-immunosuppression increases with time spent on dialysis. In this cohort, patients were far less likely to relapse from their vasculitis than to display serious infectious or cardiovascular events. Therefore, the benefit/risk balance of maintenance immunosuppressive therapies in patients on long-term dialysis should be carefully evaluated.

PO0813
Analysis of Costs, Quality of Life, and Nutritional Status Between Patients with Two Different Models of Hemodialysis in Mexico: Chronic vs. Intermittent Hemodialysis
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Background: In Mexico, access to conventional chronic hemodialysis (cHD) programs (two or three hemodialysis sessions a week) is only possible in a few patients. In the Federal District and San Lázaro Hospitals, patients treated without social security usually are under private hemodialysis (IH) sessions, this is weekly, biweekly or even monthly sessions when the signs and symptoms of dialysis urgency are present. We aim was to compare the costs, quality of life and nutritional status among two different model hemodialysis: cHD versus IH.

Methods: We performed a pilot cost study. Costs generated by HD sessions and indirect costs reported by the patient are evaluated to obtain out-of-pocket expenses (medicine, transportation, food, medical supplies). Nutritional status was evaluated through the malnutrition and inflammation score (MIS) and quality of life through the SF-36 questionnaire.

Results: Twenty patients were analyzed 55% male, with a mean age of 40.5 ± 14.9 years, median time on dialysis 3 years, 41% of patients were on cHD and 45% on IH. Time on dialysis was 2.7 ± 2.9 years. The proportion of patients with ANCA-associated vasculitis in the cHD vs. IH-D group was 30% vs. 25% and the main comorbidity was HTA (95%). Eleven in cHD and nine in IH-D. In Fig 1, shown biochemical characteristics, MIS, grip strength, and costs are presented by study group. The quality of life analysis showed worse scores in symptoms; effects of kidney disease; morbidity of kidney disease; physical component; and mental component (p < 0.05).

Conclusions: Although not statistically significant differences were identified in out-of-pocket spending between models, patients with IH-D presented worse score MIS and quality of life. A health policy is necessary that allows universal access to renal replacement therapies in Mexico.

PO0814
Potential Cost Savings Associated with the Reduction of Hospital Admissions by Using Online High-Volume Hemodiafiltration (Hv-HDF) vs. High-Flux hemodialysis (HF-HD)
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Background: On-line HDF for maintenance dialysis patients is available in Europe and Canada but is essentially absent in the US. The National Institute for Health and Care Excellence (NICE) conducted a systematic review and built economic models to compare hemodiafiltration (Hv-HDF) with HF-HD. They found HDF to be cost-effective due to benefits such as increased survival and reduced medication requirements. In addition, NICE found HDF using high convection volumes ~20 L (HvHDF) had greater mortality benefits compared to HF-HD. Economic models built upon payment systems outside of

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the US may be difficult to apply within the US due to differing payment structures. This analysis estimates the potential cost-savings associated with reducing hospital admissions with online HvHDF (vs HD-HD) based on published studies and USRDS cost data.

**Methods:** We updated the NICE systematic literature review on HDF studies, especially for articles on hospitalization by searching EMBASE (Ovid), PubMed and NHS EED from 2010 to present. We used an input-output Microsoft Excel® database to calculate the potential cost-saving of online HvHDF compared to HD-HD from reducing hospitalization and estimating the savings associated with those averted hospitalization and missed in-center HD. The average cost of hospitalization was derived from USRDS and adjusted to 2011 ($17,181), and the average hospital stay was 6.42 days and assuming thrice weekly would result in 2.75 missed HD treatments. It is assumed that reimbursement rate for in-center HD is $253.13 per treatment and costs of treating with HvHDF and HD-HD are equivalent.

**Results:** Out of 107 studies found, 4 reported hospitalization rates for HDF and HD-HD, and 1 compared HvHDF with HD-HD. This study found 10.8 fewer hospital admissions with HDF per 100 patient-years (Maduell, et al, High efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. J Am Soc Nephrol 2013: 487-97). We identified potential saving of $1,856 per patient per year (PPPY) due to averted hospitalizations and $75 PPPY due to avoiding missed HD treatment for a total of $1,931 PPPY.

**Conclusions:** The potential annual cost-savings of using HvHDF over HD-HD in maintenance in-center HD was estimated as $1,931 PPPY or $193,071 per 100 patients.

**PO00815**

**Predicting Decline in Residual Renal Urea Clearance via Random Forest Regression**

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**Background:** For incident hemodialysis patients, the decline of residual kidney function (KRU) after the first year of dialysis therapy is associated with adverse outcomes such as higher death risk. While several studies have identified biomarkers associated with higher risk of steeper KRU decline, we sought to employ more novel prediction utilizing a random forest regressor to identify important predictors of KRU after one year on hemodialysis.

**Methods:** We retrospectively reviewed a cohort of 5,141 patients who initiated in-center hemodialysis from 2007 to 2011 and had available KRU data at both baseline and during the 90 days after the one-year mark. 80% of the cohort was selected for the training dataset, with the remaining 20% used to test the model. Cross validation was utilized to optimize the number of trees and the mtry parameter. For feature selection, we used the 20 most important features from a random forest using all available predictors.

**Results:** In our cohort, mean age was 61 ± 14 years, with 66% men, 25% Black, 70% diabetes, and mean baseline albumin was 3.62 ± 0.42 g/dL. Median baseline KRU was 4.24 (6.39 – 2.69). Median KRU after one year was 1.74 (3.14-0.76). The random forest model yielded an overall mean squared error of 2.13 with noticeably stronger performance on the lower end of final KRU values. Using the median response as a classification threshold, the model achieved an AUC of 0.74. A variable importance analysis revealed that the model’s five most important predictors consist of baseline KRU, albumin, weight, post-treatment session, blood urea nitrogen level, and body mass index.

**Conclusions:** We showed that a random forest regressor can predict KRU values for hemodialysis patients after one year of treatment with moderately high accuracy. Utilizing our predictive models could aid patients and clinicians in determining the best course of treatment, which should be validated in future studies.

**PO00816**

**Predicting Time to Dialysis and Unplanned Dialysis Start Using Machine Learning Models**

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**Background:** Despite advances in nephrology care, a majority of patients are not well prepared for starting dialysis. This puts patients at a heightened risk of adverse outcomes such as increased hospitalization, higher health care costs and poorer quality of life. Most studies report prevalence of unplanned dialysis start between 40% and 60%. We have implemented a solution that allows the care team to combine their clinical judgement with the outputs of state-of-the-art machine learning models. These models learn patterns in historical data which lead to outcomes of interest.

**Methods:** We have developed and deployed a set of supervised machine learning models using gradient boosted decision trees that estimate the likelihood a patient with chronic kidney disease (CKD) requiring dialysis and having an unplanned start in the coming 18 months. Unplanned Dialysis Start (UDS) Model sits downstream of Time to Dialysis or Temporal Risk (TR) Model and scores the CKD patients who are predicted to need dialysis. We trained these models in the medical and pharmacy claims and lab data of 751,242 CKD patients spanning multiple years. Input features included demographics, medical history, social determinants of health, and medication adherence. We are using the model output for selection of beneficiaries in a kidney care management program. In addition, the care team is using the risk scores at the point of care.

**Results:** TR Model has AUC of 93% and F1-score of 0.31 whereas UDS Model has AUC of 71% and F1-score of 0.30. The models are relying on clinically relevant features in making their predictions. Top predictors include serum creatinine, serum albumin, serum phosphate, hemoglobin, CKD Stage, age, comorbidities, nephrologist visits, social determinants of health, and uremic symptoms. We are able to discover patients who are not receiving nephrology care but are at risk for an unplanned start.

**Conclusions:** Machine learning models developed in large claims and lab datasets can predict time to dialysis and risk of unplanned dialysis starts. These models can be integrated into care management programs to target high risk patients with interventions calibrated to the individual patient’s risk. An evaluation study is the next logical step.

**Funding:** Commercial Support - CVS Health
PO0818

Clinical Research Offers Potential Benefit to Patients and No Obvious Harm to Clinical Value

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Background: Randomized clinical trials (RCT) are underperformed in nephrology. This may be due to the uncertain impacts on quality measures. We assessed quality outcomes between research-conducting (RF) and research-naive (NF) dialysis facilities, as well as respective patient outcomes.

Methods: We used data from adult HD patients treated at national provider in the United States from 2017-2018. RF were 1:1 propensity score matched (PSM) to NF on patients/year, patient/facility exposure, % Medicare, % accountable care, region and quality outcomes were compared cross-sectionally. Research participants (RP) from facility analysis were 1:1 PSM to research naïve participants (RNP) at baseline (research participation start or index date) on age, sex, race, Ethnicity, vintage, access, albumin, hemoglobin (hgb), congestive heart failure, ischemic heart disease, diabetes, missed treatments, and hospital day rates. Quality outcomes were compared longitudinally at 6 and 12 months.

Results: We found no differences in quality outcomes between RF and NF facilities. We observed RP had lower hospital day rates at 6 months after research participation start compared to the NRP, as well as higher % with albumin >=4g/dL at 6 and 12 months, higher % with iPTH 150-600 pg/mL within 12 months, and lower anemia target achievement (Figure 1).

Conclusions: We observed no significant differences in quality measures between facilities that conducted clinical trials vs those that did not. Participation in trials was associated with lower hospital day rates and better achievement of nutritional targets, but lower achievement of hemoglobin and transferrin saturation targets. Anemia results might be attributable to conservative hgb repletion in trials of new investigational drugs. Trial conduct appeared to do no harm to quality achievement and provide potential benefits to participants, which may be associated with additional evaluations/monitoring provided.

Funding: Commercial Support - Fresenius Medical Care North America

PO0819

Novel Insight About Pregnancy in Women on Chronic Dialysis: Systematic Review and Meta-Analysis Correlating Dialysis Regimen and Pregnancy Outcome

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Background: Extending hours HD regimens in pregnancy improve maternal fetal outcomes. This improvement is linked both to HD rhythm and duration. The results obtained during pregnancy lead to reconsidering the concept of adequate HD at least in the young population

Conclusions: Extendend hours HD regimens in pregnancy improve maternal fetal outcomes. This improvement is linked both to HD rhythm and duration. The results obtained during pregnancy lead to reconsidering the concept of adequate HD at least in the young population

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PO0820

Thrombocytopenia Predicts Mortality in Chinese Hemodialysis Patients: An Analysis of the China DOPPS

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Background: Mortality rate was high in Hemodialysis (HD) patients. Our previous study suggested platelet counts might be a potential risk factor. However, few studies have examined the association of platelet count with mortality in HD patients. The aim is to examine if there is an association of thrombocytopenia (TP) with mortality and cardiovascular (CV) death in Chinese HD patients.

Methods: China DOPPS data was used. Fifty-eight of 1427 patients were excluded for missing platelet records. Demographic data, comorbidities, lab data, and death records were extracted. Participants were divided into 2 groups according to their platelet counts as TP group (platelet<100x10^9/L), and Non-TP group (platelet>=100x10^9/L). The Non-TP could not be further divided into normal or above normal groups as limited by the sample size. Associations between platelet counts and all-cause and CV mortality were analyzed using Cox regression models. Stepwise multivariate logistic regression was used to identify related impact factors.

Results: Of 1369 patients, 201 (14.7%) died and 102 (7.5%) died from CV disease. 11.2% (154) had TP at baseline. The mortality rates were 26.0% vs. 13.3% (p<0.01) in patients with and without TP. TP was associated with higher all-cause mortality after adjusted for covariates (HR:1.75, 95% CI: 1.12-2.74), but was not associated with CV death after fully adjusted (HR: 1.75, 95% CI: 0.89, 3.45, Figure 1). Multivariate logistic regression showed that Urine output <200 ml/day, cerebrovascular disease, hepatitis B or C, and white blood cells were independent impact factors (P < 0.05).

Conclusions: Baseline TP is associated with higher risk of all-cause mortality in HD patients. Platelet counts may be used as early available outcome predictors among HD patients, though additional study is needed.

Funding: Government Support - Non-U.S.
PO0821
Steady Exercise Improves Hand Grip and Leg Muscle Strength in Hemodialysis Patients

Background: Sarcopenia due to chronic inflammation and biochemical disturbances in chronic kidney disease is severe and more prevalent in patients on hemodialysis (HD). We longitudinally evaluated the hand grip (HGS) and leg muscle strength (LMS) in patients receiving HD and tried to find factors associated with muscle strength.

Methods: We screened (January 2020 (n=127)) and followed up (June 2020 (n=110) and December 2020 (n=104)) HGS (opposite the fistula side) and LMS (both sides) at single center by using digital hand and leg dynamometer (T.K.K.5401 and 5710e/5715, Takei scientific instruments Co. Ltd., Niigata, Japan).

Results: HGS and LMS showed good correlation (r = 0.658, p < 0.001). HGS (24.2 vs. 15.5 kg) and LMS (32.8 vs. 22.5 kg) were better in men (p < 0.001 and p < 0.001, respectively). Muscle strength was greater in men irrespective of age except for LMS in younger patients (< 60 years). Older patients (≥ 60 years) showed decreased LMS than others in women (p = 0.01). Patients who performed steady home- or hospital-based exercise showed marginally higher HGS (23.1 vs. 19.8 kg, p = 0.07) and significantly higher LMS (33.7 vs. 25.9 kg, p = 0.004). Steady exercise showed improvement of LMS throughout the study period (from January to June, p = 0.004, from January to December, p = 0.014). Multiple linear regression analysis proved male sex and steady exercise were factors associated with better HGS and LMS. Steady exercise showed greater impact on LMS in male patients with longer HD vintage (≥ 44 months) and on HGS in younger male patients with shorter HD vintage (< 44 months).

Conclusions: Sex, age, and steady exercise were important determinants of muscle strength in HD patients. And serum creatinine and dry weight, which reflects muscle mass, were also important in determining muscle strength. We need to encourage patients to do regular home- or group-exercise from the beginning of dialysis and introduce new feasible form of exercise for HD patients.

PO0822
The Association Between Prevalence of Peritoneal Dialysis vs. Hemodialysis and Patients’ Home Distance to Dialysis-Providing Facilities
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Background: Accessibility to dialysis facilities should play a role when deciding on a patient’s long-term dialysis modality. Studies investigating the effect of distance to nearest dialysis-providing unit on modality choice, however, have yielded conflicting results. We investigated the association between patients’ dialysis modality and the distances (driving and straight) to the closest HD and PD-providing units.

Methods: All ESKD patients (USRDS) who initiated in-center HD and PD in 2017, were 18-90 years old, and on dialysis for ≥ 30 days were included. Patients who resided in non-conterminous US or lived > 90 miles from the nearest HD-providing unit were excluded.

Results: Among 102,247 included patients, median driving distance to the closest HD unit was greater for PD patients (3.9 vs 2.9 miles; p <0.001). Compared to HD patients, PD patients had longer driving distances to their nearest PD unit (4.4 vs 3.4 miles; p <0.001). PD utilization increased with increasing distance from patients’ homes to the nearest HD unit (OR 1.11, 95% CI 1.08-1.14 per 10-mile increase). This association did not change whether the PD unit was farther/closer than the nearest HD unit (Figure 1). This association was not seen when analysis was performed using straight line distance.

Conclusions: PD utilization increases with increasing driving distances from the nearest dialysis providing units (HD or PD). Using driving distance, but not straight line distance affects data analysis and outcomes. Increasing the number of PD units may have a limited impact on increasing PD utilization.

PO0823
Evaluation of Frailty Assessment Tools and Their Measurement Properties in CKD
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Background: Frailty is three to seven times more common in people with chronic kidney disease (CKD) than in those with normal kidney function. Although frailty and its impact in CKD is well-recognized, the measurement properties of the tools used to assess this syndrome are not known. The aim of this systematic review was to evaluate frailty assessment tools and their measurement properties in CKD.

Methods: The study was conducted using the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) guidelines and Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols (PRISMA-P 2015). We searched ten electronic databases (eg. OVID MEDLINE, OVID EMBASE, OVID Health and Psychosocial Instruments, Cochrane Central Register of Controlled Trials (CENTRAL)) and screened studies as per the following inclusion criteria: peer-reviewed original research, adults with CKD (non-dialysis, dialysis or kidney transplant (KT)), examines at least one established multidimensional tool used for the assessment of frailty, and presents information to evaluate the measurement properties of the tool. Methodological quality assessment and data synthesis will be performed as per COSMIN guidelines. This review was registered with PROSPERO (CRD42021234558).

Results: We retrieved 647 unique citations with 58 eligible studies (N=16,026) of which 60% were prospective cohort studies. The majority (59%) included patients on dialysis, 19% were KT, and the remaining non-dialysis CKD. The dialysis populations utilized hemodialysis (HD) (38%) and peritoneal dialysis (PD) (34%) modalities. Fried’s phenotype was the most commonly tool used to assess frailty (57%). Predictive validity was the most frequently reported measurement property (86%) followed by responsiveness (12%). Thirty-one (53%) of the included studies using the Fried’s Phenotype evaluated predictive validity.

Conclusions: In this review, a majority of the studies focused on the dialysis and non-dialysis populations. Fried’s Phenotype, the most commonly administered tool, primarily evaluated predictive validity. Future research is required to identify the tool(s) that will be predictive of adverse health outcomes in the KT population and additional studies evaluating these tool’s responsiveness to change are needed.
Change in Physical Activity and Function in Patients with Baseline Advanced Non-Dialysis CKD

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Background: Progressive declines in physical activity and function are common in individuals with worsening chronic kidney disease (CKD). However, little is known about whether the transition to dialysis is associated with accelerated decline. We aimed to assess temporal rates of change in physical activity level and physical function in people with advanced CKD to determine whether the transition to dialysis was associated with accelerated decline.

Methods: Individuals with advanced CKD stages G4-G5 from the Canadian Frailty Observation and Interventions Trial (CanFIT) were included. Outcomes included change in physical activity level measured using the Physical Activity Scale for the Elderly (PASE) and physical function measured using the chair stand test, 4-meter gait speed, and grip strength. Unadjusted and adjusted generalized linear regression models were conducted to determine whether progression to dialysis was associated with greater decline in physical activity or physical function.

Results: Of 386 individuals, 162 individuals progressed to dialysis during the study period, whereas 224 did not. Both groups experienced statistically significant declines in self-reported physical activity, increased chair stand test times, and decreased gait speed. Compared to individuals with advanced nondialysis CKD, progression to dialysis was associated with greater increase in chair stand test time in unadjusted (beta estimate 6.05, 95% CI 3.26 – 9.74, p<0.001) and adjusted (beta estimate 5.23 seconds, 95% CI 0.75 – 9.71, p<0.02) models.

Conclusions: Although individuals with advanced CKD experience declines in physical activity and function over time, progression to dialysis is associated with accelerated decline in physical function as measured by the chair stand test. Future studies on interventions to delay or prevent declines associated with CKD progression and dialysis initiation are needed.

Validation of the Surprise Question in an Ethnically Diverse Population

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Background: The surprise question (SQ)—Would I be surprised if this patient...
PO0829
Symptom Clusters in a Diverse Prospective Hemodialysis Cohort
Amy S. You,1 Sara S. Kalantar,2,3 Keith C. Norris,1 Rene Amel Peralta,1 Yoko Narasaki,1 Ronald A. Fischman,4 Michael A. Fischman,4 Avedik Semerjian,5 Zahra Azadbadi,1 Danh V. Nguyen,1 Kamyar Kalantar-Zadeh,4 Connie Rhee,1 University of California Irvine, Irvine, CA;1 University of California Berkeley, Berkeley, CA;2 University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA;3 Southland Renal Medical Group, Long Beach, CA.

Background: Hemodialysis (HD) patients experience a high symptom burden similar to that of patients with malignancy, which may adversely impact their quality of life and well-being. Given that emerging data in other fields (oncology) show that symptoms often occur in clusters, we examined the presence of symptom clusters in a diverse prospective HD cohort.

Methods: In 122 HD patients from the prospective Malnutrition, Diet, and Racial Disparities in Chronic Kidney Disease study recruited across 16 outpatient dialysis clinics, the prevalence of CKD-associated symptoms was ascertained by the Dialysis Symptom Index (DSI), a 30-item validated survey that assesses symptom severity (score range of 0–10) with higher scores indicating greater severity, over 7/2020-8/2020. Using the DSI surveys, we examined the presence of symptom clusters (a 2 symptoms related to each other and occurring together) across domains categorized by organ system.

Results: The mean±SD age of the cohort was 60.9±13 yrs, among whom 51% were female, 22% were Black, and 62% were Hispanic. Across the 30-item DSI survey, the most common individual symptoms included feeling tired/lack of energy (71%), dry skin (61%), itching (42%), muscle cramps (42%), and numbness/tingling in feet (41%). Upon examining co-existing symptoms, there was a high prevalence of symptom clusters, with the most common pairings including: 1) having trouble falling asleep + feeling tired/lack of energy or trouble staying asleep, 2) having trouble staying asleep + feeling tired/lack of energy, 3) dry skin + itching, 4) dry skin + dry mouth, and 5) decreased interest in sex + difficulty becoming aroused.

Conclusions: We observed a high prevalence of symptom clusters in a well-defined, diverse prospective HD cohort. Further studies are needed to determine the physiologic underpinnings of concurrent symptoms in order to identify targeted therapies that can ameliorate the high symptom burden of HD patients.

Funding: NIDDK Support

PO0830
Implementation and Effectiveness of a Supportive Care Learning Collaborative for Hemodialysis
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Background: The objective of this study was to determine whether a learning collaborative for hemodialysis providers improved delivery of supportive care best practices.

Methods: Ten U.S. hemodialysis centers participated in a hybrid implementation-effectiveness pre-post study targeting seriously ill patients between April 2019 and September 2020. The collaborative educational bundle consisted of learning sessions, communication training and implementation support. The primary outcome was change in proportion of seriously ill patients with complete advance care planning (ACP) documentation. Healthcare utilization was a secondary outcome and implementation was assessed qualitatively.

Results: One center dropped out during the COVID-19 pandemic. Among the remaining nine centers, 22.9% (328/1440) of patients were identified as seriously ill in the post-intervention period and 18.0% (226/1254) were identified in the post-intervention period. From the pre-intervention to post-intervention period, the proportion of patients with complete ACP documentation increased, and hospitalizations and emergency department visits decreased (Table). There was no difference in mortality, palliative dialysis, hospice referral or dialysis discontinuation. Screening for serious illness was widely and sustainably adopted. Goals of care discussions were adopted with variable integration and sustainability.

Conclusions: Supportive care best practices were feasible to implement in hemodialysis centers and largely sustained during the COVID-19 pandemic. We observed increased documentation of ACP and lower healthcare utilization after the intervention which could reflect a combination of collaborative and pandemic effects.

Funding: Private Foundation Support

Table. Advance care planning and health care utilization among seriously ill hemodialysis patients

PO0828
Improve Quality of Life in Patients Starting Hemodialysis: Knowledge of Kidney Disease and Dialysis, Promote Self-Care, and Reduce Symptom Burden
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PO0831
Anxiety, Comorbid Depression, and Dialysis Symptom Burden
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Background: Anxiety is an understudied construct in patients with kidney failure. Its relationship to dialysis symptoms burden, including symptom burden, is not well known. ‘Anxiety’ describes a category of diagnoses and it is unknown if its components of general worry, somatic anxiety, and anxiety sensitivity have different relationships with outcomes. It is also not known if depressive affect moderates these relationships.

Methods: In this single center study survey, 100 participants completed an assessment of depressive affect (Patient Health Questionnaire-9, PHQ-9), worry (Generalized Anxiety Disorder-7, GAD-7), somatic anxiety (Beck Anxiety Inventory, BAI), anxiety sensitivity

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(Anxiety Sensitivity Index, ASI), and dialysis symptom burden (Dialysis Symptom Index – DSI). A mixed methods study was designed to assess the demographic information, number of missed dialysis sessions in the past 30 days (not rescheduled or due to hospitalization), and average interdialytic weight gain over the past 3 dialysis treatments.

**Results:** The characteristics of the sample are found in the table below. People with elevated somatic anxiety (BAI > 15) had significantly higher rates of depression, worry, anxiety sensitivity, and dialysis symptom burden (p<.001, all cases). In a predictive model of symptom burden, age, race, and gender were not associated with symptom burden, and only somatic anxiety remained significant once adjusting for depression. In the final model, depression accounted for 40% of the variance and somatic anxiety accounted for an additional 37%.

**Conclusions:** It appears that the impact on symptom burden of depression and worry/anxiety sensitivity overlap significantly, but somatic anxiety, commonly found in panic disorder, may be a unique contributor to excess symptom burden.

**PO0834**

**Prevalence and Demographic Correlates of Pain, Depression, Fatigue, and Readiness to Seek Treatment for These Symptoms in Hemodialysis Patients**

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**Background:** Patients with End Stage Renal Disease on hemodialysis (HD) experience a high burden of pain, fatigue and depressive symptoms. This study aims to better understand demographic differences in symptom burden and readiness to seek treatment among HD patients being recruited for an ongoing multi-center randomized controlled trial (TACare).

**Methods:** Patients on in-center HD were screened for clinical levels of pain (Likert scale ≥4), fatigue (Likert scale ≥3), and depression (Patient Health Questionnaire-9 score ≥10) within the last 2 weeks. Patients with at least one clinically significant symptom were then screened to assess readiness for seeking treatment for symptoms, and eligible to enroll if they were at least in the contemplation stage of Readiness for Behavior Change. Demographic differences in symptom screening and readiness to change (yes/no) were assessed using chi-squared tests (age) and Chi-Square or Fisher’s Exact tests (race, ethnicity, gender). Symptom burden by readiness to change status was assessed using Chi-Square tests.

**Results:** Of the 390 patients who met eligibility criteria (mean age 59 years, 45% females, 15% Black, and 32% American Indian/Alaska Native, 29% Hispanic), 303 (78%) displayed at least one clinically significant symptom - pain, fatigue, or depression. Of those experiencing symptoms, 39% reported experiencing 1 clinically significant symptom, 35% reported 2, and 26% reported 3. There were no statistically significant differences by age, race, ethnicity, or gender in those reporting symptoms versus those not reporting symptoms (80%) versus those not ready to seek treatment (20%). Of those who were experiencing symptoms, the percentage of patients willing to receive treatment increased as the number of symptoms increased (71%, 86% and 90% willing to receive treatment with 1, 2 or 3 symptoms respectively, p<.01).

**Conclusions:** The majority of HD patients report experiencing at least one clinically significant symptom and experiencing more of these symptoms increased readiness to seek treatment. Demographic difference in symptom burden and readiness for treatment were not evident in this sample and should continue to be the focus of additional research.

**Funding:** NIDDK Support

**PO0835**

**Latinx Patients’ Perspectives on Their Kidney Disease Education and Recommendations for Improvement: A Qualitative Study**

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**Background:** In most states, Latinx immigrants with kidney failure receive dialysis in acute care settings on an emergency-only basis. What and how much kidney disease education they receive, and how to improve kidney disease education and outreach among Latinx populations is unknown. The objective of this study was to understand the kidney disease educational gaps of Latín individuals who need but lack access to scheduled outpatient dialysis.

**Methods:** We conducted a qualitative, semi-structured interview study in a Texas hospital system from March 2020 to January 2021 with 15 individuals who received emergency-only dialysis when they were first diagnosed with kidney failure. We collected demographic information, and performed thematic analysis using the constant comparative method on interviews after they were audio-recorded, translated and transcribed verbatim.

**Results:** All 15 persons interviewed (60% male; mean age 51 years) identified as Hispanic, Mexican, or Mexican American. By knowing kidney disease more than 6 months before starting dialysis. The themes were: 1) lack of kidney disease awareness; 2) education provided was incomplete and poor quality; 3) lack of culturally concordant communication and care; 4) elements Latín patients receiving emergency-only dialysis want in their education; 5) facilitators of patient activation and coping; and 6) Latín patient recommendations to improve community outreach.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

*Underline represents presenting author.*
Conclusions: Latinx adults receiving emergency-only dialysis are usually unaware of their kidney disease until shortly before or after they start dialysis, and the education they receive is poor quality, and often not culturally tailored. Participants made feasible recommendations on how to improve education and outreach among Latinx communities.

Results: Of the 166 eligible patients, 101 consented to the study, and 97 completed all 12 surveys. The mean age was 56±14 years, 52% were female, and 52% were Black. The most common symptoms reported by the patients were fatigue (61%), cramping (59%), and dry skin (53%) (Figure 1). Nurses under-recognized 17/21 symptoms, mean relative difference of 34±33%. Physicians under recognized 16/21 symptoms, by a mean relative difference of 23±36%. Symptoms with the largest degree of under-recognition by nurses were dry skin (difference of 51 percentage points) and fatigue (difference of 42 percentage points). Physicians struggled most with recognition of cramping (difference of 39 percentage points) and fatigue (difference of 34 percentage points).

Conclusions: Patient symptoms were generally under-recognized by both dialysis nurses and physicians. While several symptoms such as shortness of breath, nausea, and vomiting were well recognized by nurses and physicians, nurses under-recognized dry skin and fatigue and physicians under-recognized cramping and fatigue.

Funding: NIDDK Support, Commercial Support - Renal Research Institute

PO0836
Improving Education and Satisfaction of Hemodialysis Patients Through Anonymous Feedback
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Background: Patients on outpatient hemodialysis (HD) are a particularly vulnerable population who may not feel comfortable sharing their experience given the complex and frequent nature of their care. This could lead to conceivable gaps in knowledge pertaining to improving their satisfaction and education. To account for this potential limiting factor and to build on previous surveys performed on HD patients we conducted a study in nine of our university affiliated HD units.

Methods: The study had 3 major objectives: 1) apprehend the level of satisfaction of patients with varying aspects of HD related care, 2) evaluate level of understanding and education of patients regarding issues that pertain to their health and wellbeing, 3) identify potential avenues for improvement based on patients’ input. The survey was in English, paper based, with individual answer choices graded using a 1-5 rating scale [1:very poor, 2:poor, 3:neutral, 4:good, 5:excellent]. To ensure anonymity, the completed surveys were folded and dropped into a box.

Results: Among 516 screened patients 228 did not participate. Additional 35 patients were excluded for ≥ 1 reasons: legally blind, unable to read/write/speak English, advanced dementia, too frail. 253 eligible patients completed the survey. While the overall results were reassuring with 18 out of 24 questions yielding an average of ≥ 4.2 per question, we found specific areas for improving care and education. These included providing additional resources and information regarding palliative care, mental health, cardiovascular diseases, transplant process, addressing discomfort during HD, improving privacy, and improving the time that the nephrologist spends with patients.

Conclusions: The US centers for Medicare and Medicaid service (CMS) prospective payment system and quality incentive program requires that dialysis centers meet predefined criteria for quality of patient care to ensure future funding. We took advantage of an anonymous survey to further reflect on the potential needs of this patient population to enhance their quality of life and education. Despite specific limitations, our survey demonstrated patients undergoing HD were overall satisfied and had a good understanding about their overall health. However, we identified several aspects to improve upon as requested by our respondents.

PO0837
Provider Recognition of Patient-Reported Symptoms in Patients on Maintenance Hemodialysis
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Background: Patients with ESKD on maintenance HD (HD) experience more symptoms than the general population. In order to enable better symptomatic management, it is critical that providers recognize and document these symptoms; however, recognition by nurses and physicians is unclear.

Methods: We surveyed patients that were receiving in-center HD for ≥30 days, and attended HD three times a week at the Mount Sinai Kidney Center. Patients were surveyed on if they experienced 21 symptoms over the past 24 hours at the end of their treatments for 12 sessions. The treating nurses were surveyed at the end of each HD treatment to identify if the patient had any of the 21 symptoms. We considered a positive response on any of the 12 surveys or positive during the study period. Physicians were asked during week three of the study period if the patient had experienced any of the 21 symptoms during the past 4 weeks.

PO0838
Improving Food Insecurity in Patients with ESKD on Hemodialysis: Partnership with Local Food Bank
Elaine T. McCull, Emaad M. Abdel-Rahman. University of Virginia, Charlottesville, VA.

Background: Nutrition plays an important role in the management of ESKD on HD. Barriers to appropriate nutrition include medical, behavioral and socioeconomic factors. Socio-economic factors may include poor purchase power and problems with transportation. Poverty rate at the area of University of Virginia (UVA) is 12.9%, which is 1.3 times the state average.

Methods: UVA partnered with the local food bank to meet the basic nutritional needs of our patients by delivering renal appropriate diet to patients at the dialysis unit, with an aim of reducing individual food insecurity.

Results: The current UVA food bank collaboration program distributes more than 50 bags each month and roughly 80% of the entire dialysis program has received at least one bag since the inception of the program. Presently 34 patients consistently received bags each month (bi-monthly or greater distribution of bags). There was no significant changes in weight, serum albumin, calcium, phosphorus or potassium between baseline and 6 months of consistently receiving food bags. 28/34 (82.4%) patients responded to a survey. Patients were 64.3% African American with 57.1% females with average age of 61.3 years. Average household of these patients were 2.2, receiving 2.3 bags/week with an average of 3.3 meals /week. While 50% of patients reported satisfaction with the program, 14.3% were very satisfied, 32.1% neutral and 3.6% were unsatisfied. 57.1% viewed the goal of reducing individual food insecurity.

Conclusions: Partnership with local food banks helps decrease food insecurity and improved satisfaction in patients on hemodialysis. Nutritional parameters did not improve, which may be due to consumption of supplemental food outside of the program. Expanding such programs to other dialysis units and to include fresh foods, vegetables, and meats could help decrease dependence on external sources of higher processed foods that contain high levels of potassium and phosphorus and may improve patients’ outcomes.

PO0839
Medication Burden and Prescribing Patterns Among ESKD Patients on Hemodialysis in the United States, 2013-2017
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Background: The medication burden of patients with ESKD on HD is amongst the highest of any of the chronic diseases. This study describes the medication burden and prescribing patterns in a contemporary cohort of patients with ESKD on HD in the U.S.

Methods: We used the United States Renal Data System database from January 1, 2013 and December 31, 2017 to quantify the medication burden of patients on HD aged ≥18 years. We included patients who had continuous Medicare parts A, B, and D coverage

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for at least 3 months prior to January 1 of the respective year and excluded patients with a history of trauma or kidney transplant. Patients could contribute data to multiple yearly cohorts. We calculated the average number of prescription medications per patient during each respective year, number of medications within classes, including potentially harmful medications, and trends in the number of medications and classes over the study period.

Results: We included 163,228 to 176,133 patients from 2013 to 2017. In 2013, the mean age was 63.5 years and increased to 65.1 years by 2017. The percentage in the age 18-64 years category decreased (51.3% in 2013 compared with 45.0% in 2017) and the percentage in the older age categories all increased. In 2013, 51.8% were male and 48.2% were female, compared with 53.6% male and 46.4% female in 2017. The overall burden of medications decreased progressively, with a mean of 7.4 (SD 3.8) in 2013 to 6.8 (SD 3.6) in 2017. Prescribing of potentially harmful medications decreased over time (74.0% with at least one harmful medication class in 2013 to 68.5% in 2017).

In particular, the prescribing of non-benzodiazepine hypnotics, benzodiazepines, and opioids decreased from 2013 to 2017 (12.2% to 6.3%, 23.4% to 19.3%, and 68.0% to 53.4%, respectively). This trend was consistent across subgroups of age, sex, race, and low-income subsidy status.

Conclusions: Patients on EPSD. HD continued to have a high overall medication burden, with a slight reduction over time accompanied by a decrease in prescribing of several classes of harmful medications. Continued emphasis on assessment of appropriateness of high medication burden in patients with EPSD is needed to avoid exposure to potentially harmful or futile medications in this vulnerable population patient.

P00840

The Impact of Late Initiation of Chronic Dialysis on Mortality: A National Medicare Provider Data Study

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Background: Current Canadian guidelines recommend deferring dialysis initiation in asymptomatic patients until the glomerular filtration rate (GFR) reaches 6 mL/min/1.73m2, (an “intent-to-defer” strategy). However, little is known about how dialysis initiation and post dialysis outcomes are impacted when patients start at or below this threshold.

Methods: We sought to characterize the impact of starting dialysis at or below 6 mL/min/1.73m2 in a national retrospective cohort study of incident dialysis patients and other comorbidities.

Results: A total of 63327 unique patients started dialysis from 2004-2019, of whom 39696 patients started dialysis as an outpatient after at least three months of nephrology follow-up. The mean age was 63.1 +/- 14.68% were white, and 61% were male. 24% of the population started dialysis at an eGFR by CKD-EPI at or below 6 mL/min/1.73m2 (using the CKD-EPI formula) to those initiating between an eGFR of 6-15 mL/min/1.73m2 and analyzed using an adjusted cox proportional hazard model.

Results: Using deidentified Medicare Claims data we identified 7,362 patients in the outpatient group and 862 in the inpatient group. Patients could contribute data to multiple yearly cohorts. We calculated the average number of prescription medications per patient during each respective year, number of medications within classes, including potentially harmful medications, and trends in the number of medications and classes over the study period.

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Carnitine is degraded by intestinal bacteria to metabolites that are potentially toxic and containing a mixture of D and L-carnitine is available but D-carnitine is toxic. L-carnitine deficiency can present with hyperammonia, and clinicians should have high been used as treatment reduce the ammonia levels in valproate induced hyperammonemia. Coenzyme A in the mitochondria, which inhibits degradation of ammonia. This typically at discharge.

Conclusions: In our single-center experience, a lower level of consciousness at admission, larger estimated hematoma volume, and ventricular perforation were associated with high mortality in patients on hemodialysis with cerebral hemorrhage. Survivors who underwent the lifesaving brain surgery had very poor functional outcomes at discharge.

PO0844

Hyperammonemia in an ESRD Patient
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Introduction: Carnitine is an important co-factor in long-chain fatty acid metabolism, and is involved in transport of long chain fatty acids into the mitochondria. Carnitine deficiency can present with hyperammonemia. We present a patient with ESRD with hyperammonemia and encephalopathy.

Case Description: This is a 48-year-old man with End Stage Renal disease due to nephrocalcinosis secondary to treatment complications due to X-Linked Hypophosphatemic rickets, presented to emergency room with nausea vomiting and severe confusion. He had been on valproate for seizure disorder and was not on valproate or any other psychotropic medications. His liver enzymes were normal, ALT, albumin levels but he had persistently elevated alkaline phosphatase of 313 unit / L (40-130). PCO2 levels were normal. L. His ammonia level of 578 micro mol/L. There was no intracranial abnormalities imaging. Free carnitine (FC) levels came back as 26 nmol/ml (25-54), Acyl Carnitine (AC) 13 nmol/ml (5-30) AC/FC ratio of 0.5. Even though he had low normal FC levels, his AC/FC ratio was elevated and it has been proposed that car/acyl car ratio greater than 0.4 represents carnitine deficiency. Patient initiated on IV L carnitine 20 minutes before surgery. He did not have repeat episode of hyperammonemia. It was also noted that patient no longer experienced intradialytic hypotension.

Discussion: Carnitine deficiency causes accumulation of non-oxidized fatty acyl-coenzyme A in the mitochondria, which inhibits degradation of ammonia. This typically can present with hyperammonemia, and clinicians should have high index of suspicion for this entity in malnourished dialysis patients without significant liver disease. Treatment is directed at replacement with intravenous Carnitine. Oral preparation containing mixture of D and L- carnitine is available but D- carnitine is toxic. L- carnitine has limited oral absorption and has a limited bioavailability of 15%. The unabsorbed carnitine is degraded by intestinal bacteria to metabolites that are potentially toxic and have been shown to cause cognitive impairment. These limits use of oral supplementation of Carnitine.

PO0845

Neurocognitive Function with Conventional Hemodialysis vs. Post-Dilution Hemodialfiltration as Initial Treatment: A Randomized Controlled Trial (The DA-VINCI Study)
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Background: The ideal modality-choice and dialysis prescription during the first renal replacement therapy (RRT) session remains controversial. We conducted a pilot study to determine the safety risk for hemodialysis versus hemofiltration and its relationship with neurocognitive assessment on incident RRT patients.

Methods: Twenty-four incident RRT patients were included. Patients were randomized between the conventional HD group or the post-dilution HF group. MMSE and MOCA tests were applied in all patients before and after dialysis. The study demonstrates an improvement in the Mental Component Summary scores. Larger and integrated into a dialysis treatment session. The study demonstrates an improvement in scores related to anxiety, depression, and measures of quality of life. Larger and randomized trials using this intervention are needed to better understand its benefits and adverse effects, as well as the obstacles to large scale implementation.

PO0846

Intradialytic Yoga-Based Breathing and Relaxation to Improve Anxiety, Depression, and Quality of Life: A Pilot Feasibility Study
Frans Conway,1 Martha N. Desta,2 Young sun Jung,2 Daniel M. Levine,2 Andrew Bohmert.1 Well Cornell Medicine, New York, NY; 2Roguin Institute, New York, NY.

Background: In-center hemodialysis patients have high rates of depression and anxiety. Pharmacologic interventions to ameliorate psychological burdens have proven to be limited in efficacy. Alternative therapies are increasingly used for those with chronic disease. A small number of studies have looked at the impact of meditation and yoga to improve symptoms of anxiety and depression and to promote a better quality of life. The aim of this study was to test the feasibility of implementing a chairside intradialytic yoga-based breathing and relaxation technique. A secondary goal was assessing the efficacy of such an intervention.

Methods: Eligible subjects were patients with a below average score on the Mental Component Summary (MCS) of a previously completed Kidney Disease Quality of Life (KDQOL™-36) survey both at the start and the end of the study. A Likert scale to measure anxiety was completed at each dialysis treatment both pre- and post-intervention.

Results: 11 subjects were enrolled over a 10-month period in 2020; 10 completed the study. As measured by the Likert scale, anxiety was significantly reduced after listening to the recording. Notably, there was a larger reduction in anxiety on a per treatment basis in the period after the start of the Covid-19 pandemic compared to the pre-pandemic period. Over the study period, there was a significant improvement in the scores of the Effects of Kidney Disease on Quality of Life component of the KDQOL™-36, and a trend toward significant improvement in the Mental Component Summary score over the study period.

Conclusions: A chairside intradialytic breathing and relaxation program can be integrated into a dialysis treatment session. The study demonstrates an improvement in scores related to anxiety, depression, and measures of quality of life. Larger and randomized trials using this intervention are needed to better understand its benefits and adverse effects, as well as the obstacles to large scale implementation.

PO0847

Quality of Life and Symptom Burden Before and After Start of Dialysis in Older Patients
Esther N. de Rooij,1 Yvette Meuleman,1 Johan W. De Fijter,1 Kitty J. Jager,2 Nicholas C. Chensnaye,3 Christoph Wanner,3 Friedo W. Dekker,1 Ellen K. Hoogeven,1,3 the EQUAL Study investigators ‘Leids Universitair Medisch Centrum, Leiden, Netherlands; 2Amsterdam UMC Locate AMC, Amsterdam, Netherlands; 3Jeroen Bosch Ziekenhuis, 3-Hertogenbosch, Netherlands; Universitairklinikum Wurzburg, Wurzburg, Germany.

Background: The European Quality (EQUAL) study is an ongoing prospective multicenter cohort study in late stage 4/5 CKD patients 65 years. For this analysis, we included all patients who started dialysis. QoL was assessed every 3-6 months using the SF-36, resulting in a physical (PCS) and mental (MCS) component score, with higher scores meaning better QoL. Symptom number and severity were assessed every 3-6 months using the symptom index (DIS), with higher scores meaning higher burden. With linear mixed models we examined the effect of physical QoL, symptom number and severity in the year before and after dialysis start.

Data are shown as mean ± standard deviation, median (percentile 25, percentile 75) or absolute frequency (percentage).

* p ≤ 0.05 compared to before dialysis (within same group)

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Results: We included 571 older patients at dialysis start. Mean (SD) age was 77 (6) years, 74% were men, 45% had diabetes or cardiovascular disease and mean eGFR was 8.2 (3.7) ml/min/1.73m². In the year before dialysis MICS decreased by -15.7 (95% CI: -19.5 to -11.8), PCS by -12.0 (-15.7 to -8.2), symptom number increased by +3.5 (+2.5 to +4.0) and severity by +14.8 (+10.9 to +18.8). In the year after, MICS increased by +1.9 (-2.7 to +6.4), PCS decreased by -2.1 (-6.9 to +2.7), symptom number by -0.9 (-2.1 to -0.3) and severity by -6.0 (-10.4 to -1.7).

Conclusions: Mental and physical QoL, symptom number and severity, worsened considerably in the year before dialysis, but stabilized after dialysis initiation. These results could inform older ESKD patients who consider starting dialysis.

Objective Evaluation of Quality-of-Life Assessment as Predictors of Overall Health in Hemodialysis Patients in KSA


Background: Dialysis effect on a patient’s quality of life (QoL) is associated with death in regular hemodialysis (HD) patients and is a marker of wellbeing. In addition to clinical outcome measures QoL is influenced by socioeconomic status and education. Our aim was to explore the QoL in HD patients in population of prevalent HD patients in KSA.

Methods: The study consisted of 1032 patients undergoing HD in 17 centers. Data were collected by the completion of a specially designed questionnaire The Kidney Disease Quality of Life-Short Form (KDQOL-SF™) Arabic version 1.3 for assessing QoL.

Results: The study included 1032 patients (527 [51%] males and 505 [49%] females) with mean age 54.1 (±16.6) years and undergoing HD for 57.9 (±65.3) months. Multiple logistic regression analysis was done to identify parameters that independently associated with QoL. Lowest score was for the “burden of kidney disease” 33.1 (±23.4). Both “Physical Health Composite” (PHC) and “Mental health composite” (MHC) scores were poor as well, 36.5 (±8.7) and 42.0 (±8.7) respectively. “Patient satisfaction” and “Dialysis staff encouragement” scores were relatively higher 71.5 (±22.7) and 84.4 (±18.8) respectively. Age, duration of HD, cardiac comorbidity and abnormal phosphorus level were significant negative predictors for “overall health” scores while education and home medications’ count were significant negative predictors for that domain. Abnormal phosphorus level and longer durations on HD treatment were significant negative predictors for “overall health” scores while education and “Dialysis staff encouragement” scores. Age, female gender and hypoalbuminemia were significant negative predictors of “PHC” scores. Controlling serum phosphorus level and albumin might predict better QoL.

Conclusions: Misconceptions about QoL still represent a substantial barrier among HD patients. Most are educated about fundamental clinical outcomes after initiation of dialysis. In our study, Patients on hemodialysis have a poor QoL score. Different sociodemographic and clinical characteristics affect scores. Initiatives to promote and improve onboarding dialysis education and knowledge about QoL are needed to improve the low QoL in Saudi Arabia. Such patients may benefit from efforts on the part of the health care provider to support patient QoL as part of the monthly care plan.

POO848

Fetal and Non-Fetal Gastrointestinal Events with Sodium Polystyrene Sulfonate Use in Hemodialysis: DOPPS

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Background: There are increasing concerns regarding the gastrointestinal (GI) safety of sodium polystyrene sulfonate (SPS), a medication commonly used in the management of hyperkalemia. The objective is to compare the risk for fatal, non-fatal and their composite GI events following initiation of SPS in patients on hemodialysis compared to non-use.

Methods: An international registry of adults (≥18) on chronic intermittent hemodialysis (Dialysis Outcomes and Practice Patterns Study, DOPPS, Phases 2-6 from 2002 to 2018, 17 countries, n=229,295) who were prescribed SPS (n=24,668, 10.76%) were compared with non-users of SPS. Individual patient and facility-level analysis of fatal and non-fatal GI events were examined using weighted models.

Results: Country-level variation in SPS use ranged from 0.74% (UK) to 47.42% (France). 934 fatal, and 837 non-fatal events occurred [3-year cumulative incidence for fatal GI events: SPS 9.0% vs. non-SPS 7.6%; non-fatal: SPS 0.4% vs. non-0.5%]. The weighted risk of fatal and composite GI events was elevated with SPS use compared to non-use (fatal HR 1.18 95%CI 1.05-1.32, non-fatal HR 0.73 95%CI 0.64-0.84, composite HR 1.02 95%CI 1.08-1.26). Younger age (<65), men, country (France, Belgium, Japan), dialysis vintage (≥4 years), shorter HD treatment time (<3.5 hours) and a higher K gradient (serum potassium – dialysate potassium – dialysate potassium) were associated with a higher risk of a fatal GI event with SPS. The findings were consistent when limited to individuals with known vascular access (n=135, 628) and in an analysis examining the fraction of SPS use by facility.

Conclusions: SPS use in patients on hemodialysis is associated with a higher risk of fatal GI events.

Funding: Private Foundation Support

POO850

Improved One-Year Survival and Decreased Hospitalization Rate in Incident Hemodialysis Patients with Incremental as Compared to Standard Hemodialysis Regimen: A Single-Centre Experience


Background: Preservation of residual kidney function (RKF) in maintenance hemodialysis (HD) patients is associated with better survival and quality of life. RKF may be better preserved with an incremental HD regimen in patients starting HD. Since 2013, incremental HD (frequency < 3x/week) has been used in our center.

Methods: Incremental HD is implemented in incident HD patients who have a daily residual diuresis > 600 ml, a urea clearance ≥ 2 ml/min and an interdialytic weight gain < 2.5 kgs. Patients are clinically assessed every week and a 24 hr-urine sample is collected every other month in order to measure RKF.

Results: From January 2013 to March 2020, 295 patients started chronic dialysis in our center, of whom 221 were on hemodialysis. Among them, 63 patients started maintenance HD with an incremental regimen. These patients did not differ significantly from those with a thrice-weekly HD regimen in terms of age, gender and comorbidity score. Residual diuresis, eGFR and urea clearance at incremental HD initiation were respectively 1842 ± 749 ml/day, 67.6 ± 3.1 ml/min and 4.0 ± 1.8 ml/min. Among these 63 patients, four could retrieve a sufficient RKF to become dialysis-independent after a mean 6-month duration of incremental HD and 2 were transplanted while on incremental dialysis. Among the remaining 57 patients, mean duration of incremental HD until transition to a thrice-weekly HD regimen or death was 12 ± 12 months (median, IQR: 10, 6-20). Within the first dialysis year, survival and hospital-free days (median, IQR) were higher in patients starting with incremental HD than in patients with a thrice-weekly HD regimen (91 vs 77%; p=0.02 and 344 (318-360) vs 338 (295-354) days; p=0.03).

Conclusions: These preliminary results show that incremental HD can be implemented in incident HD patients as long as regular clinical and RKF assessments are found adequate. However, randomised clinical trials assessing long-term survival and quality of life in incremental HD are necessary prior to its large-scale implementation.

POO851

Association Between Systolic Blood Pressure Changes and Residual Kidney Function Decline Among Hemodialysis Patients After 1 Year

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Background: For patients undergoing hemodialysis, large changes in systolic blood pressure (SBP) from before to after the dialysis has been associated with worse survival. Declines in residual kidney function has also been associated with worse survival. However, the association between SBP changes and residual kidney function decline has not yet been examined.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: We conducted a retrospective cohort of 6659 hemodialysis patients who started hemodialysis between 2007 and 2011 with baseline changes in SBP and renal urea clearance (KRU) at the 1st and 5th patient quarter (91-day interval from dialysis start). KRU difference was measured as KRU difference between 5th minus 1st patient quarter. The association between baseline average changes in SBP and KRU difference was examined using linear regression analyses. Covariates included age, sex, race, BMI, dialysis modality type, and comorbidities.

Results: Linear regression analysis indicated a linear relationship between change in SBP and KRU decline even after adjusting for covariates. Trends across all models showed a trend toward increased systolic blood pressure showed increased residual kidney function compared to the reference (-10 to -9 mmHg). After adjusting for covariates, hemodialysis patients with SBP levels that increased by 10mmHg or more had the greatest increase of KRU (0.12, 95% CI (-0.39, -0.62)), while patients with a decrease of SBP by 10-20mmHg had the greatest decline (-0.31, 95% CI (-0.60, 0.02)). Models adjusting for SBP measures showed similar trends, while the model without low-SBP and post-SBP showed an increased in KRU when SBP decreased by 10-20mmHg (0.23, 95% CI (0.01, 0.05)).

Conclusions: Increased in SBP was associated with a greater KRU decline in hemodialysis patients. Further studies should examine the underlying causes of this association and determine if modifications to dialysis treatments can improve preserving KRU and patient survival.

PO0853 Variability of Plasma Refill Rate and Risk of Intradialytic Hypotension During Maintenance Hemodialysis

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Background: Continuous hemocrit data can be combined with time-updated ultrafiltration data to non-invasively estimate a semi-instantaneous plasma refill rate (PRR) throughout hemodialysis. The PRR is a dynamic metric that varies throughout hemodialysis, even during periods of constant rates of ultrafiltration, and is influenced by oncotic and hydrostatic forces. We aimed to determine whether variability in PRR is associated with intradialytic hypotension (IDH).

Methods: We used data from continuous hemocrit monitoring performed at 17 dialysis units from January 2017-October 2019 to calculate intradialytic plasma refill rates standardized to weight and height. PRR variability was defined as the coefficient of variance in PRR (PRRcov) every 15 minutes and categorized into three groups: low (PRRcov < 1.0), moderate (PRRcov 1.0-2.0) and high (PRRcov > 2.0). IDH was defined in three ways: (1) nadir systolic blood pressure (SBP) < 90 mmHg, (2) SBP < 90 mmHg or associated symptoms, and (3) either drop in SBP of 20 mmHg or mean arterial blood pressure of 10 mmHg with associated symptoms. Cox proportional hazard regression was used to assess the impact of starting PRR variability on time to first IDH. Marginal structural modeling was used to assess the impact of time-updated plasma refill rate variability on the risk of IDH.

Results: Among 2350 patients and 184,453 hemodialysis sessions, mean session time was 220 ± 26 min and ultrafiltration rate was 9.0 ± 3.3 ml/kg/hr. Mean PRRcov was 1.20 (IQR 0.68, 2.18) across all sessions. Compared to hemodialysis sessions with low PRRcov sessions with high PRRcov in the first 15 minutes of treatment were associated with a 1.14 hazard of intradialytic hypotension (95% CI 1.05, 1.24). Accounting for repeated measures and changes in systolic blood pressure and ultrafiltration, sessions with high PRRcov throughout the duration of hemodialysis were associated with an increased risk of IDH based on definitions: definition 1 (OR 1.29, 95% CI 1.16, 1.43), definition 2 (OR 1.85, 95% CI 1.77, 1.94), and definition 3 (OR 1.87, 95% CI 1.78, 1.98).

Conclusions: PRR variability was associated with higher risk of IDH, independent of time-varying confounding from SBP and UFR. PRR variability could be a promising bedside metric for hemodynamic instability during hemodialysis.

Funding: NIDDK Support.

PO0854 Systemic Parameters of the Renin-Angiotsins-Aldosterone System Remain Unaffected by Changes in Fibroblast Growth Factor 23 Levels in Hemodialysis Patients

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Background: Fibroblast growth factor 23 (FGF23) is elevated in patients with chronic kidney disease and promotes the development of left ventricular hypertrophy (LVH). Decreasing the levels of FGF23 with the calcimimetic drug etelcalcetide can abate these cardiovascular disease modifying hemodialysis patients even if the prohypertrophic effect of FGF23 is modified by the renin-angiotensin-aldosterone system (RAAS). The aim of the analysis was to determine whether changes in FGF23 levels are associated with differences in RAAS-parameters in hemodialysis patients, possibly explaining its influence on LVH.

Methods: Serum samples were obtained at baseline and one year from participants in the randomized EIECAR-HD trial. In this study 62 hemodialysis patients were treated with either calcimimetic or vitamin D treatment, which have opposite effects on FGF23. We analyzed PRA-S as the angiotensin-based marker for renin activity, angiotensin II (AngII), angiotensin-converting enzyme-2 (ACE2) and aldosterone using a high throughput mass spectrometry assay.

Results: The median levels of FGF23 were 2386 pg/ml (1st to 3rd quartile 189–5166) and 1386 pg/ml (288–4068) at baseline and end of study, respectively. The association of changes between baseline and end of study in FGF23 with the levels of the RAAS-components (i.e. PRA-S, AngII, ACE2, aldosterone) estimated by linear regression models was weak, with effect sizes for log2-fold-change in FGF23 close to zero. The amount of explained variation by FGF23 fold-change was generally small (drop-in-R2 values all below 0.03). The median overall levels of PRA-S were 130 pg/ml (1st to 3rd quartile 76–2169), of AngII 70 pg/ml (28–157), of aldosterone 130 pg/ml (54–218) and of ACE2 1.4 ng/ml (1.1-1.8), as compared with healthy controls (PRA-S 196 pg/ml [98-238], AngII 137 pg/ml [76-201], aldosterone 335 pg/ml [139-454], ACE2 1.38 ng/ml [1.17-1.65]).

Conclusions: In the present study we were able to show that systemic RAAS activity was grossly unaffected by the treatment induced changes in FGF23 levels in this cohort. Overall, the levels of PRA-S, AngII and aldosterone were well below the ranges measured in healthy controls suggesting that the RAAS is not systemically activated in hemodialysis patients.

Funding: Commercial Support - Investigator-initiated research grant from Amgen.

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PO0855
Prediction of Left Ventricular Function Using Electrocardiogram Data in Patients on Hemodialysis
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Background: Left ventricular (LV) systolic dysfunction is common in patients on maintenance hemodialysis (HD). Early identification of patients with depressed left ventricular ejection fraction (LVEF) can facilitate disease modifying treatment. Electrocardiograms (ECGs) are routinely performed in patients on HD, however, they have not been used for estimating LVEF in this population.

Methods: We analyzed data from five Mount Sinai facilities. Patients on HD with a transthoracic echocardiogram within 7 days of an ECG were identified using diagnostic and procedure codes. ECG data were preprocessed to remove recording artifacts, plotted to an image, and along with patient demographics were analyzed using a model comprised of a Multi-Layer Perceptron and a Convolutional Neural Network. We developed three models: 1) trained from scratch in only HD patients, 2) pre-trained on natural images (Imagenet), and 3) pre-trained on all LVEF-ECG pairs (n=698,890) excluding those for ESRD patients. Models 2 and 3 leverage transfer learning, which reuses knowledge gained from a task to perform a similar task. All models were trained/tested on LVEF-ECG pairs for ESRD patients within a Group Stratified K Fold (K=5) Cross Validation design, and performance was compared per Area Under Receiver Operating Characteristic curve (AUROC) for each category of LVEF, ≤40%, 41 to ≤50%, and >50%.

Results: We extracted 18,626 LVEF-ECG pairs for 2,168 ESRD patients. For detection of LVEF ≤40%, models trained from scratch and pre-trained on Imagenet had AUROCs of 0.74 (95% CI: 0.67-0.80) and 0.71 (95% CI: 0.65-0.77) respectively. These were outperformed by the model pre-trained on ECG data [AUROC of 0.91 (95% CI: 0.88-0.93)]. Similar results were seen when detection of LVEF 41 to ≤50% with the AUROC being 0.85 (95% CI: 0.49-0.6) for both the model trained from scratch and the Imagenet model, while the model pre-trained on ECG data achieved an AUROC of 0.82 (95% CI: 0.78-0.87).

Conclusions: A model pre-trained on non-HD LVEF-ECG pairs using transfer learning and pre-trained on Imagenet outperformed models trained from scratch or pre-trained on Imagenet. This model will facilitate identification of LV systolic dysfunction in patients on HD.

PO0856
Clinical Outcomes of Bioimpedance Analysis-Guided Hemodialysis: A Meta-Analysis of Randomized Controlled Trials
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Background: Determination of fluid status in hemodialysis patients could be a great help to the patient and provider. Fluid overload can lead to adverse outcomes, including hypotension, pulmonary edema, and death. Bioimpedance analysis (BIA) is an emerging tool in guiding fluid removal in hemodialysis population. However, although there are some randomized controlled trials (RCT), the reported outcomes remain heterogeneous and inconclusive across studies.

Methods: Ovid MEDLINE, EMBASE, and the Cochrane Library were searched for eligible articles through May 2021. Inclusion criteria were: 1) RCT comparing BIA and clinical assessment, 2) sample size > 50, 3) adults > 18 years on hemodialysis. Methodological shortcomings were assessed using an aid for assessing risk of bias (ROB) or more liters of ultrafiltration were included. Two blinded POCUS-trained physicians obtained the following measurements within the first 30 minutes of HD: left ventricular septal and lateral E/e', portal vein (PV) pulsatility and IVS. The primary outcome was development of IDH events or post HD orthostasis. IDH was defined as a decrease in systolic blood pressure by ≥ 20 mmHg plus symptoms of IDH. Fisher’s and Mann Whitney tests were used to examine the association between IDH events and various demographic, clinical, and POCUS related parameters.

Results: 54 measurements on 27 patients were obtained. Average time required by each examiner to obtain all images was 6 minutes (95% confidence interval [CI] 4.2-7.8). Average age was 57 (95% CI 52, 62), 85% were black and 44% were females. Average BMI was 32 (95% CI 28, 36), Charlson comorbidity index (CCI) score 7 (95% CI 6,8), mean diastolic blood pressure 94 (95% CI 90, 98), and creatinine clearance 0.28 (95% CI 0.25, 0.31). 54 measurements on 27 patients were obtained. Average time required by each examiner to obtain all images was 6 minutes (95% confidence interval [CI] 4.2-7.8). Average age was 57 (95% CI 52, 62), 85% were black and 44% were females. Average BMI was 32 (95% CI 28, 36), Charlson comorbidity index (CCI) score 7 (95% CI 6,8), mean diastolic blood pressure 94 (95% CI 90, 98), and creatinine clearance 0.28 (95% CI 0.25, 0.31).

Conclusions: In this pilot study, an elevated lateral E/e' was associated with lower rates of IDH events or post HD orthostasis. The role of POCUS in guiding fluid removal during HD warrants further exploration.

PO0857
Point-of-Care Ultrasound Measurements to Predict Intradialytic Hypotension: A Cross-Sectional Pilot Study
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Background: Intradialytic hypotension (IDH) results from excessive ultrafiltration in patients on chronic hemodialysis and has been linked to increased mortality. Prescribing the right amount of ultrafiltration can be challenging, partly due to the poor sensitivity of physical examination for detection of volume overload in HD patients. POCUS is emerging as a valuable tool in the assessment of volume status. The goal of this study is to determine whether pre-dialysis POCUS measurements are associated with development of IDH.

Methods: Patients ≥18 years old on HD for at least 6 months and ordered for 2 or more liters of ultrafiltration were included. Two blinded POCUS-trained physicians obtained the following measurements within the first 30 minutes of HD: left ventricular septal and lateral E/e', portal vein (PV) pulsatility and IVS. The primary outcome was development of IDH events or post HD orthostasis. IDH was defined as a decrease in systolic blood pressure by ≥ 20 mmHg plus symptoms of IDH. Fisher’s and Mann Whitney tests were used to examine the association between IDH events and various demographic, clinical, and POCUS related parameters.

Results: 54 measurements on 27 patients were obtained. Average time required by each examiner to obtain all images was 6 minutes (95% confidence interval [CI] 4.2-7.8). Average age was 57 (95% CI 52, 62), 85% were black and 44% were females. Average BMI was 32 (95% CI 28, 36), Charlson comorbidity index (CCI) score 7 (95% CI 6,8), mean diastolic blood pressure 94 (95% CI 90, 98), and creatinine clearance 0.28 (95% CI 0.25, 0.31). 8 out of 27 patients developed the primary outcome. There was no association between age, sex, ethnicity, BMI, dialysis vintage, Charlson comorbidity index, interdialytic weight gain, IVC size, PV pulsatility, septal E/e' and the primary outcome. There was a significant association between lateral E/e' and IDH events or post HD orthostasis (p<0.05).

Conclusions: In this pilot study, an elevated lateral E/e' was associated with lower rates of IDH events or post HD orthostasis. The role of POCUS in guiding fluid removal during HD warrants further exploration.

PO0858
A Clinical Approach of Intradialytic Creatine Supplementation in Dialysis-Dependent CKD Patients: A Rationale and Study Design
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Background: There is great need for identification of new, potentially modifiable risk factors for the poor HRQoL and excess risk of mortality in dialysis-dependent chronic kidney disease patients. Creatine is an essential contributor to cellular energy homeostasis, yet on a daily basis 1.6-1.7% of the total creatine pool is non-enzymatically degraded to creatinine and subsequently lost via urinary excretion, thus necessitating a continuous supply of new creatine to remain in steady-state. Due to an insufficient ability to synthesize creatine, unopposed losses to the dialysis fluid, and insufficient intake, hemodialysis patients are prone to creatine deficiency, and may benefit from creatine supplementation. To avoid problems with compliance, fluid balance and, furthermore, to prevent intradialytic losses of creatine to the dialysate, we aim to investigate the potential of intradialytic creatine supplementation in improving outcomes.

Methods: Here, we describe the rationale and design for a block-randomized, double-blind, placebo-controlled pilot study. A total of 16 hemodialysis patients will be included, divided into four groups receiving intradialytic creatine supplementation (0.5mM, 1.0mM, 1.5mM, 2.0mM), or a placebo for six weeks. The aim of the pilot study is to explore the creative uptake in the circulation and tissues following different creatine supplementation dosages.

Results: The main parameters for the pilot study are the plasma creatine concentration and intra-erythrocytic creatine concentration of both pre- and post-hemodialysis samples. Secondary study parameters are handgrip strength as a measure of muscle strength, combined intradialytic urinary and intradialytic dialysate excretion of creatinine as a measure of muscle mass, and body composition measured with bioelectrical impedance analysis (BIA).

Conclusions: Intradialytic creatine supplementation may help to maintain creatine homeostasis among dialysis-dependent chronic kidney disease patients, and consequently improve important causes for impaired HRQoL, including protein energy wasting (PEW), fatigue, muscle weakness, depression, and cognitive impairment. The results from the pilot-study will serve as a basis for a larger double-blind, placebo-controlled supplementation trial.

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PO0859

Relationship Between Fluid Overload and Hemoglobin Concentration in Hemodialysis Patients: A Longitudinal Analysis

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Background: Quantification of fluid status by bioimpedance spectroscopy (BIS) has become routine outside United States (US). We performed the first assessment of fluid status in US hemodialysis (HD) clinics using a BIS device. We studied the longitudinal association between fluid overload (FO) and hemoglobin (Hgb) concentration adjusting for inflammation and erythropoiesis-stimulating agents (ESA).

Methods: Measurement of FO [Body Composition Monitor (BCM); Fresenius Medical Care] was conducted cross-sectionally in chronic HD patients in 4 HD clinics in New York. We built linear mixed effects models with Hgb as the dependent variable and calculated FO longitudinally to include as a fixed effect. We tested the robustness of the association to account for the influence of inflammation by including the neutrophil-lymphocyte ratio (NLR) as an additional fixed effect. As a subset analysis 2 separate models were built in subjects with or without ESAx. To corroborate the dilutional effect of FO we exchanged Hgb for albumin as a fixed effect.

Results: We studied 169 patients (Figure 1). FO was inversely associated with Hgb [Estimate -0.16 (-0.20 to -0.12) g/dl per 1 L of FO], a significant fixed effect that remained unchanged in magnitude even after inclusion of NLR [Estimate 0.04 (-0.05 to 0.06) g/dl per 1 unit of NLR]. The effect was larger in patients without ESA prescription [Estimate 0.22 (-0.32 to -0.12) g/dl per 1 L of FO] and in the subgroup of patients with albumin [Estimate 0.02 (-0.03 to -0.01) g/dl per 1 L of FO] with NLR being a significant fixed effect [Estimate 0.03 (-0.04 to -0.01) g/dl per 1 unit of NLR].

Conclusions: Hgb is inversely affected by FO, a significant effect independent of inflammation (NLR). The impact of FO on Hgb concentration is larger in those with no ESA treatment emphasizing that fluid status has to be considered in anemia management. The effect of FO on albumin supports hemodilution as the principal cause for the changes seen on Hgb.

Funding: Commercial Support - Fresenius Medical Care

PO0860

Interpreting Home Blood Pressure Measurements in Haemodialysis: A Post Hoc Analysis of a Randomized Cross-Over Study

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Background: Home BP correlates better with ambulatory BP, target organ damage and mortality in dialysis patients. We aimed to determine the agreement of in-centre BP with home BP.

Methods: A post-hoc analysis of a pilot-scale, randomised two-period cross over study comparing self-monitoring of BP over 4 weeks with usual care in 41 haemodialysis patients. www.clinicaltrials.gov. NCT0340349. Dialysis clinic BP and home BP (using average real variability (ARV). Mixed effects models for repeated measures with a moving average window of 2 weeks were used to examine associations with BP and ARV.

Results: 33 out of 41 participants had sufficient home BP measurements for inclusion (mean age: 63.7 years, 52.1% male). Post-dialysis SBP had moderate agreement with home SBP measurements (K = 0.6) compared with pre-dialysis SBP measurements (K = 0.4). The mean bias between home SBP and post SBP measurements was -4.15 mmHg (95% CI 23.5 to -31.8 mmHg) (Figure 1). Home SBP ARV (16 +/- 6) was as high as pre SBP ARV (14 +/- 5) and post SBP ARV (13 +/- 5). In univariate analysis only calcium channel blockers were consistently associated with pre-dialysis (P = 0.02), post-dialysis and home SBP (both P<0.001).

Conclusions: Post-dialysis SBP demonstrates moderate agreement with home BP when two week BP averages are used. Home BP measurements are as variable as clinic BP measurements and isolated measurements may lack interpretability. Averaging the home BP over two weeks may improve the utility of home BP monitoring.

Funding: Commercial Support - patientMpower

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PO0862

Benefit of More Frequent Dialysis on Dialysis Recovery Time in Nursing Home Patients with ESRD

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Background: Dialysis patients admitted to a skilled nursing facility (SNF) are characterized by advanced age, frailty, and multiple comorbidities. Based on prior studies which demonstrated shortened dialysis recovery time (DRT) with more frequent dialysis (MFD) in populations aged –50s living at home (FREEDOM Study 2010, FHN trial 2006), it was postulated that dialysis patients in a SNF would benefit from MFD.

Methods: Patients studied were admitted to SNFs in OH, TX, FL, NY, and PA from November-December 2019 (pre-COVID) and could reliably answer questions about DRT. 80% were undergoing subacute rehabilitation and 20% were permanent residents of the SNF. Patients received NxStage on-site staff assisted MFD 5x (80%) or 4x (20%) per week. Estimated DRT was ≤ 2.1. At every dialysis, patients were asked by their RN caregiver “How long did it take you to recover from your last HD session?” Responses were deemed unreliable if a patient had cognitive impairment. Reliable responses were used for outcome analysis. In the present study, DRT data was collected by a caregiver nurse, differing from the methodology of the FREEDOM/FHN studies which collected DRT data via KDQOL form or phone interview. The implications of these differences in data collection methods are currently unknown.

Results: 485 unique patients were included in the study. Demographics included 53% males, mean age 67.5 ± 13 years, African American 19%, Caucasian 23%, Hispanic 5%, Asian 0.4%, unknown or other 51%. Mean DRT was 1.5 ± 2.6 hours. Mean DRT was calculated using the midpoint recovery time for intervals, or 18 hours when DRT was the next morning or beyond. In 69%, DRT was ≤ 2 hours.

Conclusions: In the FREEDOM and FHN conventional HD 3x per week study arms, DRT averaged 6-8 hours. MFD reduced DRT to ≤1.0 hour in those relatively young patients living at home. In our study, HD patients residing in a SNF and receiving MFD experienced DRT of 1.5 hours. Age, frailty and comorbid conditions therefore do not prevent DRT benefits of MFD. DRT benefits could stem from more effective, gentler fluid management by MFD. Further studies are needed to fully explore the impact of shortened DRT on rehabilitation scores, hospitalizations and deaths in elderly patients residing in SNFs.

Funding: Commercial Support - Dialyze Direct

PO0863

The Combination of Arterial Stiffness and Peripheral Vascular Disease Aggravates Survival Among Hemodialysis Patient Using Competing Risk Analysis

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Background: The survival in end state renal disease (ESRD) patient is unacceptable high. The Skin autofluorescence (SAF) for advance glycation end products (AGEs), peripheral vascular disease (PVD) (ankle-brachial index, ABI ≤ 0.9) and arterial stiffness (carotid ankle vascular index, CAVI≥9) were reports as predictors of mortality. However, kidney transplantation (KT) competes the mortality outcome. We aim to explore these markers for precisely prediction of mortality using competing risk method.

Methods: Retrospective chart review in chronic hemodialysis patients was done in 3 hemodialysis centers in North Bangkok during November 2015 and March 2016. Arterial stiffness, SAF, IMAR and PVD were collected as a clinical predictor: Cumulative incidence of mortality was used as was a primary outcome. Logistic regression with competing risk model was used to analyze the factor affecting mortality.

Results: A Total of 176 patients were eligible and classified into 4 groups according to PVD and stiffness status. During follow up 44.5±14.8 months, the overall mortality rate was 27% which is 13.2, 28.6, 31.5 and 61.9% in no PVD and stiffness, exclusively PVD, exclusively stiffness, and combine group respectively. The PVD (HR 2.93, CI 1.2 to 7.14, P=0.018) and stiffness (HR 2.57, CI 1.16 to 5.73, P=0.021) were independent predictors of mortality. In competing risk method, the combination of PVD and stiffness associate with highest mortality (P=0.0002139), while the patients who no PVD and stiffness had the highest rate for KT (P=0.0050275).

Conclusions: The PVD and stiffness were an independent risk of mortality among hemodialysis patients. The combination of PVD and stiffness may stratify risk of mortality in hemodialysis patient using competing risk method.

Cumulative incidence of death and KT according to PVD and stiffness status in competing risk method

PO0864

Body: Fat Mass Plays an Important Role in Over- or Underestimation of Bioimpedance Spectroscopy-Based Dry Weight for Patients with Hemodialysis

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Background: Accurate dry weight (DW) estimation is important for hemodialysis patients. Although bioimpedance spectroscopy (BIS) is commonly used to measure DW, the BIS-based DW frequently differs from the clinical DW.

Methods: We analyzed the characteristics of patients whose BIS-based DWs were over- and underestimated. In this retrospective cohort study, we evaluated 1,555 patients undergoing maintenance hemodialysis in Chungnam National University Hospital. The gap (DW\_BIS-DW\_cl) was calculated by comparing the BIS and clinical DWs.

Results: We analyzed the clinical characteristics of patients with positive (n = 835) and negative (n = 720) gaps. Compared with other patients, the DW\_BIS-positive group was taller, had higher extracellular water (ECW) level and extracellular/intracellular water index (E/I); and had lower weight, body mass index (BMI), lean tissue index (LTI), fat tissue index (FTI), fat mass (FAT), and adipose tissue mass (ATM), as well as lower levels of hemoglobin, total protein, albumin, and phosphorous. The DW\_BIS-negative group exhibited higher levels of hemoglobin, total protein, albumin, and phosphorous, as well as elevated BMI, FTI, FAT, and ATM, however, it had lower height, ECW, and E/I. Linear regression analysis revealed that FAT significantly predicted DW\_BIS accuracy.

Conclusions: The clinical DW of patients with malnutrition and a low fat mass tended to be underestimated, while the clinical DW of patients with comparatively large fat reserves tended to be overestimated. These characteristics of dialysis patients will aid in the correction of BIS-associated DW errors.

PO0865

Consistency of the Dry Weight of Hemodialysis Patients Predicted Using Bioelectrical Impedance Analysis Between Standing and Lying-Down Positions

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Background: Although the InBody S10 is widely used for hemodialysis patients in the lying position, clinicians must make the measurements in person. In contrast, patients can use the InBody 770 to obtain measurements by themselves in the standing position according to instructions provided by the machine, which may be more convenient. Therefore, this study compared the measurements of hemodialysis patients' dry weight obtained lying down using the S10 to those obtained in the standing position using the 770.

Methods: Measurements from 56 patients before and after hemodialysis were obtained. Dry weight was calculated using the ratio of extracellular water to total body water, taking into consideration diabetes status and albumin levels, and comparing the results according to body position (lying vs. standing).

Results: The patients' median age was 64 years old, and 51% were men. Their mean dry weight before hemodialysis was 60.9±12.5 kg using the 770 device and 60.1±12.5 kg using the 770 device (paired t-test; t=6.472, P<0.001). The correlation between these data was 0.93.
measurements was high (R²=1.0000). Patients’ mean dry weight after hemodialysis was 58.4±12.2 kg using the S10 device and 58.5±12.0 kg using the 770 device (paired t-test; t=-1.560, P=0.124). The correlation between these measurements was also very close (R²=1.0000). The Bland-Altman test yielded similar results.

**Conclusions:** This study showed that patients’ predicted dry weights in the lying position using the InBody S10 device and in the standing position using the InBody 770 device were consistent in both pre- and post-hemodialysis states. It can be concluded that the dry weight of a patient in the standing position can be measured with more convenience and autonomy using the InBody 770 device.

**PO0866**

*Use of Crit-Line to Reduce Intradialytic Hypotension in Hospitalized Patients Receiving Dialysis*

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**Background:** Intradialytic hypotension (IDH) is a frequent complication of hemodialysis in hospitalized patients with acute kidney injury (AKI) and end stage kidney disease (ESKD). Crit-Line is a device that monitors absolute hematocrit and oxygen saturation during dialysis and reads out the percent blood volume change. Whether the use of Crit-Line during HD in hospitalized patients results in less IDH is unknown.

**Methods:** We performed a time series study in all hospitalized adult AKI/ESKD patients undergoing acute HD at the University of Colorado. During the control period baseline data was collected. During the intervention period, Crit-Line was used on all hospitalized patients undergoing HD including those receiving portable HD treatments in the ICU. During both time periods, nurses recorded number of hypotensive events, patient symptoms and modifications that were made to the dialysis prescription. The primary outcome was number of IDH events defined by the NKF KDOQI Guidelines.

**Results:** 328 patients were included, 161 from the control period and 167 from the intervention period. Patient characteristics were similar in both time periods and are shown in Table 1. IDH occurred in 23.5% of treatments during the control period and 18.7% during the intervention period, but the difference was not significant, p=0.22 (Figure 1). When examining portable dialysis treatments in the ICU, there was a significant reduction in IDH with Crit-Line compared to control (Odds Ratio 0.81 95% CI 0.55-1.16, p=0.24).

**Conclusions:** Use of Crit-Line in hospitalized patients undergoing dialysis in the ICU resulted in less IDH.

**Funding:** Commercial Support - Fresenius Renal Therapies

**PO0867**

*Dry Weight Adjustments for Hemodialysis Patients Using Machine Learning*

Hae Ri Kim, Youngok Ham, Kim Pyung, Yoon-Kyung Chang, Dae Eun Choi. *Chungnam National University Sejong Hospital, Sejong, Republic of Korea; Chungnam National University, Daejeon, Daejeon, Republic of Korea; Daejeon Saint Mary’s Hospital, Daejeon, Daejeon, Republic of Korea.*

**Background:** Knowledge of the proper dry weight plays a critical role in the efficiency of dialysis and the survival of hemodialysis patients. Recently, bioimpedance spectroscopy (BIS) has been widely used for set dry weight in hemodialysis patients. However, BIS is often misrepresented in clinical healthy weight.

**Methods:** As a retrospective, single center study, data of 1672 hemodialysis patients were reviewed. DW, data were collected when the dry weight was measured using the BIS (DW_BIS). The gap between the two (Gap_BIS) was calculated and then grouped and analyzed based on gaps of 1 kg and 2 kg.

**Results:** Based on the gap between DW_BIS and DW_BIS, 972, 303, and 384 patients were placed in groups with gaps of <1 kg, ≥1kg and <2 kg, and ≥2 kg, respectively. For less than 1 kg and 2 kg of GapDW, it can be seen that the average accuracies for the two groups are 83% and 72%, respectively, in using XGBoost machine learning. As Gap_BIS increases, it is more difficult to predict the target property. As Gap_BIS increase, the mean values of hemoglobin, total protein, serum albumin, creatinine, phosphorus, potassium, and the fat tissue index tended to decrease. However, the height, total body water, extracellular water (ECW), and ECW to intracellular water ratio tended to increase.

**Conclusions:** Machine learning made it slightly easier to predict DW based on Gap_BIS under limited conditions and gave better insights into predicting DW. Malnutrition-related factors and ECF were important in reflecting the differences between DW_BIS and DW_BIS.

**PO0868**

*Intradialytic Weight Gain in Long Intervals and Mortality Among Maintenance Hemodialysis Patients*


**Background:** Intradialytic weight gain (IDWG) is an important factor for sudden death on the first dialysis day right after long interdialytic intervals (i.e. 2-day breaks between dialysis treatments) in hemodialysis patients. We defined IDWG in long intervals (IDWGL) as the IDWG during 2-day breaks. In this study we examined the association between IDWG and medium-term mortality.

**Methods:** This retrospective cohort study included patients who initiated hemodialysis in a large dialysis organization in the United States from 2007 to 2011. We examined the association between IDWG and medium-term mortality.

**Results:** We examined mortality in 35225 patients. The mean age (and standard deviation) was 62±15 years, and 8112 died during the median follow-up period of 1.4 years. Higher categories of IDWG were associated with increased risk of mortality. The hazard ratios (95% confidence intervals) of all-cause mortality for 3–<4%, 4–<5%, 5–<6%, and ≥6% were 1.09 (1.03-1.16), 1.14 (1.06-1.23), 1.17 (1.06-1.29), and 1.25 (1.14-1.38) (Reference: 2–<3%) (Figure a). The restricted cubic spline analysis showed that risk of mortality increased when IDWG exceeded 2% (Figure b).

**Conclusions:** IDWG exceeded 2% was associated with higher risk of mortality. Our results suggest IDWG can be a risk parameter for medium-term mortality.
PO0870
Cardiac Arrests During Hemodialysis Among Maintenance Hemodialysis Patients in a Large Dialysis Network in India

Background: Cardiac arrest (CA) during a HD session carries a high mortality and is reported associations include age, comorbidity, dialysis characteristics. Since much is unknown in India, we aimed to study Incidence of CA, predisposing factors and outcome of CPR following intra HD cardiac arrests

Methods: Consecutive CA in a large dialysis network from July 2019 to March 2021 were reviewed for age, gender, HD frequency, adequacy, vascular access, HD facility location, size, nephrologist coverage, b/o DM and IHD, HD session timing, duration HD frequency & hospitalization in recent past & ultrafiltration rate. Survivors vs non-survivors of CPR were compared with t-test, Chi-square test or Fisher’s exact statistic and risk ratio (RR) for significance of associated factors were analyzed using STATA, v 14.2.

Results: Among 2,081,759 HD sessions, rate of 1.2441. 71 survived CPR and 51 died. Age: 55 ± 1.2 yrs, M:F = 77%/23%. Tier 1/2/3 cities: 11.4%/37.7%/50.8%, daily Nephrologist visits: 67.2%, Facilities monthly sessions: < 250: 10.6%, ≥ 250: 74.6-79.0%. Urea: 8.7 ± 2.1 mg/dl temperature: 34.3%, HD freg: 1/2/3 per wk: 36.9/28.7/33.4%, DM: 44.8% IHD: 26.2%, Morn afternoon, eve session(%): 8/15/12, P < 0.05 was considered significant.

Conclusions: Incidence of CA in India is modest compared to developed countries experience; larger facilities & smaller cities carry a high proportion of events. Age > 80 risk of death. Females, Hb ≥ adequacy, UFR >10ml/kg/hour, low HD freg in 2 months prior to CA show tendency to higher risk for non survival. Limitation includes lack of analysis of CPR and post CPR hospitalization course

PO0869
Coronary Artery Calcification Is a Risk Factor for Intradialytic Hypotension in Hemodialysis Patients
Sono Mizuiri, Yoshiko Nishizawa, Toshiaki Doi, Kazuomi Yamashita, Kenichiro Shimogoto, Koji Usui, Michiko Arita, Takayuki Naito, Shigehiro Doi, Takao Masaki, Iryo Hójín Ichiyokai Harada Byoin, Hiroshima, Japan; Ichiyokai Ichiyokai Clinic, Hiroshima, Japan; Ichiyokai East Clinic, Hiroshima, Japan; Ichiyokai Yokogawa Clinic, Hiroshima, Japan; Hiroshima Daigaku Byoin, Hiroshima, Japan.

Background: Vascular calcification and intradialytic hypotension (IDH) share common risk factors in hemodialysis (HD) patients, but there are few reports about the association. We investigated the association between IDH and coronary artery calcification (CAC) and their effects on mortality in HD patients.

Methods: Subjects were consecutive maintenance HD patients. IDH was defined as nadir systolic blood pressure <100 mmHg, or the requirement for bolus infusion of saline and vasopressor (phenylephrine hydrochloride) during at least two of 10 HD sessions. Laboratory data and Agatston coronary artery calcium score (CAC) were obtained at baseline. Logistic regression analyses for CACs and Cox analyses for mortality were conducted.

Results: In all subjects (n=173), age and dialysis vintage were 66±12 years and 10.2±9 months, respectively. IDH occurred in 37 patients (21.4%), and CACs was higher in the IDH group than in the non-IDH group [1,845 (243–3,774) vs. 884 (161–2,465)]. IDH was significantly (P<0.05) associated with CACs [odds ratio (OR): 8.10], diabetes (OR: 2.90), mean predialysis systolic blood pressure (OR: 0.93), mean ultrafiltration (OR: 1.92), Kt/Vurea (OR: 11.27) and erythropoietin responsive index (ERI) (OR: 0.91), but not with serum albumin or use of calcium channel blockers. For 3-year all-cause mortality, the cut-off value of CACs, determined by receiver operating characteristics curve analysis, was 1,829 with sensitivity of 69% and specificity of 77%. Of the 173 patients, 45 all-cause and 19 cardiovascular (CV) deaths occurred for 3 years. Patients with both IDH and CACs ≥1,829 had the highest 3-year cumulative CV death rate (33.5%, P<0.01) compared with 19.7%, 11.5%, and 4.5% in those with CACs ≥1,829 only, IDH only, and neither. In Cox models including age, sex, diabetes, albumin, phosphate, CRP, ERI and FG23, hazard ratios (HRs) for 3-year all-cause mortality of IDH, CACs ≥1,829, or IDH with CACs ≥1,829 were similar, but HR for 3-year CV mortality was the highest in CACs with CACs ≥1,829 (9.68, P<0.001) compared with 7.29 (P<0.001) and 6.77 (P<0.01), in those with CACs ≥1,829 only, and IDH only. Only CACs were independent risk factor for IDH, and CACs provide additional risk discrimination over IDH for CV mortality in HD patients.

Funding: Private Foundation Support

PO0871
Clinical Significance of Plasma Matrix Metalloproteinase-2 and Matrix Metalloproteinase-9 Levels to Assess the Cardiovascular Risk in Hemodialysis Patients
Yu Bo Lee, So-young Lee, Hyeun Jeong, Yang gyun Kim, Ju young Moon, Sangho Lee, Jin sug Kim, Kyung Iwan Jeong, Shin-Young Ahn, Dong-Young Lee, Hyeon Seok Hwang, CHA Bundang Medical Center, Seongnam, Gyeyonggi-do, Republic of Korea; Kyung Hee University Hospital at Gangdong, Gangdong-gu, Seoul, Republic of Korea; Kyung Hee University Medical Center, Dongdaemun-gu, Seoul, Republic of Korea; Korea University, Seongbuk-gu, Seoul, Republic of Korea; Seoul Veterans Hospital, Gangdong-gu, Seoul, Republic of Korea.

Background: Matrix metalloproteinases (MMPs) are endopeptidases that control extracellular matrix synthesis and degradation. Two MMP subtypes, MMP-2 and MMP-9, are known to play important roles in the development and progression of cardiovascular (CV) disease, but its clinical relevance as predictors of cardiovascular events is unclear in hemodialysis patients.

Methods: We prospectively enrolled 435 patients undergoing maintenance hemodialysis from K-cohort between June 2016 and April 2019. Plasma MMP-2, MMP-9 levels, and several biomarkers were measured at the time of study data entry. Primary endpoint was defined as a composite of cardiovascular events.

Results: Plasma MMP-2 level were increased in patients with incident CV events than those without CV events, whereas plasma MMP-9 levels were not different between groups. MMP-2 levels were positively correlated with circulating cardiac markers including brain natriuretic peptides (BNP), N-terminal proBNP, and heart-type fatty acid binding protein. The cumulative event rate of the composite of CV events was significantly greater in patients with higher MMP-2 tertile than in those with other MMP-2 tertile (p = 0.015). MMP-2 tertile 3 was associated with a 2.77-fold higher risk of the composite of CV events (95% CI, 1.40–5.45) and 4.67-fold higher risk of cardiac events (95% CI, 2.06–10.56) after multivariable adjustments. However, plasma MMP-9 levels were not positively correlated with circulating cardiac markers, and not associated with risk of incident CV events.

Conclusions: Higher plasma MMP-2 levels, but not MMP-9 levels, had the positive relationship with circulating levels of cardiac pathologic markers, and were associated with increased risks of incident CV events and cardiac events among hemodialysis patients.

PO0872
Utility of CHA2DS2-VASc Score to Predict Mid-Term Clinical Outcomes in Hemodialysis Patients
Aiko Okudo, Toshiaki Doi, Yoshiko Nishizawa, Kenichiro Shimogoto, Sono Mizuiri, Takao Masaki, Iryo Hójín Ichiyokai Harada Byoin, Hiroshima, Japan; Ichiyokai Yokogawa Clinic, Hiroshima, Japan.

Background: The CHA2DS2-VASc score has been widely used as a predictive score for stroke in patients with atrial fibrillation (AF). Recently, it was reported that the CHA2DS2-VASc score is useful for predicting cardiovascular disease (CVD) or all-cause mortality in patients with or without AF. However, few reports have examined the association between this score and mortality in hemodialysis patients. Inadequate risk factor was for 3-year all-cause mortality

Methods: We analyzed 525 consecutive patients who started hemodialysis at our facilities from March 2006 to October 2017. CHA2DS2-VASc score was calculated at time of initiation of hemodialysis. Multivariate Cox proportional hazards analysis was used to assess independent risk factors for 3-year all-cause mortality.

Results: During the 3-year follow-up period, 153 (29.1%) patients died (cardiovascular death, 98%). According to multivariate analysis, serum albumin [hazard ratio (HR) 0.62, 95% confidence interval (CI) 0.43–0.89, P=0.01], creatinine (HR 0.81, 95% CI 0.71–0.99, P=0.03), and CHA2DS2-VASc score (HR 2.31, 95% CI 1.21–4.46, P=0.001) were associated with 3-year all-cause mortality. Patients with CHA2DS2-VASc score ≥4 had higher risk of all-cause and CVD mortality than those with CHA2DS2-VASc score <4 (all-cause mortality: HR 2.20, 95% CI 1.42–3.71, P=0.001; CVD mortality: HR 2.83, 95% CI 1.37–5.44, P=0.001).

Conclusions: The CHA2DS2-VASc score is a useful predictor of 3-year all-cause and CVD mortality in incident hemodialysis patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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PO0873
Fibrosis-4 Index May Predict Mortality and Non-Fatal Cardiovascular Events in ESKD Patients Starting Dialysis
Yeonee Lee, Da won Kim, Seok Joon Shin, Hye Eun Yoon, Moo Yong Park, Jae Young Park, Iqbal Iqbal, Jawed Fareed, Loyola University Health System, Maywood, IL.
Background: CKD and ESKD are known risk factors of heart failure (HF). And liver dysfunction as congestive hepatopathy due to HF is also common. Recent studies report that Fibrosis-4 (FIB4) index (age×ALT(IU/L)/platelet count(10^9/mL)/square root of AST(IU/L)), which was known to be useful tool for evaluating liver stiffness, can be prognostic factor of HF. Therefore, this study investigated whether FIB4 index may be prognostic factor of HF.

Methods: This was a retrospective cohort study including 388 patients who started dialysis at a single center. FIB4 index at dialysis initiation was calculated. Patients were stratified into three groups according to FIB4 index(<1.45:low, 1.45~3.25:intermediate, >3.25: high). The association between FIB4 index and event free survival rates for all-cause mortality and non-fatal CVE was analyzed. In addition, the association between FIB4 index and echocardiographic findings was analyzed.

Results: During a median follow-up duration of 40.0(0.03-142.3) months, 84 deaths(21.6%) and 83 non-fatal CVE(21.4%) occurred. Event free survival rates were lower in high-FIB4 group, compared with those in low-FIB4 group(p=0.001) and intermediate-FIB4 group(p=0.005), respectively. In Cox proportional hazard model, the high FIB4 index was independently associated with event free survival rates (HR, 2.21; 95% CI, 1.17-4.18; p=0.015). When comparing echo findings, only left atrial diameter (LAD) showed difference among groups(p=0.033). However, there was no significant correlation between LAD and FIB4 index.

Conclusions: In conclusion, FIB4 index is associated with event free survival rates for all-cause mortality and non-fatal CVE in ESKD patients starting dialysis.

PO0874
NT-ProBNP for Heart Function and Volume Status in Hemodialysis Patients
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Background: N-terminal pro brain natriuretic peptide (NT-proBNP) is a biomarker that predicts heart failure and evaluates volume status in Hemodialysis (HD) patients. However, it is difficult to determine the cutoff value of NT-proBNP in HD patients. In this study, we analyzed whether NT-proBNP helps with predicting heart function and volume status in HD patients.

Methods: Retrospective study was conducted on 96 end-stage renal disease patients with HD. All patients underwent echocardiography and Bioelectrical Impedance Analysis (BIA) after a post HD session. Overhydration (OH) was measured by BIA. Laboratory data were obtained on preHD during the mid-week HD sessions. Serum NT-proBNP was measured after HD.

Results: There was an inverse correlation between NT-proBNP and ejection fraction (EF) (β = -0.34, P = 0.001). Overhydration (OH) (β = -0.33, P = 0.01) and presence of diastolic dysfunction (β = -0.226, P = 0.027) had positive correlations with NT-proBNP. In the subgroup analysis with diastolic dysfunction grade, NT-proBNP increased as the dysfunction grade increased. (diastolic dysfunction grade 0; 417±2367-10391), grade 1; 9736 (5471-21110), grade 2, 3; 24627(16975-44988) Elevation of NT-proBNP above 4058 pg/ml was associated with the presence of diastolic dysfunction (p=0.001) and Left ventricular hypertrophy (LVH) (p=0.004). Elevation of NT-proBNP above 11576 pg/ml was associated with the presence of diastolic dysfunction (p=0.001), LVH (p=0.001) as well as EF<55% (p=0.07). The group with lowered dry weight followed up NT-proBNP one month later, compared to the group with no change in dry weight, NT-proBNP showed a tendency to decrease, and the group with no change in dry weight showed a relatively low level of NT-proBNP variability. (-210 (-12899 - 3142) vs 330(-1090 - 3858); interquartile range, p=0.104).

Conclusions: We confirmed that NT-proBNP is associated with volume status as well as heart functions such as diastolic dysfunction, LVH and EF in HD patients.

Heart function according to NT-proBNP level

PO0875
Dysregulation of Fatty Acid Binding Protein and Their Relationship with Inflammatory Biomarkers in ESRD
Emily Bontekoe, Vinod K. Bansal, Fakhi Siddiqui, Omer M. Iqbal, Jawed Fareed, Loyola University Health System, Maywood, IL.

Background: End stage renal disease (ESRD) patients are at high risk of cardiovascular disorders and hemostatic complications. Fatty acid binding proteins (FABPs) regulate the transport of fatty acids and other lipophilic mediators such as cholesterol and retinoids by both intracellular and extracellular mechanisms. While upregulation of FABPs have been reported in ESRD, their relationship with inflammatory biomarkers is not fully understood. Liver fatty acid binding protein (L-FABP) also known as FABP-1 is a 14kDa protein expressed in the liver. This protein is also expressed in tubular kidney cells. Kidney damage and other pathologic conditions result in the marked upregulation of this protein.

Methods: Citrated blood samples from 95 ESRD patients undergoing maintenance hemodialysis were collected prior to hemodialysis. For comparison purposes normal (5.1 ± 0.2ng/ml SEM) with a broad range (3.4 – 9.2 ng/ml). Marked increases in IL-6, TNfa and inflammation were also noted (2 – 4 fold). FABP-1 showed varying degrees of positive correlation with inflammatory biomarkers.

Conclusions: These studies suggest that plasma levels of FABP-1 is markedly increased in ESRD patients (up to 10 fold) in ESRD patients undergoing maintenance hemodialysis. Other biomarkers of inflammation are also upregulated and demonstrate varying degrees of correlation suggesting inter-relationship between FABP-1 and inflammatory processes. These results also support that impaired renal function and tubular damage contribute to the marked increase of L-FABP in ESRD patients. Simultaneous measurement of L-FABP with biomarkers of inflammatory responses and kidney damage may be helpful in the risk stratification and prediction of the adverse outcome in ESRD patients.

Funding: Private Foundation Support
PO0876

Transcapillary Refilling Rate Profile in Hemodialfiltration
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**Background:** Reaching dry weight in end-stage kidney disease (ESKD) patients is subject to high ultrafiltration rates (UFR) during their hemodialfiltration (HDF) sessions. We seek to profile the transcapillary refilling rate (TRR) during HDF, which we infer to be an important protective factor against intradialytic hypotension (IH).

**Methods:** We studied 30 patients in HDF scheduled 3 times a week. Absolute blood volume was measured with the dilutional method and plasma volume was calculated based on the patient’s hematocrit. Each session was divided in 18 intervals of 10 minutes each. Overhydration was tested by calculating the expected plasma volume. Real plasma volume at the end of each interval was calculated on the basis of the relative blood volume. The difference between the real and the expected plasma volume was the plasma refill volume, which divided by the time of each interval gave us the TRR. The HDF session prescription was determined by the nephrologist in charge of the HDF clinical services.

**Results:** 84 HDF sessions were recorded. Mean age was 44 years (+/- 18.8), 66% were female. TRR:UFR ratio difference between patients with and without IH was statistically significant (p <0.001, CI 95%), as well as the UFR-TRR delta (p <0.001, 95% CI). This ratio achieved stability after 30 minutes. Eight patients (27%) presented an IDH episode during HDF, during a total of 9 sessions (10.7%); 8 (89%) occurred in the final hour and 1 (11%) occurred in the first 10 minutes and corresponded to a patient who presented fever and bacteremia.

**Conclusions:** Both the TRR:UFR ratio and UFR-TRR delta were statistically significant for predicting IH. Understanding each patient’s TRR will help us plan interventions in order to try and optimize it and reduce the risk of IDH.}

Figure 1. UFR (solid lines) and TRR (dashed lines) profiles.

PO0877

Impact of Hydration Status Measurement by Bioimpedance Analysis (BIA) on Haemodialysis Patients
Nasreen Samad,1 Franel Ave,1 Sara Z. Khan,2 Jerilyn Lalu.1 1Barts Health NHS Trust, London, United Kingdom; 2American University of Antigua College of Medicine, Saint Johns, Antigua and Barbuda; 3Northwell Health, New Hyde Park, NY.

**Background:** Volume status in haemodialysis patients is an important prognostic factor, where overhydration is associated with a higher frequency of mortality while diuresis-induced volume depletion is also an independent mortality risk factor. Clinical indices do not always accurately reflect volume status. Bioimpedance analysis (BIA) is used as a simple, noninvasive method which can measure normovolumic status in haemodialysis patients by measurement of height, weight, and body composition. Fluid overload is calculated by subtracting the normovolumic status from the overhydration status.

**Methods:** All patients at Queens satellite dialysis unit, Romford, United Kingdom, which has a prevalent population of 106 patients had BIA based assessment of fluid status every 3 months from July 2020 to May 2021 and dry weight adjusted accordingly. Outcomes were noted for blood pressure, overhydration, Interdialytic weight gains, intradialytic hypotension, hospitalisation and mortality.

**Results:** 121 haemodialysis patients were followed with male to female ratio of 55:66, mean age of 62 (25-87) of whom 46 were diabetics. By end of assessment period, 21 patients had died (13 due to COVID related illness). In July 2020, 31 patients had overhydration of 2 litres or more, which reduced to 20 patients, in May 2021. The number of patients who had underhydration of -1 litre or more remained similar with 12 patients in July 2020 compared to 11 in May 2021 with respect to more aggressive approach to reduction in dry weight. The dialysis population had high turnover due to deaths as well as 2 transplantations and 2 transfers out of the unit. During the time of study 15 patients were admitted to hospital with features of fluid overload.

**Conclusions:** Bioimpedance analysis (BIA) is a simple, non invasive tool helpful in assessing fluid status in haemodialysis patients. It is easier to convince a patient about their volume status by providing a machine assessed figure rather than clinical parameters. There was significant improvement in overhydration without increasing the number of death in patients. The high mortality in prevalent patients during COVID pandemic highlights the need for continued body composition measurement studies in a larger population once COVID cases subside to come to a significant conclusion about the impact of BIA in improving patient outcomes including effect on residual renal function.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
had more pericardial effusions (12.5% vs 2.3% p = 0.048) and more GIB (12.5% vs 2.2% p = 0.046) (Table 1). There were no differences in in-hospital mortality, hospital length of stay (LOS), ICU LOS, and sternal wound infections between groups across the different surgeries. 16 PD patients were converted to HD post-surgery, intent to treat analysis was applied for these patients.

**Conclusions:** In patients on maintenance dialysis, patients who underwent CABG, VS, and combined surgery had similar outcomes. PD patients appeared to experience more GIB and pericardial effusions requiring intervention in the CABG group.

### Table 1

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**PO0881**

Prevalence and Risk Factors for Development of Cardiac Arrhythmias and Electrocardiographic Abnormalities in Hemodialysis Patients: A Single-Center Experience in Mexico.

Andrea San-German Morales,1 Pedro A. Escamilla Galindo,2 Armando Castillo García,3 Paulina Paniagua,1 Juan M. Ardavin Ituarte,2 Mario Jimenez Hernandez1,2 Universidad de las Americas Puebla, Cholula, Mexico; 2Medica Santa Carmen, Puebla, Mexico.

**Background:** Mexico is among the countries with the highest number of patients on kidney replacement therapy (RRT). Despite this, the incidence and prevalence of CKD in Mexico is unknown, due to the lack of a national registry as a result we do not know risk factors associated to this population. Electrocardiographic abnormalities or arrhythmias are among the most frequent cardiovascular pathologies, being the first cause of death during the first month in RRT. That is why the present study aims to identify the prevalence of arrhythmias in a group of Mexican patients on hemodialysis as well as their associated risk factors.

**Methods:** A non-experimental, observational, descriptive, and cross-sectional study was carried out in the period from March to July 2020 with Mexican patients older than 18 years in maintained hemodialysis. The electrocardiograms and blood test analysis were taken on the day of hemodialysis therapy.

**Results:** The mean age of the population was 42.37 years, 57% were male. Arrhythmias were found in 50 patients (41.67%), the prevalence of arrhythmias found was bundle branch block (17.50%), sinus tachycardia (12.50%), sinus bradycardia (7.50%), atrial fibrillation (2.50%), extrasystoles (1.67%). A significant difference in mean ages was found between patients with (47.14) and without arrhythmia (38.97) (p = 0.041). A history of heart disease (OR 7.54 95% CI 1.05-184.7), and the diagnosis of chronic renal failure secondary to diabetic nephropathy (OR 2.5459 95% CI 1.1026-5.8785) were identified as risk factors. The diagnosis of chronic renal failure secondary to arterial hypertension was no related as risk factor (p=0.86). No laboratory study was identified as a risk or protective factor for the development of arrhythmia either the vascular access type.

**Conclusions:** The studied population presented similar characteristics to the described previously, a high prevalence of electrocardiographic abnormalities was identified, laboratory studies were not related to the presence of arrhythmias. History of heart disease and kidney disease secondary to diabetic nephropathy were associated as a risk factors, while the presence of arterial hypertension was not identified as risk factor.

**PO0882**

Evaluation of Venous Congestion in Chronic Hemodiafiltration Patients During Ultrafiltration: A Prospective Cohort Study


**Background:** Fluid overload is deleterious in chronic hemodialysis patients. The combination of multiple POCUS markers can identify significant venous congestion. These markers have not been prospectively studied in this population.

**Methods:** We measured inferior vena cava (IVC) diameter, portal vein pulsatility fraction (PVPF), jugular vein at rest (YVR) and hepatic vein flow (HVF) at five points: pre-dialysis, three times during dialysis and post-dialysis. All measurements were done three times and averaged. All patients had at least 3% weight gain based on their estimated dry weight. We recorded ultrafiltration volume at each point.

**Results:** We performed measurements during 30 on-line post dilution hemodiafiltration sessions in 20 patients (13 were female, mean age 38.6 years old). The average total ultrafiltration (UF) volume was 250.1 cc (1250-4250 cc). There was a significant reduction in PVPF, IVC diameter, YVR, HVF during sessions. See Figure 1. Likewise, UF volume correlated with IVC diameter: R -0.38 p<0.001; PVPF: R -0.31 p<0.001; and HVF: R -0.19 p<0.035.

**Conclusions:** In chronic hemodialysis patients, even in the absence of a dilated IVC, markers of venous congestion tracked ultrafiltration volume. This study warrants further research with regards to clinical decision to continue fluid removal in chronic hemodialysis patients.
PO0883

Knowledge and Practice of Incremental Dialysis: A Survey of Canadian Nephrologists


Background: Incremental hemodialysis, a strategy to individualize dialysis prescriptions at initiation, is being linked to enhanced quality of life and acceptability by patients and decreased health care costs. We aimed to explore knowledge and practice pattern regarding facility-based incremental hemodialysis in Canada.

Methods: A web-based survey of nephrologists, elicited current incremental hemodialysis (HD) prescribing practices, clinical and patient factors used to determine suitability for treatment, and potential barriers to implementation. The survey was circulated over a period of six weeks (September 21, 2020 and October 30, 2020).

Results: The overall response rates 35% (243/691 nephrologists surveyed). Majority (66/111, 59%) of respondents prescribed incremental HD using an individualized approach at the discretion of the nephrologist. Most centers (200/203, 98%) did not report policy or guidance for implementation. Residual urine output was identified as the most important factor for eligibility (112/172, 65%), electrolyte stability (76/172,44%) and existing patient goals of care (69/117, 49%). The majority of nephrologists agreed that dialysis prescriptions are dynamic and should take residual kidney function into consideration; however, 74% of nephrologists did not think there was strong evidence supporting incremental dialysis. Potential barriers identified were patient safety, logistics of scheduling, limited evidence, and acceptance of dose escalation. Despite these barriers, 82% of participants felt that that facility-based incremental dialysis is feasible with their current resources and 78% agreed that with specific exclusion and inclusion criteria, incremental dialysis is a safe option.

Conclusions: Incremental hemodialysis is commonly practiced amongst Canadian nephrologists despite a lack of formal criteria for initiation and treatment escalation. This highlights a need for research to guide policy and practice for incremental hemodialysis in Canada.

PO0884

Thrice vs. Twice Weekly Hemodialysis in a Rural Community Center

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Background: Converting stable ESRD patients from thrice to twice weekly HD sessions for at least 3 months duration were screened for eligibility for conversion to 2xWkly HD session in a university-affiliated community dialysis program. Eligibility criteria were: residual renal function > 3ml/min; urine output >500mL/day; intradialytic weight gain <2.5kg; hemoglobin >8gm/dL; manageable phosphorus and potassium levels. Clinical parameters on 3xwkly vs. 2xwkly HD sessions were then performed in the eligible patients. Patients were followed for 6 months post conversion.

Results: 9.8% of total HD pts were eligible. Baseline characteristics: age 65±14.5yrs, P 57.1%, HTN 71.4%, DM 14.2%, MM 14.2%. Major indication for HD initiation was symptomatic progression of disease. Less than 50% of pts had a functioning arteriovenous fistula at initiation of HD. In the current cohort, residual renal function > 3ml/min was maintained for > 200 days after initiation of HD. There were no significant changes in electrolytes, hemoglobin, nutrition status or adequacy of dialysis. PTH levels were not significantly different: 3xwkly, 625.7±546.2pg/mL vs. 2xwkly, 399±344.2pg/mL; p=0.374). Karnofsky Performance Status Scale improved post conversion but did not achieve statistical significance (3xwkly, 57.1 ± 2.5xwkly, 70; p=0.316). There were no hospital admissions since conversion to 2xwkly schedule during the study period.

Conclusions: 10% of total HD patients qualified for conversion from 3xWkly to 2xWkly maintenance HD without significant changes to laboratory or clinical performance measures. These observations stimulate discussion regarding increased application of incremental dialysis initiation strategies to preserve residual renal function, increase dialysis-free days and alleviate transportation and care provider-related burden to patients and families, especially in underserved areas.

PO0888

Comparison of Clinical and laboratory parameters.

PO0885

Impact of the Ratio of Monocyte to High-Density Lipoprotein Cholesterol on Cardiovascular Outcome in Incident Dialysis Patients


Background: Monocyte count to high-density lipoprotein ratio (MHR) is a well known marker of cardiovascular risk and atherosclerosis. We evaluated the impact of the MHR value on the CV outcomes in end-stage kidney disease (ESKD) patients. The primary outcome was comparison of cardiovascular event-free survival rate between the low MHR group and the high MHR group. The secondary outcome included all-cause mortality, overall CV mortality and possibility of MHR as an independent risk factor for CV complication.

Methods: The medical records of 719 ESKD patients who started maintenance dialysis between January 2006 and July 2017 were reviewed. Patients were divided into low MHR and high MHR groups based on the median MHR value.

Results: Overall CV event was 130 cases, 55 in the low MHR group and 75 in the high MHR group, respectively. The CV event-free survival rate was significantly lower in the high MHR group compared to the low MHR group (47.6% vs. 57.5%, P = 0.017). Of the 577 enrolled patients, there was no statistical difference in all-cause mortality between the two groups during a mean follow-up of 3.2 years (P = 0.371). Overall CV mortality rate was also comparable between the two groups (P~ 0.615). In multivariate Cox regression analysis, high MHR was an independent predictor for CV events (HR 1.463, 95% CI, 1.019 – 2.102, P = 0.039) even after adjustment for age, smoking, diabetes, body mass index, C-reactive protein, and previous CV disease.

Conclusions: In conclusion, high MHR at the time of dialysis initiation in the incident ESKD patients may be a simple and useful method for predicting development of CV complication.

PO0886

Differences in Clinical Characteristics and Outcomes Between Hemodialysis-Dependent and Non-Hemodialysis-Dependent Patients with Gram-Negative Bacteremia

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Background: Gram-negative bacteremia (GNB) is a common and potentially lethal infection among hemodialysis (HD)-dependent patients. The determinants of clinical outcomes in HD-dependent patients with GNB are incompletely understood. We compared clinical characteristics and outcomes between HD- and non-HD-dependent patients with GNB in a large cohort of hospitalized patients and subsequently examined associations between specific characteristics and all-cause mortality among HD-dependent patients.

Methods: Hospitalized, non-neutropenic adults with GNB were prospectively enrolled from Jan 1, 2002 to July 1, 2015. Clinical characteristics and outcome data were collected. Differences between HD- and non-HD-dependent patients were estimated using means/standard deviations or counts/percentages with statistical significance evaluated with independent sample T-tests or Pearson’s chi-squared test. Associations between clinical characteristics and outcomes were estimated using logistic regression. Results: Among 1,827 unique participants, 180 were HD-dependent (9.9%). Compared to non-HD-dependent patients, HD-dependent patients were younger (58.6 vs 61.0 years, p<0.05) and more likely to be Black (55.6% vs 26.4%, p<0.001), to have diabetes (56.1% vs 32.1%, p<0.001), and to die prior to hospital discharge (28.9% vs
Predictors of Hyperkalemia Among Chronic Hemodialysis Patients Transported to the Emergency Department

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Background: Chronic hemodialysis (HD) patients often present to the emergency department (ED) with hyperkalemia, which in turn, is associated with morbidity and mortality. In this study we sought to identify pre-hospital predictors of hyperkalemia in patients transported to the ED via ambulance (ambulance-ED).

Methods: We analyzed all ambulance-ED transports in a cohort of chronic hemodialysis patients from 2014-2018 (using a province-wide emergency medical services database). The outcome was severe hyperkalemia using the first blood draw after ambulance-ED transport defined as ≥ 4.6 mmol/L. Characteristics of interest included vital signs prior to transport, days from last dialysis and prehospital electrocardiograms (ECGs) interpreted by paramedics prior to transport. The association between prehospital factors and hyperkalemia was analyzed using adjusted logistic regression.

Results: A total of 270 dialysis patients had 704 ambulance-ED transports followed by an ED potassium blood draw. Severe hyperkalemia occurred after 75 (11%) transports. In an adjusted parsimonious model (Table 1, N=609), age, dialysis vintage, bradycardia and days from last dialysis were associated with severe hyperkalemia. Among those with prehospital ECGs (N=377), presence of a prehospital ECG abnormality (i.e. peaked t-waves and/or first-degree atrioventricular block) was strongly associated with ED hyperkalemia (odds ratio 6.64, 95% confidence interval 2.31-19.12). Overall, 45% of hyperkalemia patients versus 24% of non-hyperkalemic patients re-required transport to another hospital to facilitate dialysis in a monitored setting after initial presentation.

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Results: We studied 15,190 persons on HD without prior AF diagnosis; average age was 76 yrs, 49% were male, 69% were white, 26% black, and 8% Hispanic. At baseline, 7183 persons had a S-K+ ≥4.5 and 6988 <4.5 mEq/L. With the exception of race and ethnicity, all other characteristics, including D-K+, which was 2 mEq/L in 52% and 3 mEq/L in 34%, were balanced across groups. During a mean follow-up of 527 days the overall incidence of AF was 13/100 person-years. S-K+ and T48 were significantly variable fit the data best. After multivariable adjustment, AF was associated with lower, but not with higher S-K+ concentrations unless extreme values >6.5 mEq/L were reached. D-K+ of 3 mEq/L, vs. 2 mEq/L, was associated with 14% (95% CI: 5-24%) lower adjusted rates of AF. No interaction between S-K+ and D-K+ was present.

Conclusions: Hypokalemia was strongly and independently associated with incident AF whereas hyperkalemia was not. However, choice of D-K+ of 2 mEq/L vs. 3 mEq/L did associate with higher AF rates, independent of S-K+ and other measured characteristics.

Funding: NIDDK Support

PO0891

Serum Potassium Changes in US Veterans Receiving Patiromer with Dialysis-Dependent ESKD and Hyperkalemia

Christopher G. Rowan, Jared Hansen, Brian C. Bauer, The University of Tennessee Health Science Center, Memphis, TN; 2Albany Medical College, Albany, NY; 3Vitor Pharma, Inc., Redwood City, CA; 4COHRDATA, San Clemente, CA; 5Salt Lake City VA Medical Center (IDEAS), Salt Lake City, UT.

Background: Patiromer is a sodium-free, non-absorbed, potassium (K+) binding polymer approved for the treatment of hyperkalemia (HK). This retrospective cohort study aimed to describe serum K+ changes in Veterans with HK and end-stage kidney disease (ESKD) receiving dialysis who initiated patiromer.

Methods: Serum K+ concentrations were evaluated pre- and post-patiromer initiation using the National VA Corporate Data Warehouse (1/1/16–8/31/18). Changes in mean serum K+ concentration were compared at 1, 3, and 6 months following first patiromer dispensing (index date) using the paired t-test (pre K+ versus post K+). All patients had a baseline K+ ≥5.1 mEq/L and ESKD. Patients with continuous exposure to patiromer were analyzed. Follow-up began on the index date and ended at first censoring event (discontinuation or switch of index K+ binder, death, end of follow-up, or 6 months post-index).

Results: 98 patients with ESKD requiring dialysis and HK initiated patiromer. Patient characteristics at baseline were median age 66 years, African-American race 39%, diabetes 71%, heart failure 40%, and mean K+ value of 6.1 mEq/L (standard deviation ±0.7). The initial dose of patiromer was 8.4 g in 96% of patients with few observed increases in unit dose during the follow-up period. Following patiromer initiation, statistically significant reductions in serum K+ concentration were observed at 1 month (–1.24 mEq/L), 3 months (–1.15 mEq/L), and 6 months (–1.36 mEq/L; Figure). Changes were maintained post-dispensing during follow-up years. Mean changes with HK, as squared, was associated with clinically relevant reductions in serum K+ concentrations at all study time points. These findings warrant additional investigation in a larger dialysis cohort with HK.

Funding: Commercial Support - Vitor Pharma, Inc.

PO0892

Hyperkalemia: Medical Management vs. Hemodialysis

Joseph A. Gatesman, Mari A. DeVita, Lenox Hill Hospital, New York, NY.

Background: Hyperkalemia is a life-threatening electrolyte disorder for which there exists a paucity of data regarding benefit of urgent hemodialysis over medical management. We hypothesized there would be no difference in potassium levels among hyperkalemic patients who received only medical management compared to those who received hemodialysis, with or without hemodialysis.

Methods: This is a retrospective study of patients 18 years old with hyperkalemia (K ≥5.5 mEq/L). One group (medical management, or MM) had medication(s) including insulin/dextrose, sodium zirconium cyclosilate, sodium polystyrene sulfonate, calcium gluconate, albuterol, or furomide—or defined within 3h of initial elevated potassium. The other group (hemodialysis, or HD), had hemodialysis ordered—with or without medical management—within 3h of elevated potassium. The initial potassium level was considered “time-zero” and subsequent timepoints were followed up to 100h. T1 readings were established between 0-3 hours; T6: 3–8h; T12: 8–16h; T24: 20-28h; T48: 40–56h; T72: 60–100h.

Conclusions: Among patients presenting with hyperkalemia, we found no difference in potassium levels between those who received only medical management and those who received hemodialysis, with or without medical management. Further studies are necessary to confirm these findings. Nationally standardized treatment algorithms ought to be developed; a randomized trial would be conducive to that end.

PO0893

Metabolic Alkalosis in Hemodialysis Patients

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Background: Hemodialysis (HD) typically employs a high dialysate alkali concentration to counteract interdialytic acid production. Since acid production varies due to the amount and type of protein consumed, some patients may remain alkalotic throughout the interdialytic period and be more alkalotic during HD. This could have adverse effects including arrhythmias, hypotension, hypoventilation, and vascular calcification but dialysate alkali is rarely adjusted. Pre-HD alkalosis is usually ascribed to chronic illness and poor nutrition, but this has not been carefully examined.

Methods: We conducted a retrospective case-control study of all in-center HD patients from 2010-2020 at 4 outpatient HD units using citrate-containing dialysate (34.6 mEq/L HCO3, 0.4 mEq/L acetate, 2.4 mEq/L citrate; citrasate, Fresenius). Interdialytic alkalosis was defined as pre-HD serum [HCO3] ≥26 in ≥ 7 months of any 12-month period. Patients with serum [HCO3] ≥26 in ≥ 7 months of every 12-month period constituted the control cohort.

Results: Of 1271 patients with at least 12 months of HD, 444 met the alkalosis criteria for at least 1 one 12-month period and 73 had persistent alkalosis. 189 patients met the control criteria for every 12-month period. Patients with persistent alkalosis were older (66 vs 55 years, p<0.001) and weighed less (69 vs 82 kg, p<0.003), but the prevalence of comorbidities including cardiovascular disease, neoplasia, and diabetes was not increased. HD dose (kT/V) was greater (1.47 vs 1.37, p<0.001), protein catabolic rate was lower (0.85 vs 0.96 g/kg/day, p<0.001), and interdialytic weight gain was less (1.62 vs 2.28 kg, p<0.001). Despite significant weight loss over time (7 ±3 vs 0 ± 3.9 kg, p<0.001), mortality was not increased when adjusted for age, serum albumin was only slightly lower (3.71 vs 3.81 g/dl, p=0.01), and a lower mean eGFR/creatinine/chronic illness such as serum cholesterol and hemoglobin did not differ from control patients.

Conclusions: Transient interdialytic alkalosis was common in this HD population and persistent alkalosis was not rare (~5%). Alkalosis appeared to result from a greater dialysis dose and lower protein intake but not chronic illness. Further studies are needed to determine whether this alkalosis is detrimental and adjustment of dialysate [HCO3] is indicated.

PO0894

Metabolic Alkalosis in Hemodialysis Patients: Worse Outcomes


Background: The ideal serum bicarbonate levels in prevalent hemodialysis (HD) patients is still debatable. Metabolic alkalosis in these patients has been associated with increased morbimortality. The aim of this study was to evaluate the association between serum bicarbonate and nutritional and cardiovascular risk markers, hospitalizations and mortality.

Methods: This was a single-center, retrospective study, of a cohort of 158 in-center HD patients, with a duration of 24 months. Serum bicarbonate levels were evaluated predialysis every 3 months. Body Composition Monitor was used to assess nutritional and hydration status. Electrocardiogram and echocardiogram data were obtained to calculate the QTc interval and the left ventricular mass index, respectively. Vascular calcifications were assessed using the Adrágão score (SVCS).

Results: Mean age of the population was 69±12.6, 73% were male and 45% had diabetes. Median HD vintage was 59 months (IQR: 65 months). Mean serum bicarbonate levels were evaluated at 12-month period. Patients with serum [HCO3] 19-23 in ≥ 7 months of every 12-month period were considered to have persistent alkalosis was defined as pre-HD serum [HCO3] ≥26 in ≥ 7 months of any 12-month period. Patients with serum [HCO3] ≥26 in ≥ 7 months of every 12-month period constituted the control cohort.

Conclusions: Persistent alkalosis was associated with higher HD mortality (r=0.08, p=0.001), and interdialytic weight gain was less (3.71 vs 3.81 g/dl, p=0.01), and a lower mean eGFR/creatinine/chronic illness such as serum cholesterol and hemoglobin did not differ from control patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Posterior reversible encephalopathy syndrome (PRES) appears to be related to cerebral blood flow dysregulation and endothelial cell disease, and immunosuppressive states, common diseases in ESKD. The pathophysiology understood. Reported cases of PRES have been linked with hypertension, autoimmune disease, and calcium channel blocker use. The clinical presentation is characterized by headache, altered mental status, and posterior brain white matter edema on imaging studies. PRES is a radiological syndrome first reported in 1996 which describes the presence of a wide range of neurological symptoms, and posterior brain white matter edema on imaging studies. As such, there is an association with an increased number of infection-related hospitalizations and mortality, as well as higher all-cause mortality. Serum bicarbonate levels ≥24.5 mEq/L were associated with lower survival at 24 months. Prospective studies are needed to determine the ideal serum bicarbonate levels in HD patients.

PO0895
The Use of Caffeine to Treat Intradialytic Hypotension

Introduction: Intradialytic hypotension (IDH) affects between 15% to 70% of patients on hemodialysis (HD) and may cause long-term multisystem ischemic damage. One proposed mechanism for IDH is the accumulation of local adenosine causing vasodilation. Agents such as midodrine and caffeine counter these vasodilatory effects. Herein we present a case of IDH where the ingestion of caffeine prior to HD sessions significantly reduced the severity of IDH.

Case Description: A 77-year-old female with CKD-5, longstanding hypertension, and type 2 diabetes mellitus was admitted for initiation of HD. During her 1st HD session, she experienced IDH with a sudden drop in her systolic blood pressure (SBP) from the 193 to 113, accompanied by loss of consciousness and convulsions of the bilateral upper extremities, and diffuse confusion. She recovered consciousness without a postictal state and no significant changes on ECG. Echocardiography ruled out pericardial effusion. On subsequent HD sessions, the patient continued to experience IDH with average decreases of over 100mmHg in her SBP. Initial management by lowering blood flow rate, lowering dialysate temperature, and holding the patient’s pre-dialysis antihypertensive regimen had only a mild effect in preventing IDH. Given previous studies showing the efficacy of 250 mg caffeine capsules in preventing IDH, we tested the effect of caffeine on this patient’s IDH. 30 minutes prior to her next inpatient HD session, we administered 10 oz of coffee (150 mg of caffeine). Her drop in SBP during that session was markedly reduced from 187 to 149.

Discussion: Non-pharmacological measures to prevent IDH have been previously implemented but lack well-powered clinical trial evidence. Using coffee as a vehicle for caffeine administration was an effective preventive measure for IDH in our patient. We hypothesize that this effect is adenosine inhibition mediated. Adenosine is released by cells undergoing localized ischemia during HD, causing vasodilatation. Studies show an increase of serum adenosine during HD. Caffeine is a non-selective adenosine receptor antagonist, and can prevent sudden vasodilatation during dialysis. Thus, coffee may be an effective alternative to midodrine for the prevention of IDH. In conclusion, coffee provided a readily available, inexpensive, patient-centered, non-pharmacological measure to reduce IDH while also decreasing the risk of polypharmacy.

PO0896
A Case of Posterior Reversible Encephalopathy Syndrome (PRES) in an ESKD Patient with COVID-19
Viktor J. Martinez, Darancie Chewaprook. Albert Einstein Medical Center, Philadelphia, PA.

Introduction: Posterior reversible encephalopathy syndrome (PRES) is a clinicoradiological syndrome first reported in 1996 which describes the presence of a wide range of neurological symptoms, and posterior brain white matter edema on imaging studies which may be reversible. The clinical presentation is characterized by headache, altered consciousness, visual disturbances and seizures; hypertension is frequent, although not invariably.

Case Description: A 37-year-old male with past medical history of hypertension and diabetes mellitus, admitted to the hospital with complaints of headache, altered consciousness, visual disturbances and seizures; hypertension is frequent. He was admitted in the ICU with a blood pressure of 274/147 mmHg, RR of 16, HR 98 bpm and oxygen saturation of 89% on room air. Due to acute visual loss, a stroke alert was initiated. A head CT scan showed subcortical hypodensities in the bilateral occipital lobes consistent with PRES. He was started on Nicardipine drip in the ICU with subsequent decrease in blood pressure to 166/105 mmHg. His vision restored fully without further episodes of vision loss. Patient was found to be positive for COVID-19 and did not receive treatment for it as his hypertension and hyperglycemia was well controlled and hypertension was resolved. The patient received maintenance HD with Nicardipine drip was weaned, and he was transitioned to oral blood pressure medications.

Discussion: The relationship between kidney disease and PRES is not fully understood. Reported cases of PRES have been linked with hypertension, autoimmune diseases, and immunosuppressive states, common diseases in ESKD. The pathophysiology of PRES appears to be related to cerebral blood flow dysregulation and endothelial cell dysfunction. The proinflammatory response in COVID-19 produces dysfunction and death of endothelial cells which may increase vascular permeability, promoting the cerebral edema seen in PRES. The estimated prevalence of PRES in COVID-19 patients is between 1-4%. Reports of PRES in ESKD are rare. PRES may not be readily recognized given the heterogeneity of presentation. Therefore, high index of suspicion is needed in the ESKD population.

PO0897
Eye Pain During Hemodialysis: Ocular Dialysis Disequilibrium?
Sarah Abbass Massih,1 Monika Aggarwal (Gupta).1 Virginia Commonwealth University Health System, VA; 2VA Richmond Medical Center, Richmond, VA.

Introduction: Changes in Intracocular pressure (IOP) during hemodialysis (HD) are underrecognized. We report a case of increased IOP during HD, successfully treated with adjustments to dialysis prescription.

Case Description: 59-year-old African American man with End Stage Renal Disease (ESRD) secondary to diabetic nephropathy on HD since 2017, presented with excrecuting right eye pain during HD for 2 weeks. He described increasing right eye pain during HD, requiring early termination of dialysis after 3 hours. He has known right eye glaucoma with no vision. He was on atropine sulfate, prednisolone acetate, latanoprost, dorzolamide/timol, and brimonidine tartrate eye drops. IOP in right eye were 63 and 80 mm of Hg, before and after hemodialysis, respectively. Left eye IOP were ≤20 mm Hg and did not change significantly with dialysis. Due to concerns for ocular dialysis disequilibrium; blood flow rate, dialyse rate flow rate, dialysate temperature, and dialysate sodium were changed to 400 ml/minute from 450 ml/minute, 500 ml/minute from 800 ml/minute, 35.6 C from 37 C, and 145 mEq/L from 140 mEq/L, respectively. Subsequent to changes to dialysis prescription, patient was able to complete dialysis with no worsening of right eye pain and IOP (62 and 64 mm of Hg before and after dialysis, respectively).

Discussion: Increase in IOP during HD is thought to be due to rapid decline in plasma osmolality relative to aqueous humor, creating an osmotic gradient that causes movement of water into the eye. Patients with normal eye outflow have minimal rise in IOP as aqueous humor is drained simultaneously. However, patients with glaucoma are not able to drain excess water, causing increase in IOP and eye pain. Older age, diabetes mellitus, and African-American race are risk factors for ESRD and Glaucoma. Early recognition of ocular dialysis syndrome can allow for safe delivery of dialysis in patients with glaucoma. While acetazolamide is an effective treatment for raised IOP, it’s efficacy and safety in ESRD remains unknown. Similarly role of Mannitol in mitigation of ocular dialysis disequilibrium is unclear. Our patient had resolution of ocular dialysis disequilibrium in decrease in blood and dialysate flow rates, increase in dialysate sodium and, decrease in dialysate temperature. Increase in ultrafiltration may also reduce risk of ocular dialysis disequilibrium by raising extracellular osmotic pressure.

PO0898
The Association of Interdialytic Weight Gain in Long Intervals with Residual Renal Function Decline
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Background: Preservation of residual renal function (RFR) in dialysis patients is important for better prognosis. The effect of interdialytic weight gain (IDWG) on change of RFR has not been investigated well. We examined the association of IDWG in long intervals (i.e. 2-day breaks between dialysis treatments) with rapid decline of RRF.

Methods: This retrospective cohort study included 6425 patients who initiated hemodialysis in a large dialysis organization in the United States from 2007 to 2011. We examined the association between seven categories of IDWG in long intervals (IDWGIL) and rapid decline of RRF using logistic regression model. Rapid decline of RRF was defined as the percent decline in renal urea clearance (KRU) greater than the median value of the cohort in the first year after dialysis initiation. Seven categories of IDWG were as follows: 0-<1%, 1-<2%, 2-<3%, 3-<4%, 4-<5%, 5-<6%, and ≥6%. We also examined continuous associations between IDWGIL and rapid decline of RRF using restricted cubic spline analysis.

Results: Higher categories of IDWG were associated with increased risk of rapid decline of RRF. The odds ratios (95% confidence intervals) of rapid decline of RRF for IDWGIL of ≥4%, ≥5%, ≥6%, and ≥6% were 1.04 (0.90-1.20), 1.31 (1.09-1.56), 1.19 (0.94-1.51), and 1.60 (1.49-1.71) (Figure a). The restricted cubic spline analysis showed that risk of rapid decline of RRF increased when IDWGIL exceeded 2% (Figure b).

Conclusions: Our results showed higher IDWGIL was associated with higher risk of rapid decline of RRF. IDWGIL exceeded 2%, especially ≥4%, seems to be thresholds for higher risk of RRF decline.
Prevalence of Anti-Erythropoietin Antibodies in Patients with ESRD on Regular Hemodialysis: A Single-Centre Experience

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Background: Recombinant human erythropoietin (rHuEPO) is a glycoprotein that acts as a biological substitute for the endogenous substance used to treat anaemia in individuals with end-stage renal failure. Patients with rHuEPO resistance have been described, requiring higher and higher dosages of the drug to maintain an appropriate haemoglobin level. These antibodies probably cross react with the patient’s endogenous EPO and lead to anaemia that can be more severe than even before the onset of EPO therapy. The prevalence of anti-erythropoietin antibodies in renal patients who respond poorly to erythropoietin is unknown.

Methods: We screened 262 patients who were on maintenance haemodialysis and excluded patients who were malnourished and had chronic liver disease, hypothyroidism, ongoing active autoimmune disease, active infection, on steroid therapy, with bleeding or hemolysis and elderly. 96 ISRD patients who were on recombinant human erythropoietin > 6 months and hemoglobin < 10 g/dL were included. Serum anti-erythropoietin antibodies were detected by enzyme-linked immunosorbant assay technique. All patients were subjected to full history taking and clinical examination. Complete blood count, reticulocyte count, serum creatinine, blood urea, serum albumin, serum ferritin, and haemoglobin tests were performed for all patients.

Results: Results showed that 26 patients (27.08%) had the anti-EPO antibodies in their blood, while 70 patients (72.91%) did not have the circulating antibodies. The mean hemoglobin (Hb) level was significantly lower in the antibody positive group (8.4 g/dL ± 1.52) than in the antibody negative group (9.68 g/dL ± 1.14) (P = 0.000). The dose of EPO administered in both studies groups were significantly different. Logistic regression analysis also revealed that gender or age were not associated with any significant variation of serum antibody level. High levels of serum antibodies to EPO are a risk factor for EPO resistance.

Conclusions: Many anaemic ESRD patients treated with recombinant human erythropoietin have a low-affinity immune response to the recombinant protein that is readily detected. Antibodies to rHuEPO were shown to be greater in patients who received high EPO weekly dose. More research into anaemia management protocols in HD patients with positive anti-EPO antibodies is needed.

Poster:

PO0909

Posterior Ischemic Optic Neuropathy After Hemodialysis In a Patient with Uncontrolled Diabetes Mellitus


Introduction: Posterior ischemic optic neuropathy (PION) results from ischemic damage to the retrolubar optic nerve and presents as severe acute painless unilateral or bilateral loss of vision. Any procedure that results in sufficient optic nerve hypoperfusion can cause retrolubar optic nerve damage. Hemodialysis (HD) as a cause of peri-procedural bilateral PION is a rare complication. While there are reports of successful cases of treatment with hyperbaric oxygen treatment and steroids, there is no established treatment protocol and the prognosis for recovery of vision in patients with peri-procedural PION is poor.

Case Description: A 34-year-old male with end-stage renal disease on HD presented with respiratory complaints and hypertension emergency (BP 224/135 mmHg). His procedural PION is poor.

Results: Results showed that 26 patients (27.08%) had the anti-EPO antibodies in their blood, while 70 patients (72.91%) did not have the circulating antibodies. The mean hemoglobin (Hb) level was significantly lower in the antibody positive group (8.4 g/dL ± 1.52) than in the antibody negative group (9.68 g/dL ± 1.14) (P = 0.000). The dose of EPO administered in both studies groups were significantly different. Logistic regression analysis also revealed that gender or age were not associated with any significant variation of serum antibody level. High levels of serum antibodies to EPO are a risk factor for EPO resistance.

Conclusions: Many anaemic ESRD patients treated with recombinant human erythropoietin have a low-affinity immune response to the recombinant protein that is readily detected. Antibodies to rHuEPO were shown to be greater in patients who received high EPO weekly dose. More research into anaemia management protocols in HD patients with positive anti-EPO antibodies is needed.

PO0901

Ocular Dysequilibrium with Eye Pain During Hemodialysis


Introduction: Eye complications may occur in patients with hemoglobinosis. Hemodialysis (HD) may lower plasma osmolality at a faster rate than changes in ocular osmolality can adapt. Here we are presenting two cases of ESRD patients who repeatedly developed eye pain only during HD.

Case Description: A 54 y/o Hispanic male with ESRD, right eye blindness & glaucoma who developed right eye pain only during dialysis treatments. The maintenance HD prescription was with duration of 4.5 h, blood flow rate (BFR) 450mL/min, dialysate flow 800 mL/min, Sodium (Na) 138 mEq/L, Calcium 2.7 mEq/L, Potassium 4.0 mEq/L, CO2 30mEq/L, & an average 2L fluid removal per HD. His BP was 130-140/80-90 mmHg. In response to the eye symptoms, the BFR was reduced to 350 mL/min & time was increased to 4.5 h. This change gave the patient initial relief from intradialytic eye pain. However, the patient continued to perform HD in the same manner. The period of HD treatments was enough to eliminate the intradialytic eye pain. The 2nd case was a 64 y/o AA female with ESRD and glaucoma developed recurrent left eye pain with headaches only during HD. She went to her Ophthalmologist who renewed her glaucoma medications. This relieved her eye symptoms, and normalized her intradialytic pressure off of dialysis. By taking her eye medications, she no longer developed eye pain or headaches during HD.

Discussion: Glaucoma is an ocular disorder where there is an increased IOP most commonly >22mmHg, this elevated pressure can cause blinding optic neuropathy. The current hypothesis for the rise of IOP during HD is related to an osmotic disequilibrium between the plasma & IO fluid, where the IO fluid is slightly hypertonic compared to plasma. Several medical therapies have been reported to mitigate the IOP increase during HD, such as the use of daily acetazolamide, mannitol infusion or 20% hyperosmolar glucose solution, or modified dialysis parameters with colloid infusion to raise plasma tonicity and decrease fluid shift during HD. However, these maneuvers have not been proven to relieve ocular symptoms. In general, use of higher dialysate Na conc. at hemodialysis are not considered a long term solution to intradialytic ocular hypertension, due to the tendency for increase fluid intake between HDs. Lower BFR with longer duration of hemodialysis treatments has been beneficial in some cases.

PO0902

Transient, Severe, Unilateral Eye Pain and Vision Loss Associated With Hemodialysis

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Introduction: Acute on chronic angle-closure glaucoma with elevated intracocular pressure is a well-established etiology of severe eye pain and profound vision loss, if not treated immediately. This case is a recurrent and episodic eye pain with transient visual loss during HD.

Case Description: 64 year-old Caucasian female with comorbidities including poorly-controlled insulin dependent type 2 diabetes, uncontrolled hypertension, obesity. She is on intermittent hemodialysis twice a week on weekdays. She was previously followed by a retina specialist for proliferative diabetic retinopathy with neovascular glaucoma. Initial onset approximately 1 year prior, with episodic transient palsy and complete unilateral vision loss lasting 30 minutes. The right eye developed recurrent episodes of left eye pain, maxillary topical and oral analgesic therapy was started, but her disease was refractory to conservative management. Surgical intervention was pursued, Valved Drainage Device (New World Medical) was placed under topical anesthesia. Post-operatively, the patient was able to undergo dialysis sessions without ocular symptoms and compliance has improved.

Discussion: The effect of hemodialysis (HD) on intraocular pressure (IOP) is variable and the exact mechanisms are still not clear. Previous reports in the literature suggest both increased and decreased intraocular pressure during fluid shifts associated with hemodialysis. Argon Pot assisted photocoagulation is known to reduce angle neovascularization induced by peripheral retinal ischemia in Neovascular glaucoma patients, IOP reduction is typically achieved with topical and systemic medications. Shunting and filtering procedures, including glaucoma valve implants and trabeculectomy surgery, may restore outflow and reduce IOP. After appropriate surgical intervention, the patient reported resolution of symptoms and improved tolerance to dialysis sessions.

PO0903

Caffeine Overdose Requiring Extracorporeal Mechanical Oxygenation (ECMO) and Hemodialysis

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Introduction: Caffeine (1,3,7-trimethylxanthine) is the most widely consumed psychostimulant in the world. It is considered safe if consumed in moderate amounts as it leads to cardiovascular collapse if the dose exceeds 150-200mg/kg. Extracorporeal removal of caffeine with intermittent hemodialysis (ICH) has been reported to improve outcomes. However, continuous veno-venous hemofiltration (CVVHDF), which is a routinely used extracorporeal therapy in patients with severe poisoning, is less favorably regarded for caffeine overdose because of inadequate rate of clearance. We present a case of combination therapy using both IHD and CVVHDF in the treatment of life-threatening caffeine overdose.
Case Description: A 33-year-old female weighing 63 kg presented after ingestion of approximately 100g of guanima powder (22g of caffeine). She presented with tachycardia (140-170 BPM) and severe hypotension (blood pressure 50/40 mmHg) resistant to 4 vasopressors at maximal dose. She required extracorporeal membrane oxygenation (ECMO). Baseline renal function was normal. IHD was initiated with blood flow rate (BFR) 200ml/min and dialysate flow rate (DFR) 500ml/min, which was gradually increased over 4 hours to a BFR of 400ml/min and DFR of 800ml/min; IHD continued for an additional 4 hours at this rate. During this 8-hour IHD treatment, her initial 4 pressor doses were halved, and she was transitioned to CVVHDF; the caffeine level was not available. However, after 12 hours of CVVHDF, the patient did not experience continued hemodynamic improvement, so IHD was reinitiated for 12 hours. Following this second prolonged session of IHD, she was weaned down to moderate doses of just two pressors. She was then transitioned back to CVVHDF for an additional 36 hours. At this time she was able to come off ECMO and all pressors. She had a full neurologic recovery. We later received a serum caffeine level of 425 mg/L (drawn soon after arrival at the hospital), which is the second-highest level ever reported; the established lethal concentration is 80 mg/L.

Discussion: Despite continuous dialytic therapies being generally favored in patients with ventricular tachycardia, IHD and CVVHDF may be used for hemodynamically unstable patients who ingest extremely high dose of caffeine. However, in such patients, continuous therapies are unlikely to supplant prolonged and repeated IHD treatment sessions.

PO0904
Anaphylaxis Secondary to Citric Acid Allergy in ESKD Patients
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Introduction: Dialysis reactions are common in ESKD patients undergoing hemodialysis (HD). We report first case of anaphylaxis related to citric acid solution used for dialysis disinfection & defloculation.

Case Description: 61-year-old male with history of ESKD on HD for 7 years, presented after missing dialysis. Patient underwent urgent HD upon presentation and developed signs of angioedema within first 30 minutes, requiring nasal intubation & treatment with epinephrine, steroids, & antihistamine. While intubated and hypotensive, patient had uneventful Slow Low Efficiency Dialysis. Angioedema was presumed secondary to antiemetics, which patient required due to severe nausea shortly after starting HD. Post extubation, patient developed similar reaction with milder symptoms with HD that responded to stopping HD and medical therapy. He had normal complement and mildly elevated tryptase. He was presumed to have a dialyzer reaction therefore, the dialyzer was changed from Revaclear to REXEED & it was tolerated well. He had similar severe reaction a week later while using the REXEED dialyzer. Investigations showed elevated anti-citrulline antibodies (EOTO) but clinical significance was questionable given the reaction only developed in inpatient setting. Later we discovered that dialysis machines are disinfected/descaled differently between inpatient & outpatient dialysis, even though both utilize citric acid, which might have led to more exposure to citric acid solution in inpatient setting. For next 2 weeks, patient was dialyzed using different combinations of dialysis machines, dialyzer & dialysis circuits including ones sterilized with ETO, however, all machines were disinfected/descaled using a combination of bleach & heat. After elimination of citric acid, patient had no further anaphylactic reaction.

Discussion: Dialyzer membrane reactions have been commonly described as Type A reactions mediated by dialyzer membrane (Igf mediated) and Type B membrane reactions mediated by complement activation. In our case clinical significance of ETO antibody was not clear, & angioedema was eliminated after removing citric acid from the machine disinfection. Industrial citric acid mediated angioedema has not been reported before, & it might be an important mediator of allergy in ESRD, & careful review of the dialysis machine preparation should be reviewed in every case of severe allergic reaction.

PO0906
Reverse Shoulder Arthroplasty in Dialysis Amyloidosis
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Introduction: The use of high-flux over cuprophane dialyzers, has led to Beta-2 microglobulin amyloidosis (B2M) becoming rare in long term hemodialysis (HD) patients. Amyloid fibers embed systemically, skeletal involvement producing bone cysts, tendinopathy and fractures.

Case Description: A 65-ya male on chronic HD for 30 years presented with progressive, right (R) shoulder intractable pain and limited range of movement (ROM). X-ray/MRI identified severe glenohumeral osteoarthrosis (OA), tendinopathy and large irreparable rotator cuff tear. Past history included heart failure, pulmonary hypertension, hepatitis C, severe secondary hyperparathyroidism and chronic anemia. Surgical history included bilateral (b/l) total hip arthroplasties, b/l carpal tunnel release, R nephrectomy for renal cell carcinoma in renal cystic disease. Due to the intractable pain, disability and failure of physical therapy and corticosteroid injection therapy he underwent reverse shoulder arthroplasty. Operative findings showed large soft tissue deposits about the subscapularis, glenoid and labrum, attributed to amyloid. Histology of intra-articular soft tissue, labrum and synovium confirmed amyloid (apple-green birefringence by Congo Red Staining) with focal calcium pyrophosphate deposition. Undecalcified histology of humeral head showed moderate secondary hyper-parathyroid bone disease with peri-trabecular amyloid deposits. Following surgery patient noted marked improvement in pain and partial improvement in shoulder ROM.

Discussion: No treatment exists for HD patients with B2M, ineligible for kidney transplant. Physicians are tasked with treating clinical manifestations that severely impact quality of life (QOL). Concern for adverse outcomes and paucity of surgical precedent should not deter appropriate surgical intervention. This patient illustrates the clinical and surgical decision-making targeted to improving (QOL).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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Prediction of Severe Gastrointestinal Bleeding Events in Hemodialysis: Collaborative Development of Machine Learning Model Within INSPIRE

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On behalf of the INSPIRE Core Group 1Fresenius Medical Care, Global Medical Office, Waltham, MA; 2Fresenius Medical Care, Global Medical Office, Bad Homburg, Germany; 3University College London, London, United Kingdom; 4Karolinska Institutet, Stockholm, Sweden; 5RWTH Aachen University Hospital, Aachen, Germany; 6Fresenius Medical Care AG and Co KGaA, Bad Homburg, Germany.

Background: InInitiativeS on advancing Patients’ outcomes In ReNal disease (INSPIRE) is an industry and industry collaboration set forth to identify critical investigations/models needed to advance the practice of nephrology. As an inaugural effort, INSPIRE group aims to develop a machine learning (ML) model that can identify a hemodialysis (HD) patient’s 30-day risk for hospitalization due to gastrointestinal (GI) bleeding.

Methods: We used data from adult (age ≥ 18 years) HD patients (Jan 2017–Dec 2020) in the United States to build a XGBoost model considering 2,292 variables for classification of 30-day GI bleed hospitalization risk. Data were randomly split in 50%:20%:30% ratio for model training, validation, and testing. Unseen data by model (testing) was used for assessing performance via area under the curve (AUC) and feature importance of predictors via Shapley (SHAP) values.

Results: Among 58,187 HD patients included in the testing dataset, 1150 had a GI bleed hospitalization. ML model showed AUC=0.67 and top predictors of a GI bleed hospitalization in 30 days were the minimum hemoglobin level in prior 180 days, time since prior GI bleed hospitalization, and higher vitamin D levels (Figure 1).

Conclusions: ML model appears to have suitable performance for identifying a patient’s 30-day risk for GI bleed hospitalization. Albeit further model iterations/tuning are needed, ML techniques that account for collinearity and missingness hold promise for early detection of potentially avoidable GI bleeding admissions. Model identified an important association between higher vitamin D levels and GI bleeding events, which is consistent with the increasing evidence suggesting antithrombotic and anticoagulant actions of vitamin D derivatives.

Funding: Commercial Support - Fresenius Medical Care
Methods: We used EHR data on pts new to HD between 2003-2016 from a national provider (n=54,148) linked with USRDS. We abstracted 86 predictor variables organized into person-mth and divided into training (n=32,488) and testing sets (n=21,660). The dynamic training set contributed 3.80k person-months. The static training set contained the first pt-month for those who initiated HD within 90-day (n=24,026). We fit LASSO logistic regression to predict mortality in the next 6-months and assessed both models on a time-varying test dataset. We report overall predictive performance metrics as well as visualization of time-varying patient risk in the 24 mths before a pt dies.

Results: Pt median age at initiation was 64 yrs; 43% female, 63% Caucasian; 7% died w/in 6 mths of initiation and 53% w/in 5 yrs. Top predictor variables were similar between the two models: age, serum chloride and serum albumin. The table shows performance metrics for the two models on the test data with the dynamic model performing significantly better. The plot shows the predicted risk for pts in the 24 mths prior to mortality. The dynamic model more quickly responds to pts changing risk, producing a higher predicted probability leading up to mortality.

Conclusions: A risk model built using time-varying data performs better than one using baseline data. Incorporation of dynamic models in dialysis-EHR could be used to direct appropriate population health interventions to the highest risk pts. Examination of dynamic risk models can elucidate pt-risk trajectories.

Funding: NIDDK Support

PO0910

Machine Learning Classification of Tweets for Patient Dialysis Experience

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Background: Popular microblog (e.g. Twitter, Facebook) services provide a continuous stream of public health information. This data has been used to monitor viral spread, medication adherence, and false health information. There are thousands of posts on Twitter daily regarding personal dialysis experience, access, and side effects. While these posts include valuable public health information, evaluating these posts to meaningfully assist dialysis patients is difficult as there are even more tweets mentioning dialysis in a professional context. We aimed to modify a state of the art natural language model to classify posts about dialysis as personal or professional.

Methods: We filtered posts containing the word dialysis. Posts were manually labeled as personal or professional by a nephrologist depending on the context dialysis was mentioned. The data was randomized and split for 60% training, 20% validation, and 20% testing. The text was preprocessed to remove extraneous characters and input into a Bidirectional Encoder Representations from Transformers (BERT) model for fine tuning, and a term frequency inverse document frequency vectorized Multinomial Naive Bayes Classifier.

Results: We collected 6011 tweets from May 3, 2021 to May 14, 2021.1000 tweets were randomized and labeled. 57% were categorized as professional. BERT and Naive Bayes models attained 88% and 82% accuracy, respectively, on the testing data. The BERT model classified far less false negatives with a small increase in false positives (Figure 1).

Conclusions: BERT’s semantically rich word embeddings can enhance social media mining algorithms on dialysis content. We show superiority of a BERT model over a traditional count-based language model. This method can be easily applied as a pre-processing step to remove noisy posts to better study dialysis and other health trends in social media. This novel processing task and pipeline have broad clinical and public health implications for reducing the amount of data and time required for accurate, real-time monitoring of patient level posts.

PO0911

Automating Dialysis Machine Alarms During Sustained Low-Efficiency Dialysis (SLED)

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Background: Sustained low-efficiency dialysis (SLED) with regional citrate anticoagulation (RCA) is frequently employed at our institution. RCA requires constant monitoring because a dialysis machines alarm that stops the blood pump (BP) or bypasses dialysate leads to an increased rate of citrate infusion into the patient, with consequence of ionized hypocalcemia. To enhance safety and surveillance efficiency, we developed an innovative computer/phone system that identifies SLED machine alarms and notifies clinical care staff directly via an appropriate phone network.

Methods: In 2017, we linked onboard SLED computer Wi-Fi systems to the hospital’s internal phone network (ASCOM). An alarm recorded by the SLED machine’s computer delivers an email to a dedicated email account that is subsequently transmitted to the ASCOM MailGate System. Mailgate produced and relayed text message alarms to dedicated ASCOM phones of dialysis technicians or nurses. Importantly, no additional training or changes in workflow are required for adoption of this method.

Results: This innovation has increased safety and efficiency. Response times for machine alarms improved and downtimes on dialysis were reduced, increasing dialysis dose of dialysis. To ascertain end-user satisfaction of the automated alarming system, we conducted a survey that demonstrates high-level satisfaction with the system (Table 1).

Conclusions: Currently, no medical alert companies connect dialysis machine information to a medical alert phone system. ASCOM provides wireless messaging systems for dedicated hospital applications. Notably, ASCOM does not directly connect to dialysis machines. In addition, Email Alerts can be browsed by managers for archival retrieval, quality and safety report generation, and investigation of unanticipated events.

Funding: Clinical Revenue Support

PO0912

Users of a Web-Based Communications Platform for Care Coordination of Hospitalized Dialysis Patients

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Background: Better care coordination between dialysis clinics and hospitals may improve outcomes among hospitalized dialysis patients. To fill the gap created by separate electronic health record systems across the two settings, we rolled out a web-based communications platform (“DialysisConnect”) in four dialysis clinics and one hospital in Atlanta. Here, we examine usage patterns of DialysisConnect.

Methods: DialysisConnect included automatically uploaded clinical information from dialysis clinics, forms for entering critical admission and discharge information, and a direct communications channel. Two nephrologists and two hospitalists served as project champions at the dialysis clinics and hospital, respectively. DialysisConnect was made available to 106 potential users [hospitalists, nephrologists, advanced practice providers (APPs)] at the hospital and dialysis clinics, care coordinators (hospital), and nurses/nurse managers (dialysis clinic) starting 10/29/20. Descriptive statistics were used to describe patterns overall and by user role through 4/15/21.
Results: While physicians comprised most of the potential users, APPs and dialysis nurses were the most prevalent users (Table). Admission activity was more evenly distributed among users; e.g., one hospital-based APP recorded most of the admissions (n=225, 89%) and discharges (n=226, 93%) among patients treated at the dialysis clinics included in the pilot.

Conclusions: We found that physicians were unlikely to use DialysisConnect. Our user statistics suggest that APPs and nurses may be the most likely to engage with a care coordination system, which informs future pragmatic research in this area.

Funding: NIDDK Support

PO0913

Family-Friendly, Work-Friendly, Home-Hemodialysis and In-Center Hemodialysis Hybrid: The First of Its Kind

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Introduction: Hybrid dialysis is traditionally defined as the combination of peritoneal and hemodialysis (HD) in patients with end-stage renal disease. Its reported use is quite limited outside of Japan. We recently encountered major family-related and employment-related constraints that prevented a 39-yo man with ESRD on HD from completing the four-times weekly HD treatments with HD inadequacy and worsening of patient’s physiology. We successfully switched him to a new hybrid of twice-weekly HD + twice weekly In-Center HD. This is the first such report.

Case Description: A 41-ya male with ESRD secondary to SLE and hypertension on home HD, 4 x weekly, for some years experienced family-related constraints including non-availability of daycare for two young children due to COVID-19 pandemic, spousal illness and new work-related challenges with more travel and was missing his HD sessions. The result was inadequate HD delivery and worsening laboratory indices. He now receives 2 in-center HD treatments on Tuesdays and Thursdays, and 2 home HD treatments, one during the weekend and one during the week. This was started in February 2021. Each HD session lasts for 3.5 hours, 2000 units Heparin bolus, and his left brachiocephalic AVF is accessed by the button-hole method. The Home Dialysis Staff coordinates his dialysis care. Standardized Kt/V for May 2021 was 2.6.

Discussion: Hybrid dialysis is traditionally defined as the combination of peritoneal and HD in patients with ESRD. A 2020 Italian report described another type of hybrid dialysis that consisted of once-weekly in-hospital HD and home peritoneal dialysis to limit patient exposure to the hospital environment during the COVID-19 pandemic. We have described the successful application of a new Hybrid HD system that combined In-center HD with a mobile HD system. To our knowledge, our report is the first of its kind and was designed and implemented primarily for the purpose of overcoming increasing family and employment demands on the patient. This new hybrid dialysis option was designed to facilitate a family-friendly work-friendly HD on a long-term continuous basis. The patient, his family with two young children and his employers are happy and very satisfied. Simultaneously, the patient has continued to do well with adequate dialysis and meeting all the required goals of management in the past 3 months.

PO0914

Triple I Study: Hubs of Care Survey

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Background: The Can-SOLVE CKD Triple I Study identified continuity of care; access to a primary care provider (PCP) in the (CM) hemodialysis (HD) unit; and access to care for other medical conditions as key challenges to in-centre HD care (www. betterkidneycare.ca). The Hubs of Care project aims to address these challenges by incorporating health care providers (HCPs) from other settings in the HD unit; firstly, we identify current practice, potential interest and need and desire for different HCPs in HD.

Methods: A cross-sectional self-reported survey administered Feb-May 2021 with HD patients and staff at four academic sites across Canada. Eligible participants included adults fluent in English or French who could complete the survey independently. The survey asked which HCPs are currently in HD units, which additional HCPs would be most useful to add and whether patients are in favor of other HCPs visiting them either virtually or in-person. Additional data were solicited by free text. Preliminary analyses using descriptive, median (IQR) and proportion and summative content analysis, are presented.

PO0915

Utilization of the Tablo Hemodialysis System’s Data Platform: An Analysis of 100,000 Acute Dialysis Treatments

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Background: The Tablo® Hemodialysis System (Tablo) is an all in one, easy-to-learn device featuring integrated water purification, on demand dialysate production and two-way wireless data transmission capable of providing therapy up to 24 hours in a hospital setting. Limited connectivity of traditional hemodialysis systems constrains the ability to drive improvement in quality and efficiency of dialysis care. Tablo’s cloud-based data platform expedites care delivery in real time and informs on dialysis program metrics to facilitate quality improvement. The objective was to demonstrate Tablo’s automated wireless data capabilities through analysis of 100,000 Tablo acute treatments.

Methods: Tablo data were collected through real-time transmission via a cloud-based, HIPAA compliant platform. Analysis was performed by combining prescribed and achieved data on consecutive treatments. Treatments were divided into groups based on treatment time of less than 6 hours (conventional therapy) or greater than 6 hours (extended therapy).

Results: A total of 100,000 treatments between April 2020 and May 2021 were analyzed. Treatments ranged from 2-24 hours. Treatment time success, defined as achieved within 10% of prescribed time, was 90.7% across the population. The most common reason for early termination was “User ended” (8.6%), with 0.7% due to “Device Directed”. Mean total number of alarms per treatment was 2.5 across the population with no difference in alarm frequency (0.7 alarms per hour) between treatment groups. The most frequent clinically significant alarms were high and low venous pressures. Mean time to alarm resolution was 4.3 minutes, with shorter alarm resolution time demonstrated in the HHD group (13 vs 22s).

Conclusions: With high utilization across a wide range of treatment times in the acute setting, Tablo successfully achieved treatment goals. The few observed alarms were quickly resolved by clinical users. Tablo’s robust data reporting capability enables the identification of treatment trends that can be used to drive quality improvement.

Funding: Commercial Support - Outset Medical, Inc.

Summary of Tablo Treatment Parameters

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Treatment Protocol</th>
<th>Clinically Significant Alarms</th>
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</thead>
<tbody>
<tr>
<td>HD (100%)</td>
<td>04500</td>
<td>3.43 ± 0.49</td>
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<tr>
<td>(24%)</td>
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Impact of Medication Reconciliation by a Dialysis Pharmacist

PO0916

Summer Dyer, Linda Awadish, Sally Rafie, Victoria T. Nguyen. University of California San Diego, La Jolla, CA.

Background: Medication reconciliation (MR) improves patient outcomes, reduces cost, and is a reporting measure for the CMS End-Stage Renal Disease Quality Incentive Program. Most dialysis facilities do not have a clinical pharmacist to perform MR. The purpose of this study is to evaluate the impact of a pharmacist performing MR and medication management for patients receiving outpatient chronic hemodialysis at an academic institution.

Methods: We conducted a retrospective study from 10/1/18 to 11/2/20 to determine if MR by a pharmacist reduced medication discrepancies (MDs) and medication related problems (MRPs) over time. Secondary outcomes were to describe the type of MDs, type and severity of MRP, impact of a pharmacy delivery service, and number of emergency department (ED) visits and hospitalizations pre- and post-pharmacist integration. Discrepancies were categorized as: unintentional discrepancy, undetected intentional discrepancy, and MRPs. MRP severity was categorized using the National Coordinating Council for Medication Error Reporting and Prevention index. Descriptive statistics were calculated for each variable and a repeated measures ANOVA test was conducted to determine if MDs or MRPs changed over time.

Results: A total of 135 patients with 479 unique pharmacist encounters were included. The mean (SD) age was 61.7 (14) years, 58% were male, 63% Caucasian, mean (SD) time on dialysis was 6.4 (4.6) years and most common comorbidities were diabetes and hypertension. The pharmacist conducted 3.5 MR/client with a mean time spent of 39.7 (16) minutes and 16% required an interpreter. Unintentional discrepancies were noted in 53% encounters, undetected intentional discrepancies in 71%, and MRPs in 59% but decreased significantly from the first to the second encounter (1.9 vs 0.9, 1.9 vs 1.2, and 1.1 vs 0.5 per patient, respectively, p<0.05). Most common MD types included non-adherence, prescription renewals, and excessive drug doses. On half (54%) were enrolled in a pharmacy delivery service and had significantly fewer undetected intentional discrepancies compared to non-enrollees (p<0.05). ED visits and admissions pre- and post-pharmacist integration were not statistically different.

Conclusions: Integrating a pharmacist into a hemodialysis unit enabled effective medication reconciliation and management to significantly reduce medication discrepancies and problems, and improve safety.

Interim Analysis of the Extension of Tablo Treatment Duration (XTEND) Study

PO0917

Yaadveer Chahal, Josh Schumacher, Michael A. Aragon. Outset Medical, Inc., San Jose, CA.

Background: The Tablo® Hemodialysis System (Tablo) is an all in one, easy-to-learn device featuring integrated water purification, on-demand dialysate production and two-way wireless data transmission and is approved for use in the acute, chronic and home settings. Prior reports have demonstrated Tablo’s ability to achieve clinical goals, seamlessly integrate into hospitals and reduce cost across a wide range of treatment times. Extension of the Tablo cartridge to 24 hours (extended therapy; “XT”) allows even greater flexibility for prescribers in the acute setting. The objective is to report on the experience with Tablo extended therapy between 12 and 24 hours utilizing an interim review of the XTEND study (NCT04912050).

Methods: Nursing staff were trained during a single training session on Tablo XT. After a run-in period of 5 treatments, Tablo data were collected via real-time transmission to a cloud-based, HIPAA compliant platform and reviewed by site staff. Clinical treatment success was defined as either ending within 10% of prescribed time or site investigator assessment that all patient treatment goals were met.

Results: Fifty (50) Tablo XT treatments had a median prescribed treatment time of 24 hours and a median achieved treatment time of 23.5 hours. Median cartridge use was 1.0 per treatment. Clinical treatment success was 84%. Treatments ended due to clotting/clogging were 4% (2 of 50). Median total ultrafiltration (UF) rate was 1.7 mL/kg/hr. Clinically significant alarms occurred at a median rate of 7 per treatment with a resolution time of 14 seconds. Most frequent alarms experienced were arterial and venous pressure (39% and 58%, respectively), of which none resulted in an end treatment.

Conclusions: Tablo’s XT successfully achieves prescribed treatment time and favorable ultrafiltration rates with minimal therapy interruptions from alarms or cartridge changes. This data demonstrates the effectiveness of Tablo’s newly expanded versatility in achieving personalization of treatments necessary for unstable patients and enabling successful delivery of extended therapy with minimal clotting. Tablo’s 24-hour therapy meets the needs of critically ill patients that require renal replacement therapy for greater than 12 hours.

Funding: Commercial Support - Outset Medical, Inc.

Feasibility Study of Wrist-Based Wearable Activity Tracker in Hemodialysis Patients

PO0918

Maggie Han,1 Ohmar Thwin,1 Xia Tao,1 Lemuelt Rivera Fuentes,1 Amrish U. Patel,1 Nadja Grobe,1 Priscila Preciado,1 Leticia M. Tapia Silva,1 Mohammad I. Hakim,1 Stephan Thijssen,1 Peter Kotanko,1,2 Renal Research Institute, New York, NY; Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Increased physical activity (PA) is associated with reduced risk of cardiovascular disease which is prevalent in hemodialysis (HD) patients. Wearable activity trackers (WAT) allow remote monitoring of PA. We aim to explore the feasibility of using a WAT for 1 year in HD patients.

Methods: HD patients from 4 NYC clinics were enrolled on a rolling basis starting June 2018 and followed for up to 1 year. Ambulatory patients ≥18 years, on maintenance HD, and owning a mobile device were included. Each patient was provided with and taught how to use the Fitbit Charge 2. A stepwise intervention plan was used to assess feasibility (Figure 1). We used Kaplan-Meier analysis to determine mean and median time to withdrawal for non-compliance (TW) and predictors of TW were assessed by univariate Cox Regression.

Results: 119 patients were enrolled into the study. Patients were 54±12 years old, 59% African American, 37% lived alone, and 54% had an education level of college and above. 16% of patients were withdrawn for non-compliance. Mean and standard deviation TW was 175 ± 103 days. Median and interquartile range of TW was 133 and 181 days (98 to 280 days), respectively. The probability of not being withdrawn for non-compliance is shown in Figure 2. Age, gender, race, living status, and education were not associated with non-compliance.

Conclusions: A small portion of patients were continuously non-compliant with wearing/syncing their Fitbit devices in our study. Based on a low risk (<20%) of being withdrawn for non-compliance, we determined that it is feasible to use a wrist-based wearable device in HD patients for up to a year. However, prolonged use of these devices may require additional counseling to patients.

Funding: Commercial Support - Fresenius Medical Care

P00916

Impact of Medication Reconciliation by a Dialysis Pharmacist

PO0917

Interim Analysis of the Extension of Tablo Treatment Duration (XTEND) Study

PO0918

Feasibility Study of Wrist-Based Wearable Activity Tracker in Hemodialysis Patients
PO0919
Glycemic Status Ascertained by Continuous Glucose Monitoring in a Prospective Hemodialysis Cohort

Background: Hemodialysis (HD) patients with diabetes are at heightened risk of hypo- and hyperglycemia due to multiple pathways. While self-monitored blood glucose is the standard approach for glucose assessment in HD patients, it may not adequately capture glycemic status given its infrequent nature. We thus sought to measure glucose levels using continuous glucose monitoring (CGM) as a more frequent (every 5-minutes), convenient, and automated method of glycemic status in a prospective HD cohort with diabetes.

Methods: Among 18 HD patients with diabetes hospitalized during 10/2020-5/2021, we conducted simultaneously protocolized glucose measurements using 1) CGM measured by Dexcom G6 devices vs. 2) blood glucose levels using capillary fingertip or venous blood glucose, with the latter measured 2-4 times per day (before each meal and at night), plus every 30 minutes during HD (total of 6-8 measures during HD). Using American Diabetes Association (ADA)-defined CGM targets, we examined the prevalence of patients achieving the recommended percentage (%) of CGM levels in the ranges of <54, <70, 70-180, >180, and >254mg/dL (ADA target % of glucose levels <1%, <4%, >70%, <25%, and >5%, respectively).

Results: Whereas 64% of CGM measurements (N=9444) were within target glucose range (time in range [TIR] 70-180mg/dL, 80% of blood glucose levels (N=100) were within TIR. The proportion of patients achieving the recommended % of CGM measurements within ADA-defined glycemic ranges of <25% were 180-180 (target range), <70, and >254mg/dL were 67%, 44%, 44%, 89%, and 78, respectively.

Conclusions: In a cohort of hospitalized diabetic HD patients who underwent concomitant CGM and blood glucose measurements using the Dexcom G6 remote access system, blood glucose testing overestimated the % of time patients were in target glycemic range as compared with CGM. CGM showed that less than half of patients achieved the recommended % of CGM measurements within target range. Further studies are needed to determine whether CGM can improve the glycemic management of HD patients compared to conventional approaches.

Funding: Commercial Support - Dexcom, Inc.

PO0920
Validation of Automated Sodium Control in a Novel Dialysis System

Background: The Diality Hemodialysis Machine will provide a range of hemodialysis modalities to expand the population of patients that may benefit from hemodialysis. One modality uses a sorbent filter that will accommodate the decentralization of dialysis delivery. Specific Aims: To test an automated feedback program designed to regulate the infusion of an alkali needed to maintain proper sodium concentration in a dialysate solution

Methods: A 125L volume of simulated dialysate was circulated at ~400 mL/min and ~37 C through a sorbent cartridge which removed the urea from the solution. The fluid exiting the cartridge had no Ca, Mg or K. These chemicals were reinfused through a pump in a solution containing Ca, K and Mg salts. A conductivity sensor (cond) was used in a feedback control of the alkali infusion pump. The feedback control adjusted the pump flow rate to maintain the conductivity of the infusate at 14.0 mS/cm. The sensor was programmed from a curve model of the alkali over time from previous experiments. Occasional spikes of Na+ was programmed from a curve model of the alkali over time from previous experiments. The dialysate sodium concentration [Na+] in the dialysate at pump 1, after mixing in a 125L tank was in the range 139.8 – 141.7 mEq/L. TP2, the mean dialysate [Na+] at pump 2 after leaving the sorbent filter was 124.2 (±2.4) mEq/L. This correlates with cond1 and was 12.8 (±0.4) mS/cm. TP3, the mean dialysate [Na+] after being replenished with the alkali solution immediately prior entering the tank for remixing was 139.5 (± 1.9) mEq/L and correlated with cond2 of 14.1 mS/cm.

Conclusions: The results validate the accuracy of the conductivity sensor in correctly regulating the alkali infusion.

Funding: Commercial Support - Diality Inc.
PO0922

Nanostructured Capillary Membranes for Size-Selective Hemofiltration
Peifu Cheng,1 Francesco Fornasier,2 Nicholas J. Ferrell,2 Shuvo Roy,2 William H. Fissell,1 Piran Kidambi,1 1Vanderbilt University, Nashville, TN; 2University of California San Francisco, San Francisco, CA; 2Lawrence Livermore National Laboratory, Livermore, CA.

Background: Size-selective separations offer potentially transformative advances for hemofiltration. In the context of hemodialysis, the tradeoff between selectivity and permeability often results in large package sizes and high driving pressures that limit wearable and implantable options of therapy. Here, we report on composite membranes with vertically aligned precise nanoscale capillaries with improved permeability.

Methods: Arrays of carbon nanotubes (CNTs) were synthesized via chemical vapor deposition and the catalyst composition was carefully selected to achieve a uniform distribution of diameters. The area between the CNTs were filled with a polymer to form a membrane. The CNT membranes were backed with microporous silicon supports and mounted into a filtration cell. Hydraulic permeability was calculated from gravimetric flow rates at stepped transmembrane pressures. Size-selectivity was measured by filtering fluorescently-labeled polydisperse Ficoll in phosphate-buffered saline. Size-specific Ficoll concentrations in feed and filtrate were measured by size-exclusion chromatography.

Results: CNT membranes membrane exhibited a cut-off ~6nm and the measured hydraulic permeability was 102.3 ml h⁻¹ m⁻² mmHg⁻¹ compared to published data of 30 ml h⁻¹ m⁻² mmHg⁻¹ for conventional high flux dialyzers. CNT membranes retained large molecules while passing small and medium-sized molecules. Sieving coefficient at 2 nm, approximately the size of β2 microglobulin, was unity (Figure).

Conclusions: The CNT membranes provide excellent middle molecule clearance with vertically aligned precise nanoscale capillaries and improved permeability.

PO0923

Delivered Dialysate Potassium Is Higher Than What Is Prescribed When High Sodium and Low Bicarbonate Are Prescribed
Saied W. Ali, Andrew I. Chin. University of California Davis Department of Internal Medicine, Sacramento, CA.

Background: Most hemodialysis machines utilize the 3-stream method of making dialysate. In hospital settings, dialysate prescriptions are customized to the clinical setting. We determined the differences between delivered and prescribed dialysate K⁺ in unusual prescriptions.

Methods: Dialysate samples drawn 15 minutes into HD were analyzed via indirect ion-specific electrodes for Na⁺, K⁺, and HCO3⁻. 5200 HDs with extremes of ordered Na⁺ and HCO3⁻ were analyzed. Outcome was measured versus ordered K⁺. Analysis used ANOVA using SPSS.

Results: Means of the difference between measured and ordered K⁺ and Na⁺ are shown in figure 1. For K⁺ there was significant difference amongst the groups (p<0.001). There were no differences amongst the groups for Na⁺.

Conclusions: When a very high Na⁺ is prescribed along with a low HCO3⁻ the the dialysate Na⁺ remains close to prescribed Na⁺. As the acid concentrate contains both Na⁺ and K⁺, a high Na⁺ and low HCO3⁻ prescription will use a relatively more of the acid concentrate and less of the bicarbonate concentrate. Dialysate prescriptions with a high Na⁺ and low HCO3⁻ resulted in delivered dialysate K⁺ by an average of 0.5 mEq/L; we observed some HDs where dialysate K⁺ was 1 mEq/L, higher than prescribed.
PO0925

Increasing the Clearance of Protein-Bound Uremic Solutes by Introducing an Activated Carbon Block into the Dialysate Stream

Sochiluy L., Tammy L. Sirich, Timothy W. Meyer, Stanford University School of Medicine, Stanford, CA; VA Palo Alto Health Care System, Palo Alto, CA.

Background: The hemodialytic clearance of protein-bound solute is limited because only the free solute concentration drives diffusion across the membrane. This study tested whether an activated carbon block could reduce accumulation of these solutes in the dialysate and thereby increase their clearance.

Methods: In vitro dialysis of artificial plasma containing urea and the protein-bound solute p-cresol sulfate (PCS) and indoxyl sulfate (IS) was performed using two dialyzers in series with and without an activated carbon block at the midpoint of the dialysate stream (Figure). Six dialysis experiments were performed each with plasma flow 240 mL/min and dialysate flows of 200 mL/min and 600 mL/min. Nine additional experiments tested the capacity of the carbon block to take up solutes by measuring solute removal from spent dialysate collected at patient treatments. Spent dialysate was passed through the carbon block at 600 mL/min.

Results: Use of the carbon block increased the clearances of the tightly bound solutes PCS and IS by 70% and 64%, respectively, when the dialysate flow was 200 mL/min. Lesser increases occurred when the dialysate flow was 600 mL/min (PCS 38% ± 5%, IS 33% ± 8%). Urea clearance was unchanged. The carbon blocks removed 97 ± 4% of PCS and 96 ± 2% of IS but only 2 ± 5% of urea from spent dialysate flowing at 600 mL/min.

Conclusions: Use of a carbon block can increase the clearance of protein-bound solutes particularly at the low dialysate flows often used for home hemodialysis.

Funding: NIDDK Support, Private Foundation Support

Clearances of solutes with or without activated carbon block

<table>
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<th>Solutes</th>
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<th>Clearance with carbon block (%)</th>
<th>Clearance with carbon block (%)</th>
<th>Clearance with carbon block (%)</th>
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</thead>
<tbody>
<tr>
<td>PCS</td>
<td>95.5 ± 6.0</td>
<td>96.0 ± 6.1</td>
<td>95.0 ± 6.4</td>
<td>95.1 ± 6.5</td>
<td>95.0 ± 6.4</td>
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<td>IS</td>
<td>11.9 ± 27.2</td>
<td>13.9 ± 29.2</td>
<td>12.9 ± 25.6</td>
<td>13.9 ± 26.8</td>
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</tbody>
</table>

*P < 0.01, clearances with vs. without carbon block, Qd = dialysate flow

PO0926

Comparative Effectiveness Between Novel Medium Cut-Off Membrane Hemodialysis and Mixed-Dilution Online Hemodiafiltration on Middle Molecule Uremic Toxins Reduction: A Prospective Cross-Over Study

Jirarat Eiamcharoenying, Pajaree Chariyavalgluk, Kullaya Takkavatarkarn, Paweena Susantithaphong, Yingyos Avihingsanong, Somchait Eiam-On, Khajiron Tanirathanagul, King Chulalongkorn Memorial Hospital, Bangkok, Thailand.

Background: Mixed-dilution online hemodiafiltration (mixed HDF), one of the best hemodialysis (HD) modes, provides superior removal of middle molecule uremic toxins to standard HD using high flux dialyzer. Due to the limited availabilities and high cost of HDF, we performed standard HD utilizing a novel medium cut-off membrane with a larger pore size and compared the effectiveness in removal of middle molecule uremic toxins with mixed HDF.

Methods: A prospective cross-over randomized controlled trial was conducted in 14 prevalent HDF patients who were randomly allocated into group 1 (=7): mixed-dilution online HDF with high flux dialyzer ELIS1021H and group 2 (=7): standard HD with MCO membrane, Theranova 500. In this 8-week study, the primary outcome was a reduction ratio (RR) of B2M, microglobulin (B,M). Other small to middle molecules and protein-bound uremic toxins reduction ratio, dialysate albumin loss, and nutritional parameters were also compared.

Results: In this 8-week study, B,M RR from both modalities was higher than the survival benefit cut-point of 80%. In comparison, B,M RR was slightly lower but significant in MCO HD than mixed HDF (82.57±5.34% vs 85.12±3.87%, respectively) with the mean difference of 2.55 (95% confidence interval [CI], 4.07 to 1.03; P = 0.001). The spKt/Vurea and URR, a small urmic toxin removal marker, were comparable. xFLC and Indoxyl sulfate RR also were similar in mixed HDF and MCO HD. Whereas RR of the larger middle molecule uremic toxin, Alpha M and JFLC was lower with mixed HDF compared to MCO HD (30.13±15.90 vs 41.49±11.46 and 40.85±13.92 vs 50.81±13.18, respectively; P<0.001). Dialysate albumin loss was 3.51 ± 1.97 g/session with mixed HDF and 6.19 ± 2.70 g/session with MCO HD (P = 0.0025). Regarding, nutritional parameter, serum albumin levels were not different.

Conclusions: Mixed HDF and MCO HD provided the RR values of B,M and small uremic toxins above the recommended cut-off point. Despite mixed HDF provided higher B,M RR, MCO HD also provided more performance in the clearance of the larger middle molecules, particularly Alpha M and JFLC. However, mixed HDF loss lower albumin than MCO HD. Therefore, both techniques can be used as alternative options.

Funding: Government Support - Non-U.S.

PO0927

Clearance of Protein-Bound Uremic Toxins on the Tablo Hemodialysis System

Logan Rivas, Dean Hu, Michael A. Aragon. Outset Medical, San Jose, CA.

Background: The Tablo Hemodialysis system (Tablo) is an all-in-one, easy-to-learn device. While clearance of small and middle molecules has been documented in modern dialysis, the clearance of Protein Bound Uremic Toxins (PBUTs) merits further exploration. Clearance of albumin bound toxins such as indoxyl sulfate (IS) and p-cresol sulfate (PCS) can be limited in dialysis where removal is based on molecular size. Although a clear association has yet to be demonstrated, PBUTs have been considered to be a possible cause of adverse outcomes in patients requiring renal replacement therapy.

Methods: A simulated hemodialysis treatment using Tablo was performed with solution of bovine serum albumin and urea. PCS and IS were added to the solution to maintain a constant concentration. A screening design of experiment was performed utilizing the factors of dialysis flow rate (Qd), blood flow rate (Qb), and ultrafiltration (UF). After each factor was changed and allowed to equilibrate, samples were collected from the venous, arterial and spent dialysate lines. Samples of Urea, PCS and IS were analyzed and compared to predicted values from previously published models.

Results: The Tablo system cleared PCS and IS as predicted or better at all conditions. See table and images for details.

Conclusions: The Tablo system aligned with the PBUT clearance model over the range of system flow settings. Continued investigation into the clinical benefits of PBUT removal is merited to better understand their impact on the overall quality of care for dialysis patients.

Funding: Commercial Support - Outset Medical

Clearance Data

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<th>Protein</th>
<th>Flow Rate</th>
<th>Delivery (mL/min)</th>
<th>Urea (mg/dL)</th>
<th>PCs (μmol/L)</th>
<th>IS (μmol/L)</th>
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<tr>
<td>100</td>
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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO0928
Dialysis Disequilibrium Syndrome (DDS) in Hemodialysis Patients: Systematic Review
Rupesh Rama,1,2 Siddhartha S. Singh,1,2 Ronith Chakraborthy,1,2 ‘Cleveland Clinic, Akron, OH; 3 Akron Children’s Hospital, Akron, OH.

Background: Dialysis disequilibrium syndrome (DDS) affects patients who have missed multiple dialysis treatments, especially new initiates of hemodialysis (HD), and presents as a rare neurological complication. The conceptual pathogenesis of DDS is likely a result of multiple physiological abnormalities which we explore in this systematic review alongside preventive measures with focus on effective management strategies.

Methods: A literature search was conducted on PubMed/Medline and Embase and included studies if the patient developed DDS irrespective of age and gender. Two independent reviewers conducted the process of article selection with a third reviewer present to resolve any conflicts. The data was analyzed and a summary table was extracted with the following variables: study type, population group, age, patient characteristics, blood and dialysate flow rate, and study outcomes. A descriptive analysis was performed analyzing the population size and frequency of symptoms and treatments utilizing the R software.

Results: A total of 49 studies (321 samples) were identified and analyzed. There were 72.4% of patients (based on 48 studies) who reported having DDS with most common symptoms of headache (39.4%), nausea (40.4%), vomiting (39.1%), confusion (66.7%) and seizure (78.6%). Within this sample, 12 studies switched from HD to alternative dialysis modalities including continuous venovenous hemofiltration/hemodiafiltration (CVVH/CHFID) or peritoneal dialysis (PD) with no further reported DDS symptoms.

Conclusions: We have provided a comprehensive clinical practice points for both the pediatric and adolescent and young adult population; interestingly, DDS was reported more often in the early dialysis era prior to recent advances and improvement of resource allocation. Existing literature shows it is crucial to recognize symptoms of DDS and implement timely prevention to improve outcomes.

PO0929
Protein Loss with Medium Cut-Off and High Flux Dialyzer: A Proteomic Analysis
Xiaolan Wang,1 Xia Tao,1 Leticia M. Tapia Silva,1 Amrish U. Patel,1 Mobhamad I. Hakim,1 Nadja Grobe,1 Stephan Thijssen,2 Peter Kotanko,1,2 1 Renal Research Institute, New York, NY; 2 Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Hemodialysis (HD) patients frequently suffer from low serum albumin levels, making dialytic albumin and protein loss a concern. Medium cut-off (MCO) dialysis membranes reportedly show a greater albumin loss compared to high-flux (HF/HiFlux) membranes. To better understand the spectrum of proteins cleared with MCO membranes, we set up an ex vivo dialysis system and perform proteomic analysis of the dialysate.

Methods: Eight liters of human plasma (EDTA added) are split into two 4-liter batches and dialyzed for 4 hrs in single-pass, either with an MCO (Theranova 400) or HiFlux dialyzer (Optiflux F180NR) using a Fresenius 2008T machine. Blood flow was 400 ml/min. Dialysate flow was 600 ml/min for the first 3 hrs and zero for the 4th hr. Ultrafiltration rate was zero for the first 2 hrs and switched to 1 L/hr thereafter. This design allowed us to study three HD modes: diffusion only (2 hrs); diffusion with convection (1 hr); and convection only (1 hr). Dialysates were sampled at multiple time points (Fig 1B).

Results: Three µg of initial plasma and 23 µl dialysate were loaded on an SDS-page gel and silver stained (Fig 1A). Lanes 3 and 5 were from MCO, lanes 4 and 6 from HiFlux. Lanes 3 and 4 were collected 15 mins into dialysis, lanes 5 and 6 at 240 mins. Results show that dialysates contain less high molecular weight proteins compared to plasma, and MCO dialysates contain much more proteins compared to HiFlux dialysates. The strong band at ~62 kD is most likely albumin. Using mass spectroscopy, we can identify 56 different protein species in MCO dialysate. Dialysate protein levels (measured by Bradford assay) with the 3 dialytic modalities are shown in Fig 1B, the total protein losses are listed in Fig 1C. The ratio of protein loss between MCO and HiFlux dialyzers is 17-fold in the convection only mode.

Conclusions: Our results show a higher diffuse and convective protein loss with MCO compared to HiFlux membranes. Further characterization and quantitation of proteins cleared in vivo during HD are necessary to better understand the clinical impact of our ex vivo observations.

Funding: Commercial Support - Renal Research Institute

PO0930
Intradialytic and Interdialytic Urea Dynamics in Blood and Cerebrospinal Fluid in Hemodialysis Patients
Xia Tao,1 Lin-Chun Wang,1 Xin Wang,1 Ohnmar Thwin,1 Nadja Grobe,1 Amrish U. Patel,1 Stephan Thijssen,2 Joshua E. Chao,1 Ludovic Debure,2 Thomas Wisniewski,2 Peter Kotanko,1,2 Renal Research Institute, New York, NY; ’NYU School of Medicine, New York, NY; 1 Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Modern, highly efficient hemodialysis (HD) results in rapid decline of blood urea. Urea gradients across the blood-brain barrier (BBB) can drive water movements. A positive urea gradient, i.e. brain urea to plasma urea, can result in brain swelling and impair brain function. We explored the dialytic changes of urea in blood and cerebrospinal fluid (CSF) to better understand intradialytic osmotic gradients across the BBB and provide insights that support the development of brain-protective HD.

Methods: Two HD patients (39 and 26 years old) with ventriculo-peritoneal (VP) shunts were enrolled into this one-week IRB-approved study with a Monday/Wednesday/Friday dialysis schedule. CSF was collected via VP shunt tap 2 hrs before and 2 hrs after HD (Wednesday and Friday), and Tuesday and Thursday. Plasma samples were collected concurrently with CSF and during HD. In addition, the patients underwent test of executive function (Trail Making Test Part B; TMT B) and global cognitive function (Montreal Cognitive Assessment; MoCA) on Monday.

Results: Urea was removed efficiently from patients’ blood by HD. While patient A showed a small post-HD plasma-to-CSF urea gradient, it was highly positive (~ 60 mg/dL) in patient B (Fig 1). TMT B and MoCA score were normal for patient A but not patient B (TMT B 415 sec; TMT B error count: 2; MoCA score: 11).

Conclusions: Our patients showed very different post-HD plasma-to-CSF gradients. Theoretically, the positive gradient in patient B would favor intradialytic brain swelling. Patient B showed impaired neurological testing results which are not related to patient’s pre-existing neurological conditions. We can only speculate if and to what extent trans-BBB water movements driven by dialytic urea dynamics may have impacted the patient’s cognitive functions. We believe that patient-specific levels of osmotic stress need to be considered when developing neuro-protective HD technologies.

Funding: Commercial Support - Renal Research Institute
PO0931

High-Throughput Analysis of Changes in Protein Biomarkers During Hemodialysis
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Background: The impact of hemodialysis on the concentration of circulating protein biomarkers remains unclear. Biomarkers may decrease in concentration due to filter adsorption, diffusive clearance, or convective clearance, while others may increase in concentration due to production and secretion or intracellular release. Ultrafiltration of water is also expected to increase biomarker concentration. We sought to evaluate the impact of hemodialysis on 1,163 protein biomarkers in a high-throughput fashion.

Methods: A nested cohort of 44 patients (25 male, 19 female) including 29 with intradialytic hypotension and 15 without was selected from the prospective Hemodialysis Outcomes and Symptoms assessment (HOST) cohort. Intradialytic hypotension was stringently defined as a 60 mmHg drop in systolic blood pressure or a nadir systolic blood pressure of less than 70 mmHg during hemodialysis treatment. All hemodialysis treatments were done using the same hemodialysis filter type. 1,163 unique biomarkers were measured in each patient before and after hemodialysis using the Olink proximity extension assay (www.olink.com). Paired sample t-tests were used to compare pre- and post-dialysis concentrations with a Bonferroni-corrected significance threshold (P < 5 x 10^-5).

Results: 54 biomarkers (5%) significantly increased during hemodialysis treatment, while 243 (24%) significantly decreased. Change in biomarker concentration was significantly correlated with biomarker molecular weight (r = 0.37, P = 2.8 x 10^-10), isoelectric point (r = -0.26, P = 6.4 x 10^-10), and pre-dialysis concentration (r = -0.21, P = 3.0 x 10^-10). There was a significant enrichment of cardiovascular biomarkers in the top 20 biomarkers associated with a drop in systolic blood pressure (P = 2.8 x 10^-10), including Kidney Injury Molecule 1 (KIM1, P = 0.005).

Conclusions: Hemodialysis is associated with significant changes in protein biomarker concentrations related to protein properties and clinical events during treatment. These changes are measurable on a high-throughput platform. Further high-throughput biomarker studies could assess dialysis adequacy, test biomarker-symptom associations, and improve risk prognostication.

Funding: Private Foundation Support

PO0932

Feasibility of Allo-Hemodialysis: First Experience from Porcine Studies
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Background: Annually, millions of kidney patients, predominantly in low and low-middle income countries, die prematurely because of unavailability of affordable kidney replacement therapy. We previously demonstrated through mathematical modeling and bench testing the feasibility of alloHD, an alternative low-cost hemodialysis treatment approach where the blood of a kidney failure patient flows counter-current to that of a healthy subject (“buddy”) through a dialyzer. Herein we report first results from an alloHD feasibility study in a porcine model. We aimed to specifically address questions around hemolysis and coagulation in our experiments. Upcoming studies in a porcine renal failure model will be evaluated and compared between the plasma filter reuse group (GP-1) and no reuse group (GP-2).

Methods: Ethics protocol was approved by Committee for the Purpose of Control and Supervision of Experiments on Animals, India. Under general anaesthesia, healthy female white Yorkshire pigs of 30 to 80 kg with central venous catheter as vascular access were dialyzed 1-3x weekly for 2-4 hours. Ultrafiltration volume goals were set between 0 and 1000 mL. “Patient” and “buddy” pigs were connected to the dialysate and blood compartments, respectively, of a Nipro Cellentia 17H (Fig. 1). Pigs were anticoagulated with 5000 IU heparin per hour. Pre- and post-treatment blood samples were collected for biochemical measurements.

Results: We successfully completed 10 alloHD sessions. No coagulation was observed. Visual inspection of plasma samples indicated no signs of hemolysis. This was further corroborated by measurements of lactate dehydrogenase and haemoglobin, which were available in seven experiments (Fig. 2). Adhesions on the filter surface, which were also noticed in GP-1 (P=0.08). No difference in patient survival was noticed between the two groups (97% vs 96%, p=0.5). The cost of overall treatment was 2.5 times higher in GP-2, (P=0.003).

Conclusions: Reuse of plasma-filter is a safe and effective method for cost minimization in patients requiring TPE. This method can effectively be utilized in resource-poor settings without any increased risk of adverse effects.

Funding: Commercial Support - Renal Research Institute

PO0933

Can Plasma Filters Be Reused for Plasmapheresis in Resource-Poor Settings? Experience from a Tertiary Care Hospital
Priti Meena, Sandip Panda, Rishita Mondal, Swati Das. All India Institute of Medical Sciences - Bhubaneswar, Bhubaneswar, India.

Background: Therapeutic plasma exchange (TPE) is used in the management of various life-threatening illnesses. It is widely performed by nephrologists, intensivists, pathologists, or experts of transfusion medicine worldwide. However, the costs of TPE sessions are exceedingly high and it has a huge impact on patients’ financial burden. Most of the patients cannot afford such a high-cost treatment. Herein, we investigated the outcomes of plasma filter reuse in TPE for several occasions.

Methods: This was an ambidirectional study that included retrospective analysis of patients receiving TPE from January 1, 2020, to December 31, 2020, whereas the patients receiving TPE from January 1, 2021, to April 30, 2021, were prospectively analysed. The procedure was performed in our hospital’s dialysis unit. Formulation of 4% peracetic acid and 24% hydrogen peroxide acid with RO water was used for reprocessing. Fresenius Plasma Flux P2 (0.6 m2) was used in the study. Clinical outcomes, risks, and cost-benefit were evaluated and compared between the plasma filter reuse group (GP-1) and no reuse group (GP-2).

Results: 46 patients were included in the study. 26 patients were in the Plasma filter reuse group. 122 and 119 TPE sessions were performed in GP-1 and GP-2 respectively. A total of 58 plasma filters were used in GP-1. In six patients single plasma filter was used on 3 occasions whereas, it was used for 2 occasions in other patients. The most common indication for TPE in both groups was Guillain barre syndrome. The rates of clinical improvement in disorders for which the TPE were performed were similar in both GP-1 and GP-2 (88% vs 90%, p=0.4). None of the patients in either group had clotting of plasma filter, any allergic reaction, or increased bleeding risk. No higher chances of sepsis were noticed in GP-1 (P=0.08). No difference in patient survival was noticed between the two groups (97% vs 96%, p=0.5). The cost of overall treatment was 2.5 times higher in GP-2, (P=0.003).

Conclusions: Reuse of plasma-filter is a safe and effective method for cost minimization in patients requiring TPE. This method can effectively be utilized in resource-poor settings without any increased risk of adverse effects.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
PO0934
A Forgotten Technique of RRT for Correction of Severe Hyponatremia in CKD: Case Report
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Introduction: Patients with chronic kidney disease (CKD) present electrolyte disorders. This represents a challenge when hyponatremia is below 125mmol/L associated with any criteria for urgent renal replacement therapy (RRT) with conventional hemodialysis because of higher risk of over correction above the security threshold of 10mmol/L/day and osmotic demyelination syndrome.

Case Description: A 49-year-old Guatemalan female with history of 15 days of edema and slurred speech. Only history of T2DM. Was brought to the ER with BP 100/80mmHg and anaesthesia. Initial laboratories: negative COVID-19Ag, Cr 5.12mg/dl, (previous 2mg/dl) BUN 105mg/dl, glucose 156mg/dl, Na 108mmol/L, K 5.2meq/L, Cl 70meq/L, SOsm 224mOsm/kg, UNa 28meq/L, UNa 119mmol/L in 48 hours, but because of persistence of neurologic symptoms plus fluid overload >10% of body weight and hyperkalemia, we initiated RRT. In the absence of CRRT or CVVH we planned a conventional HD with blood flow of 100ml/min, dialysate flow 600ml/min, dialysate Na 130mEq/L (the lowest Na possible) and 3 hours duration. After the first session had neurological and edema improvement. After two sessions with interdialytic period of 48 hours, Na control of 122mmol/L and 132mmol/L respectively with resolution of uricemic syndrome. Later was diagnosed with hospital-acquired pneumonia receiving antibiotic treatment for 14 days and was discharged home with ambulatory HD.

Discussion: In undeveloped countries where the access to CRRT or CVVH is unavailable, conventional modalities can be used with low blood flows and modifications of the dialysate Na to a minimum (130mmol/L) offering a safe option to Na correction for patients with severe hyponatremia and any other HD criteria.

PO0935
Single-Bolus Tinzaparin Anticoagulation in Extended Hemodialysis Sessions: A Feasibility Study
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Background: Few studies have assessed the use of low-molecular weight heparins for anticoagulation during extended hemodialysis (HD) sessions. This study aimed to evaluate the safety and efficacy of tinzaparin for anticoagulation of the extracorporeal circuit and dialyzer in extended, 8-hour, sessions.

Methods: This single-center study included all patients who underwent a single in-centre 8-hour session as part of their nocturnal home HD training between 2009 and 2020. Tinzaparin was delivered as a single bolus injection at time 0 with dosing based on the patient’s weight and doubling of standard 4-hour session dose. Tinzaparin safety was assessed via anti-Xa measured at 15-, 30-min, 1-, 2-, 4-, 6-, 8-hour. Efficacy was examined via visual observations (score 1-4) of the dialyzer and venous bubble trap at the end of dialysis. Predictors of clotting levels were assessed in exploratory logistic regressions.

Results: Forty-seven patients were included: age 45±14 yrs, 28% women, 9% on warfarin, 42% on antiplatelets, BMI 29±7 kg/m², hemoglobin 114±15 g/L and platelet 203±61 10³/L. Mean tinzaparin dose was 107±20 IU/kg. Anti-Xa levels peaked at 15-min with 1.3±0.4 IU/mL and progressively declined reaching 0.9±0.3 IU/mL at 1-hour, 0.2±0.1 IU/mL, 4-hour, and 0.15±0.15 IU/mL after 8-hour. Figure 1. After the 8-hour session, none of the patients had severe clotting of their dialyzer or venous chamber. Moderate blood clotting was observed in the dialyzer of 6 (20%) patients and in the venous chamber of 22 (61%) patients. Tinzaparin dose was increased for 27 (81%) patients with a mean maintenance dose of 123±28 IU/kg. None of the main baseline characteristics (including tinzaparin dose per kg) were associated with clotting scores.

Conclusions: This study shows that anti-Xa levels stabilize rapidly after administration on tinzaparin for 8-hour HD. Administration of a single bolus tinzaparin at the start of an eight-hour dialysis session appeared safe and effective, although dose adjustment may be required.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Targeted Alteplase Administration to Improve Hemodialysis Catheter Patency: A Quality Improvement Pilot Study
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Background: Catheter dysfunction (CD) is a frequent complication during the provision of hemodialysis. Thrombotic agents (i.e. alteplase) are the mainstay for resolving CD, however, alteplase usage has increased 16% (~440,000CD) annually in the Alberta Kidney Care South program without improved patient or dialysis outcomes. We assessed the implementation of a protocolized algorithm to reduce alteplase usage.

Methods: In this pilot quality improvement study, we designed an algorithm where CD was treated with high-dose (2mg) alteplase therapy to the problematic lumen only, after meeting pre-specified criteria (Fig 1). This protocol was implemented in a satellite hemodialysis unit (~110 patients) from Jan 2021 to Mar 2021. The baseline comparison period was Jan 2020 to Dec 2020 when CD was treated with low-dose 1mg/lumen alteplase. Outcome measures included total alteplase usage, changes in Kt/V, recirculation, clearance, line interventions and hospitalization rates. Statistical analysis was completed using Mann-Whitney and Z-score calculations.

Results: Sixty-nine alteplase administrations occurred over the two-month period, versus 438 in the baseline period. Patients in the 2mg group were more likely to achieve an increase in Kt/V of at least 10% in the next dialysis session (34.7% vs 28.9%, p<0.04). Otherwise the 2mg alteplase with our protocol was not inferior to baseline with respect to blood volume processed (26.1% vs 20.1%, p=0.13) and average clearance (37.7% vs 28.5%, p=0.37). A 12% decrease (88 vs 100mg/mo p<0.05) in alteplase use was observed with no differences in frequency of hospitalizations (8% vs 5.9% p=0.39) or line interventions (12.3% vs 7.3% p=0.20).

Conclusions: Our protocol with 2mg alteplase therapy to the problematic lumen was not inferior with respect to patient outcomes compared to baseline practices and resulted in lower alteplase use. An expanded multi-center prospective study is underway to further assess the broader applicability of these findings.

PO0938
The Effect of Predilution Online Hemodiafiltration on Body Composition, Nutritional Status, and Mortality
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Background: We evaluated the effect of predilution online hemodiafiltration (HDF) on body composition, nutritional status and all-cause and cardiovascular (CV) mortality in maintenance dialysis patients.

Methods: All subjects (n=215) had blood flow rate of ≥200 mL/min and underwent HDF with a convective volume of 40 L/session or hemodialysis (HD), 4h/session, 3 times/week. Predialysis clinical data and same day postdialysis body composition parameters based on BCM (Fresenius) were obtained at baseline in 46 patients on HDF and 169 patients on HD, and followed over 5 years. Logistic regression analysis for HDF, Kaplan–Meier analysis and Cox hazard analysis were conducted.

Results: In all subjects, age and dialysis vintage were 72±12 years and 73±6 months, respectively. Body mass index [22.4 (20.6–27.0) vs. 19.8 (16.4–22.7) kg/m²], lean tissue index (LTI) [13.2 (10.8–15.7) vs. 11.0 (9.3–13.2) kg/m²], geriatric nutritional risk index [94 (88–97) vs. 88 (81–93)] serum albumin [3.6 (3.3–3.8) vs. 3.3 (2.9–3.5) g/dl], creatinine, phosphate and magnesium were higher, but LDL-cholesterol (LDL-C) was lower in patients on HDF than those on HD (P<0.05). There were no significant differences in fat tissue index (FTI) [9.0 (5.5–11.2) vs. 7.8 (5.7–10.6) kg/m²], overhydration (OH) [0.8 (–0.5–2.2) vs. (0.3–2.1) L], C-reactive protein (CRP), Kt/Vanat or β2-microglobulin (β2m) between the groups. HDF was significantly (P<0.05) associated with serum albumin [odds ratio (OR) 3.0], LDL-C (OR 0.98) and LTI (OR 1.22), but not with FTO, OH, CRP, Kt/Vanat or β2m. Cumulative 5-year survival rate was significantly higher in patients on HDF than those on HD (67.9% vs. 43.7%, P<0.01). For 5-year all-cause mortality, HDF [hazard ratio (HR) 0.31], age (HR 1.03), albumin (HR 0.48) and LTI (HR 0.91) were significant predictors (P<0.05), while FTO and OH were not. For 5-year CV mortality, HDF (HR 0.20), age (HR 1.05), diabetes (HR 2.61) and LTI (HR 0.80) [or even HR 0.91 (0.73–1.11) or OH (HR 1.22)] were significant predictors, respectively (P<0.05).

Conclusions: Predilution online HDF with substitution volume 40 (20–40) L/session, 3 times/week is associated with better nutrition, increased muscle mass, and improved all-cause and CV mortality, but not with body fat and OH in dialysis patients.

Funding: Private Foundation Support

PO0939
Monitoring of Intradialytic Sleep Apnea in Hemodialysis Patients
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Background: Breathing disorders are frequent in end-stage kidney diseases, with more than 50% of hemodialysis (HD) patients experiencing sleep apnea syndrome (SAS). SAS is associated with lower health-related quality of life and represents a significant cardiovascular risk factor. HD patients with SAS are at greater risk of mortality. The study aimed to monitor intradialytic SAS in HD patients using oxygen saturation (SaO2) measurements.

Methods: C-Link® monitor was used to record SaO2 at 1 Hz, for 2 HD sessions with a mean duration of 3.5±0.5 h. For each patient, we calculated: oxygen desaturation density (ODD), which counts 3% drops in SaO2, from a baseline for at least 10 s; a10-order permutation entropy to quantify complexity; and optimal recurrence threshold (εa10) to account for dynamic variations and degree of predictability in the SaO2. These quantities were subjected to machine learning methods to predict intradialytic SAS, as quantified by the ODDa10 value and the SAS classification by the American Sleep Disorders Association.

Results: We examine intradialytic SAS severity in 16 patients (age of 54±11 years, 63% males, 66% Black) with arteriovenous vascular access. Mean SaO2 was 94.3±2.1%. Figure 1A shows a typical SaO2, annotated with the SAS intensity assessed by ODDa10 (Fig. 1B). The two calculated metrics are plotted in Figs. 1C–D. The results reveal dynamic characteristic patterns of SAS with differential severity scores during HD. Figures 1E–G show the ROC for the classifiers when considering episodes of at least mild, moderate, or severe SAS, respectively. The maximum AUC is 0.93 for severe SAS episodes.

Conclusions: Our analysis suggests that entropy and recurrence-based quantifiers could be used as predictive indicators of intradialytic SAS. However, further studies are needed to assess their relationships to clinical outcomes.

PO0940
DENALI, a Phase 3b Multicenter, Open-Label Single-Arm Study of Roxadustat Use in Dialysis Patients with Anemia via a Semi-pragmatic Evaluation of Roxadustat Use in Dialysis Patients with Anemia via a Semi-pragmatic Evaluation
Arnold L. Silva,1 Gopal Saha,2 Jeffrey L. Hymes,3 Lynda Szczecz,4 Yemisi Oluwatosisin,5 Zhiqun Cherif,6 Gong Kong,7 Cooper,8 John W. Larkin,9 Boise Kidney & Hypertension Institute, Meridian, ID; 2FibroGen Inc, San Francisco, CA; 3Fresenius Medical Care North America Nashville, Nashville, TN; 4AstraZeneca, Wilmington, DE; 5Fresenius Medical Care North America, Waltham, MA.

Background: Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitor that promotes erythropoiesis and improves iron availability in patients with anemia of chronic kidney disease (CKD). This trial aims to provide practical data on roxadustat use in dialysis patients with anemia via a semi-pragmatic evaluation of introduction into providers’ practices (Fresenius Medical Care).
PO0942

Validation of Urea Removal in Novel Sorbent Dialysis System


Background: The Dality Hemodialysis Machine will provide a range of hemodialysis modalities to expand the population of patients that may benefit from hemodialysis. One modality uses a sorbent filter that will accommodate the decentralization of dialysis delivery. Specific Aim: To assess urea mass removal during a simulated dialysis utilizing a novel sorbent filter.

Methods: Nine simulated dialysis sessions were conducted utilizing between 50L and 125L volumes of dialysate circulated at approx. 400 mL/min & 37 C through a sorbent cartridge with a standard dialysate. (Table 1) It is expected that with each pass through the filter the dialysate urea mass will decline. The experiment is continued until breakthrough occurs or the infused outlet reaches 10 ppm of NH4. A solution containing K+, Ca and Mg salts were constantly infused to replenish electrolytes lost in each pass. Another solution was infused at a variable rate as determined by conductivity to maintain Na Balance.

Results: The results are provided in Table 1. The average URR was 63.8% ranging from 53.3 to 87.0%. The average starting HUN was 48.2 mg/dL and the average ending HUN was 16.8 mg/dL.

Conclusions: The initial experiments using a sorbent filter demonstrate a URR of near 65 is feasible. Future design changes will be scaled to handle larger amounts of urea and provide acceptable clearances.

Funding: Commercial Support - Dality Inc

Table 1:

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PO0943

Effect of Hemodialysis on Amyloid-β in Cerebrospinal Fluid and Plasma

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Background: Hemodialysis (HD) can reduce amyloid-beta (Aβ) species in whole-body circulation by 30 to 50%. Due to the dynamic exchange of Aβ between the brain and the blood, we hypothesized that HD might lower Aβ levels in the cerebrospinal fluid (CSF).

Methods: In a dialysis network with over 160,000 patients, we identified three maintenance HD patients (age 36±9 years) with ventriculo-peritoneal (VP) shunts who were subsequently recruited for this IRB-approved research study. Study subjects were dialyzed on Monday, Wednesday, and Friday. Plasma samples were collected at 6 timepoints during the 3 HD sessions. One subject was withdrawn over safety concern related to the VP shunt tap procedure. Two subjects further underwent VP shunt taps for CSF sample collection before and after the Wednesday and Friday HD sessions, and once on interdialytic days (Tuesday, Thursday). Aβ1-42 and Aβ1-40 were quantified by Neuro 3-Plex SIMOA assays (Quanters, MA, USA).

Results: HD effectively reduced plasma Aβ1-42 by 41% and Aβ1-40 by 34% (Fig 1a and 1b, p < 0.01). In CSF, levels of Aβ increased after Wednesday HD sessions in subject 1 (Aβ1-42: 4.2-fold, Aβ1-40: 5.5-fold) and subject 2 (Aβ1-42: 1.06-fold, while Aβ decreased after Friday HD sessions in both subject 1 (Aβ1-42: 0.1-fold, Aβ1-40: 0.1-fold) and 2 (Aβ1-42: 0.7-fold, Aβ1-40: 0.7-fold) shown in Figure 1c-e.

Conclusions: This is the first report of Aβ dynamics in the CSF and plasma of HD patients. While plasma levels were in similar ranges, we found high inter-individual variations of CSF levels. Different plasma-to-CSF ratios after HD may reflect individual brain Aβ pools that are accessed by HD. We corroborate previous reports demonstrating the removal of Aβ from the blood compartment by HD.
Circulating Microbiome and Cardiovascular Death in Patients with ESRD

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Background: Patients with end-stage renal disease (ESRD) suffer from disproportionately high cardiovascular (CV) mortality. Accumulating evidence suggests a role for the circulating microbiome (CM) in the pathogenesis of CV disease; however, little is known about its association with premature CV mortality in ESRD.

Methods: In a pilot case-control study of 17 hemodialysis (HD) patients who died of a CV event and 17 matched HD controls who remained alive during a median follow-up period of 2.0 years, we compared the levels and composition of CM, including Bacteria, Archaea, and Fungi in serum samples by quantitative PCR and 16S or Internal Transcribed Spacer (ITS) ribosomal RNA (rRNA) sequencing, respectively. Association of the CM with CV death were examined using multivariable conditional logistic regression.

Results: 16S and ITS rRNA was detectable in all (except 3 for ITS) examined patients’ serum samples. Despite no significant difference in 16S rRNA levels and α diversity between cases and controls, taxonomic analysis demonstrated differential community membership between groups, with significantly greater Actinobacteria and less Proteobacteria observed in cases than controls at the phylum level. At the genus level, Staphyloccocus was numerically higher in cases than in controls, albeit not reaching statistical significance. Proportions of Actinobacteria and Proteobacteria phyla were marginally associated with risk of cardiovascular death (adjusted ORs [95% CI], 1.12 [0.98-1.29] and 0.88 [0.76-1.02] for 1% increase, respectively; Table). Although circulating fungal community α diversity was significantly elevated in cases than controls, no significant association was observed with CV death.

Conclusions: Altersations of the CM may be associated with a higher risk of premature CV mortality in ESRD patients.

Funding: NIDDK Support

Association of circulating microbiome with cardiovascular death in hemodialysis patients

![Table showing association of circulating microbiome with cardiovascular death in hemodialysis patients](image)

Model was adjusted for age, sex, race, dialysis vintage, and vascular access type.

PO0945

Dysregulation of Fibrinolytic Process Contributes to the Thrombotic and Bleeding Complications in ESRD Patients

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Background: End stage renal disease (ESRD) is a complex syndrome involving both cellular and humoral mechanisms. Both thrombotic and bleeding complications are observed which may result in cardiovascular and cerebrovascular adverse outcomes. Fibrinolytic system placed an important role in the regulation of hemostatic process. A comprehensive profiling of the components of fibrinolytic process may provide additional understanding of the bleeding and thrombotic complications in ESRD.

Methods: Citrated whole blood samples were collected from a cohort of ESRD patients (n=95). Normal citrated plasma were obtained from healthy male and female individuals. These samples were analyzed for prothrombin time (PT), activated partial thromboplastin time (aPTT), prothrombinase-induced clotting time (PicT) and thrombin time (TT) using clot based technique. Fibrinolytic parameters such as urokinase type plasminogen activator (uPA), plasminogen activator inhibitor-1 (PAI-1), and D-Dimer were measured by using ELISA method. Functional PAI-1 was measured by using an amyloidylic method. All results were compiled as group means ± SEM and respective ratios were calculated.

Results: All of the clotting results showed varying levels of elevated values in comparison to normal plasma. uPA levels showed wide variations and were increased (1.6 fold). D-Dimer was markedly increased in the ESRD patients (11.53 fold). Both functional (1.2 fold) and antigenic (3.07 fold) levels of PAI-1 were increased. Interestingly, the PAI-1 antigen levels was much higher in contrast to the functional levels suggesting a progressive consumption of this mediator.

Conclusions: These results suggest that the overall hemostatic system in ESRD patients is dysregulated due to the imbalance of the inhibitors such as PAI-1. The persistent activation of fibrinolysis is due to the increase production of uPA which facilitates endogenous fibrinolysis resulting in the elevation of D-Dimer. The generation of fibrinolytic enzymes results in increased fibrin/fibrinogen degradation products which may contribute to the observed intrinsic and extrinsic coagulation defects as measured by the elevation of PT and aPTT. Monitoring of fibrinolytic parameters along with clotting test may be helpful in the risk stratification and prediction of adverse outcomes in ESRD patients

PO0946

Successful Treatment of Systemic Calcinosis in a Teenager on Hemodialysis

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Introduction: Systemic calcinosis is rare in pediatric ESKD patients compared to adults. The subcutaneous tissues are most frequently involved. We present teenager in whom calcinosis was detected incidentally on chest radiograph, and review its successful treatment.

Case Description: A 15 yo anuric female who had received hemodialysis(HD) for 18 months after renal transplant failure, was treated for progressive respiratory distress in the ICU. Significant history included osteoporosis, hypertensive cardiomyopathy, and renal failure since age 1. Chest-XR revealed bilateral pulmonary infiltrates and calcified lesions. Thoracic CT scan demonstrated calcified tracheal and bronchial cartilage rings. Flexible bronchoscopy revealed diffuse white/gray nodules throughout the wall of tracheobronchial tree. All cultures were negative. When noticed of the finding of calcifications on CT scan, patient’s mother also asked about the firm nodules in the space between patient’s fingers. Dialytic phosphate (P) clearance, and non-calcium(Ca), non-aluminum(Al) based binder use were maximized, using sevelamer and lanthanum carbonate. Sodium thiosulfate and etalcalcetide were given iv post each dialysis. Dialysate Ca varied between 0.98 to 1.05 mEq/L. Although calcium levels were increased with calcium carbonate, the elevation of PT and aPTT. Monitoring of fibrinolytic parameters along with clotting may contribute to the observed intrinsic and extrinsic coagulation defects as measured by the elevation of PT and aPTT. Monitoring of fibrinolytic parameters along with clotting test may be helpful in the risk stratification and prediction of adverse outcomes in ESRD patients

Discussion: Calcinosis is uncommon, yet treatable condition in pediatric dialysis patients. Combined use of old and new therapies was successful. Adverse side effects of therapies affect dosing. Etelcalcitide often causes hypocalcemia. Thiosulfate use is contraindicated. Ferrous citrate, sucroferric oxyhydroxide, and bixalomer will offer exciting new treatment options.
Severe Thrombocytopenia due to Electron-Beam Sterilized Polysulfone Dialyzer Membrane Reaction


Introduction: We describe a case of severe thrombocytopenia due to reaction with an electron-beam sterilized polysulfone (PS) membrane. This phenomenon has been previously described but is rarely reported. E-beam sterilized PS membranes are classically more biocompatible than cellulose-based membranes but adverse reactions may occur as demonstrated in our case.

Case Description: A 74 y.o. woman with CKD Stage 4 and secondary hyperparathyroidism presented for evaluation of generalized weakness, anorexia, and weight loss. Her past medical history included gout, short bowel syndrome following prior bowel resection and osteoporosis. Home medications were allopurinol, calcitriol, gabapentin, fluoxetine, and mitazapine. She was started on hemodialysis (HD) for suspected progression to ESRD. She developed progressive thrombocytopenia (Figure 1) that was worse, following HD with improvement on non-HD days. Evaluation of usual culprits of thrombocytopenia was unrevealing. Reaction to the polysulfone filter was suspected and she was switched to a cellulose-based filter with resolution of her thrombocytopenia. She was dialyzed with a PS membrane on HD20 as proof of concept with recurrent thrombocytopenia following HD. She was dialyzed with cellulose-based filter thereafter with no further thrombocytopenia.

Discussion: We describe a case of PS-membrane induced thrombocytopenia. It is hypothesized that e-beam radiation may affect membrane integrity or structure, or produce intermediary products which may cause platelet activation, aggregation, and adhesion and therefore thrombocytopenia. This entity should be considered in the differential diagnosis of patients undergoing HD who develop thrombocytopenia. Early recognition may reduce incidence of bleeding and need for blood products in these patients.

Results:

- PLT counts during admission. HD days with PS membrane were denoted with a diamond label and HD days with cellulose-based membrane were denoted with a circle label. Single unit PLT transfusions are denoted with arrows.

PO0947

Feasibility of a Staff-Assisted Peritoneal Dialysis Program in the United States: Results of a Pilot Study

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Background: Staff-assistance can support patients to utilize peritoneal dialysis (PD) and is available in many countries but not in the US. We report on the initial experience from a feasibility study for staff-assisted PD in the US.

Methods: An assisted PD program was initiated at one home dialysis center in Aug 2020, and expanded to a total of 6 centers by Feb 2021. Home assistance by non-registered nurse staff was offered to patients with barriers to self-care with the aim to support patients and families to become independent from staff assistance.

- Participants: 33 patients (range: 0 – 16 referrals/center). 16 referrals were cancelled [admission from HD to the home program cancelled (3 referrals), transition to oral medications (2 referrals), staff-assistance (6 referrals), and death (1)]. 17 patients started staff assistance (5 referrals, and staff assistance (10 referrals). Staff assistance (12 referrals), and death (1)). 3 referrals are pending, and 14 patients received staff assistance at home. Of those who received assistance, median age was 72 years (range 43-87 years), and 8 Were new to PD. Indications included: physical weakness (10 patients), cognitive impairment (8), and psychosocial issues (7). One prevalent PD patient required assistance following a PD peritonitis episode. Anxiety and lack of confidence were common among referred patients. Staff member attending the patient’s home assisted with removal and replacement of PD bags (5 patients), machine setup (9), dressing of exit site (7), checking the blood pressure (2), and other requests (8) such as documentation. Assisting staff worked with patients to build problem-solving skills, gain self-confidence, and arrange a safer home environment. Median length of time on the service was 17 (IQR: 6 – 23, range: 2 – 49 days), and median number of visits was 15 (range: 4 – 38, IQR: 5 – 26). Seven of the patients who finished were more than 90 days after starting assistance. Six of them remain on PD and 1 patient transferred to HD.

Conclusions: Staff-assistance can support patient transition to, and maintenance on, PD. Such programs are operationally feasible with non-RN staff in the US and should be supported by Medicare and regulatory agencies.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

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Increasing the Prevalent Peritoneal Dialysis Patient Population Can Be Challenging

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Background: Peritoneal dialysis (PD) can provide better quality of life for patients requiring renal replacement therapy compared to in centre dialysis. It can be challenging to increase prevalent patient population on PD after a certain number is reached. We did a retrospective analysis to assess the turnover of patients on PD over a 8 year period and to understand the reasons for a stagnant prevalent PD population in the renal unit in Royal Derby Hospital.

Methods: Electronic data (vital, data, ICM) were used to document the number of patients starting and stopping PD each year from 2013 to 2020. The reasons for stopping PD and duration of technical survival were noted. If technique failure resulted in conversion to haemodialysis (HD) for more than 3 months, the cause of the failure was also noted. Patients who converted to HD for less than 3 months were excluded from the study.

Results: The number of patients starting (n=324) and dropping off PD (n=322) was similar for each year between 2013 to 2020. Modality switch to haemodialysis accounted for 40-60% of patients stopping PD, followed by death (15-30%) and patients receiving renal transplantation (10-35%). Modality switch to haemodialysis was primarily due to infection (60-80%), poor clearances and ultrafiltration failures (10-30%), social reasons (10-15%). Among patients who switched to HD due to an infection, peritonitis accounted for 75-85% of the cases followed by exit site and tunnel infections (15-25%). Introduction of Kidney Quality Improvement project in 2018 reduced numbers switching from PD to HD, with no affect on prevalent patient population due to decrease in incident patient population.

Conclusions: Increasing the prevalent population on PD can be challenging even with a high incident patient population. Having mechanisms which prevent infections, early identification and treatment of infections may help improve prevalent PD population.

Disparities in Kidney Care: Where Care Needs to Be Equal

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Background: Disparities in kidney care are widespread and gaining more attention. This research focuses on care differences that existed between home hemodialysis (HHD) and in-center hemodialysis (ICHD) patient from 2017 to 2020.

Methods: Using a HIPAA-compliant, online chart review tool, nephrologists submitted de-identified clinical and non-clinical demographic information beginning at the time of patient referral and concluding with details from the most recent visit. These data, from 2017 through 2020, were then merged with the physicians demographic profile and attitudinal responses. The full data set of 4,002 patient charts submitted from 1,021 nephrologists was analyzed in SPSS.

Results: Given the new efforts to promote home modalities, nephrologists are following status quo and continue to initiate new dialysis patients on in-center hemodialysis. Nephrologists’ current patient loads consists of, on average, 5 HHD patients and 90 ICHD patients. On average, they initiate one new patient on HHD compared to 17 new ICHD patients per year. When comparing HHD and ICHD patient charts there are substantial differences between the two patient types. IHD patients tend to be Caucasian and from higher education and socioeconomic levels: 52% are Caucasian and 25% are African American, 37% have some college (14% have an advanced degree), and 67% are middle or upper class. Conversely, ICHD patients tend to be more diverse (40% are Caucasian, 40% are African American), less educated (24% have some college and 5% have an advanced degree) and from lower socioeconomic classes (44% are lower or lower-middle class). Further, 40% of patients on home modalities are employed part- or full-time, versus 18% of patients on ICHD. Insurance coverage – both at dialysis center and current – influence modality choice as well. Notably, 70% of patients on home modalities were followed prior to dialysis, whereas only 48% of patients on ICHD were followed pre-dialysis, and patients on home modalities are substantially more likely to be on the transplant list versus ICHD patients (62% versus 37%).

Conclusions: Disparities in care exist between patients receiving home hemodialysis versus in-center home hemodialysis. As kidney care continues to evolve, physicians will need to account for these differences in their treatment paradigms to ensure they provide comparable care across patients.
Recent Trends in Utilization of Home Dialysis Modalities, Overall and by Duration of ESKD
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**Background:** The Executive Order on Advancing American Kidney Health and the End Stage Renal Disease Treatment Choices payment model have focused attention on increasing utilization of home dialysis. We assessed trends in home dialysis utilization between 2016 and 2021, including variability in trends among strata defined by duration of end stage kidney disease (ESKD).

**Methods:** We analyzed dialysis facility admission and discharge data extracted from the End Stage Renal Disease Quality Reporting System in May 2021. During the epidemiologic week of each year from 2016 to 2021, we identified patients undergoing maintenance dialysis at the beginning of the week. For each patient, we identified the current dialytic modality. We estimated trends in utilization of each modality, overall and by duration of ESKD at the beginning of the week (<2, 2-4, 5-9, and ≥10 years).

**Results:** Between 2016 and 2021, home dialysis utilization increased from 11.5% to 14.3%, with the majority of growth occurring since the beginning of 2019 (figure). Concurrently, HD utilization increased from 1.57% to 2.23%, whereas PD utilization increased from 10.0% to 12.0%. Among patients with ESKD duration <2 years, home dialysis utilization increased from 14.8% in 2016 to 20.0% in 2021, with >90% of utilization in this stratum due to PD. Among patients with ESKD duration 2-4 years, home dialysis utilization increased from 11.7% in 2016 to 13.7% in 2021. Among patients with ESKD duration ≥10 years, home dialysis utilization hovered around 9%, although HD utilization reached a high of 3.65% in 2021, representing nearly 40% of home dialysis utilization in this stratum.

**Conclusions:** Growth of home dialysis utilization has accelerated since 2019, with greater absolute growth of PD and greater relative growth of HHD. Longer duration of ESKD is associated with lower utilization of PD, but higher utilization of HHD.

**Funding:** NIDDK Support

**PO0957**

**The Impact of Seasonality on Crash Starts and Home Dialysis Use**
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**Background:** The US has made a concerted effort to increase home dialysis use. Dialysis “crash starts,” when patients emergently initiate dialysis in the hospital, are a barrier to home dialysis because they often preclude successful planning. We studied whether the season of the year was associated with crash starts and with home dialysis use among incident patients with end-stage kidney disease (ESKD).

**Methods:** From the United States Renal Data System, we identified all adults with at least 30 days of continuous Medicare Parts A and B coverage initiating dialysis from 2007-2017. We identified home dialysis use and whether patients were hospitalized within 14 days prior to the first outpatient dialysis treatment (ie, “crash start”). Using multivariable logistic regression, we studied the association between season, likelihood of crash start, and starting dialysis at home. We used a Cox model to study whether crash starts were associated with ever using home dialysis in the first year. We adjusted for demographics, comorbidities, facility and geographic characteristics, and year of dialysis start.

**Results:** After adjusting for confounders and year of dialysis start, patients were less likely to start dialysis in the winter versus the summer (OR: 0.86, 95% CI: 0.82, 0.90). Conversely, patients were more likely to “crash start” into dialysis in the winter versus the summer (OR: 1.14, 95% CI: 1.11, 1.17). Patients with a crash start were substantially less likely to initiate with home hemodialysis (OR: 0.16, 95% CI: 0.15, 0.16) and were less likely to ever use home dialysis in the first year (HR: 0.41, 95% CI: 0.40, 0.42). We observed seasonal heterogeneity in the admission diagnoses. Hospitalizations due to pneumonia, myocardial infarction, and congestive heart failure were 1.6, 1.4, and 1.3 times more likely to occur in the winter versus the summer, respectively. Hospitalizations due to diabetes, complications of devices, and chronic kidney disease were 1.05, 1.08, and 1.08 times more likely to occur in the winter, respectively.

**Conclusions:** We observed more dialysis crash starts in the winter and a subsequent decrease in home dialysis use in the first year. Winter hospitalizations were more often associated with cardiac and pulmonary etiologies. Clinicians should remain vigilant that patients may be prone to crash starts in the winter and should accelerate dialysis planning accordingly.

**Funding:** Commercial Support - Nierstichting/Dutch Kidney Foundation = non-profit organisation. Grant no: A2D4P02.

**PO0958**

**Comorbidity Is Not Associated with Home Dialysis Choice**
Sanne Vong,2 Anna A. Bonenkamp,1 Yolande Vermeeren,2 Anita van Eck van der Sluijs,1 Tiny Hoekstra,1 Aflero C. Abrahams,2 Frans J. van Itersum,2 Brigit C. van Jaarsveld,1 DOMESTICO ‘Amsterdam UMC Locatie VUMc, Amsterdam, Netherlands; 2University Medical Center Utrecht, Utrecht, Netherlands; 3Department of Internal Medicine, Apeldoorn, Netherlands.

**Background:** Over the past 15 years the proportion of Dutch home dialysis patients has decreased markedly. In addition, the rate of home dialysis varies significantly among centers. It is unclear whether this is the result of increased comorbidity, other patient characteristics or because dialysis centers perceive barriers for home dialysis differently. Our aim was to investigate the association between comorbidity and home dialysis choice.

**Methods:** The DOMESTICO study is a multicenter retrospective cohort study on home dialysis and randomly selected in-center hemodialysis patients. Comorbidity data was collected of patients who started dialysis between 2012 and 2017, including those who had previously received dialysis or obtained a kidney transplant. Patients who stopped dialysis or died within 30 days were excluded. Comorbidity was assessed with the Charlson comorbidity index (CCI). Home dialysis was defined as any peritoneal dialysis or home hemodialysis treatment during follow-up. Patients were followed until kidney transplantation, wish to stop dialysis, death or study end on 1 January 2017. Multivariable logistic regression analysis was used to assess the association between comorbidity and home dialysis, with a mixed model approach to adjust for dependency of patients within dialysis centers and for other patient characteristics including age, sex, and body mass index (BMI).

**Results:** Of 1358 included patients, 46% were treated with home dialysis. A high comorbidity score (CCI ≥5) was associated with a lower probability to receive home dialysis compared to patients without comorbidities (unadjusted OR 0.74, 95% CI 0.54–1.00). After adjustments for patient characteristics including age and BMI, there was no association between comorbidity and home dialysis. Only obese patients (BMI ≥30 kg/m²) with comorbidities had a significant lower likelihood to receive home dialysis compared to obese patients without comorbidities (medium comorbidity score (CCI 1-4) adjusted OR 0.40, 95%CI 0.18–0.86 and high comorbidity score (CCI ≥5) adjusted OR 0.43, 95%CI 0.20-0.93).

**Conclusions:** Comorbidity is not associated with home dialysis, after adjustment for several confounding factors including age and BMI. Future studies should aim at unraveling the center-specific characteristics that play a role in dialysis treatment.

**Funding:** Commercial Support - Nierstichting/Dutch Kidney Foundation = non-profit organisation. Grant no: AZ2D4P02.
PO0959

Reducing Routine Bloodwork in Home Dialysis Patients: A Quality Improvement Initiative

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Background: There is a paucity of evidence for routine bloodwork frequency in maintenance dialysis patients to assess and manage complications such as anemia and mineral bone disease (MBD). Recent studies showed that decreasing the frequency in conventional in-center hemodialysis (ICHD) patients had no negative impacts. Given the strain on lab services from the COVID-19 pandemic, Alberta Kidney Care-South (AKC-S) decreased the frequency of routine labs from monthly to every 2 months in home hemodialysis (HHD) and peritoneal dialysis (PD) patients. We studied the effect of this change on patient outcomes.

Methods: We retrospectively compared prevalent home dialysis patients (>3 months) in AKC-S over two 6-month periods: a) Pre-pandemic May-Oct 2019 and b) Pandemic May-Oct 2020. Primary outcomes were number of routine bloodwork days and percentage of patients within target for anemia (hemoglobin, iron saturation) and MBD (calcium, phosphorus, parathyroid hormone). We also compared hospitalizations, mortality, technique failure (defined as transition to ICHD for >60days), and cost.

Results: There were 366 home dialysis patients in 2019 (270 PD, 96 HHDD) and 400 in 2020 (296 PD, 104 HHDD). The number of routine bloodwork days decreased in 2020 compared to 2019 (p=0.01) (Fig 1). The proportion of patients who achieved anemia (33% vs 35%, p=0.44) and MBD (34% vs 28%, p=0.1) targets was similar. There was no difference in the number of hospitalizations (155 vs 141, p=0.34), deaths (13 vs 17, p=0.71) or technique failure (8% vs 5%, p=0.06). Projected cost savings were $102 per patient year from reduced labs.

Conclusions: AKC-S reduced the frequency of routine labs during the pandemic in home dialysis without negative consequences on patient biomarkers or outcomes. Our study suggests that bloodwork frequency in home dialysis patients may be safely reduced.

Figure 1. Distribution of the number of routine bloodwork days in Home Dialysis patients had during the pre-pandemic (blue) and pandemic (orange) periods.

PO0960

On-Demand Automated Peritoneal Dialysis Solution

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Background: While automated peritoneal dialysis (APD) is an effective treatment for kidney failure, ordering, delivery and storage of supplies can be challenging. The APD Solution Generation System (SGS) allows for dialysate solution generation using tap water in a patient’s home with fewer supplies (Figure 1).

Methods: A 12-week single-arm, prospective, descriptive study was conducted with in-home APD patients. Patients were screened, trained and treated with the SGS. Endpoints included testing the final product against specifications for Dianeal and water purification ISO Standard 13959 and measuring PD adequacy. Adverse events and device deficiencies were collected.

Results: 22 patients were enrolled: 14 patients completed the study. Demographics are shown in Table 1. See Figure 1 for primary efficacy and safety endpoint results. All tested post-sterilization filter and final dialysis solution samples passed. Missing data for water purity attributed to only 56.9% of samples passing. Mean (SD) change from baseline for Kt/V was -0.15 (0.370). There were 2 peritonitis events (0.43 episodes per patient-year), 1 occurring in a patient with HIV. There were no safety signals.

Conclusions: The SGS has the technical capability to accurately and safely generate dialysate at home using tap water. Logistical challenges with lab sampling require further exploration to understand the impact in future trials and real-world settings. Lessons learned from the study allow for transition of the device to future development.

Table 1. Demographics (n=22)

| Age (Mean [SD]) | 66.9 ± 13.7 |
| Perf. SBP [mm Hg] | 134 (74) |
| Black (n%) | 70 (61) |
| Hispanic or Latinx (n%) | 20 (18) |
| Transient RVT change (Mean [SD]) | 2.4 ± 1.6 |

Figure 1. APD Solution Generation System and Main Results

PO0961

SmartPD™ Automated Peritoneal Dialysis System as a New Sophisticated Choice for Urgent Integration in Replacement Therapy for a Patient with ESRD

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Introduction: Peritoneal dialysis (PD) is used to treat approximately 11% of dialysis patients globally despite wishes for 30%, due to Covid-19 pandemic. Expanded use of PD is impacted by clinician experience and confidence with “efficient”, and “in home friendly” automated peritoneal dialysis (APD) system.

Case Description: A 60 years old lady presented from a remote island -under Covid-19 pandemic- with uremic features and started APD with SmartPD™ (Newsol technologies). SmartPD™ continuously monitors the intra-peritoneal pressure (IPP) during the dwell. SmartPD™ enables the formulation of prescribed dialysate at the point-of-care, maximizes dialysis performance, and optimizes treatment protocol. Remote monitoring capability by SmartPD™ allows remote supervision and management, an efficient choice especially in Covid-19 times.
PO0962

Animal Trial of Sorbent Cartridge for Portable Artificial Kidney (PAK)

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Background: The NextKidney/Dialysis HD Sorbent Cartridge (SC) uses a novel type of sodium-neutral sorbent to regenerate spent dialysate for standard hemodialysis (HD) therapies. The SC is intended to be used with the NextKidney sorbent HD device, where it produces fully physiological dialysate meeting today’s industry standards. We tested the safety and efficacy of the sorbent system in a total kidney failure pig model. The animals were maintained exclusively on sorbent HD for up to 2 weeks.

Methods: Three highly uremic pigs (60–75Kg) underwent a total of 14 alternate-day, 4h sorbent HD therapy sessions. Total renal failure was induced via bilateral renal artery embolization (pig #1), or bilateral laparoscopic ligation of renal arteries (pigs #2 and #3). A palindromic catheter provided blood flow rates of 200 – 300mL/min. A hemoperfusion machine was used for the blood circuit, coupled with a prototype device controlling the dialysate circuit. Dialysate was continuously purified in the SC at a flow rate of 300 mL/min. Therapy efficacy and mass balances were calculated from blood and dialysate samples collected before and after the dialyzer at specific time points.

Results: The animals tolerated the therapies well. The incision site at the femoral artery did not leak, and the animals were maintained euvolemic and biochemistry for 30 days in a porcine model.

Conclusions: The biocompatibility of the sorbent system has been confirmed in fourteen 4h HD therapies conducted on three highly uremic pigs. The sorbent system was able to maintain the highly uremic animals. There were no severe adverse events related to the sorbent HD therapy. We currently plan to proceed to a first-in-human trial to evaluate the safety and efficacy of the sorbent cartridge for human use.

Funding: Commercial Support - AWAK Technologies Pte Ltd and Neokidney B.V.

Average Dialysate Concentrations

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PO0964

Smartphone Application to Assist Peritoneal Dialysis Patients for Timely Detection of Peritonitis

Mia Garbaccio,1 Xia Tao,1 Xiaoling Wang,1 Xin Wang,1 Zain H. Saq,1 Amrish U. Patel,1 Lela Tisdale,2 Ohnmar Thwin,2 Lin-Chun Wang,3 Nadja Grobe,1 Peter Kotanko,1,2 Renal Research Institute, New York, NY; 2Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Timely detection of peritonitis in patients undergoing peritoneal dialysis (PD) is critical to lower the risk of catheter loss, morbidity and mortality (Muhucumaranu, 2016). Current practice of screening potential peritonitis events at home relies on patients’ visual detection of turbid spent dialysate and symptoms recognition. To assist patients with the timely capture of a potential peritonitis episode, we developed a smartphone app, which uses light detection to quantitate cloudiness and estimate white blood cell (WBC) count in PD effluent (PDE).

Methods: The app uses the built-in light sensor and compares measurements taken from the ambient light (Iambient) and light through PD bags (Ibag) to estimate dialysate cloudines. PDE samples were obtained as part of two IRB-approved clinical studies over a period of 6 months. Cloudiness of each sample was measured 3x with the app. Cloudiness (in %) was calculated as (1 - Iambient / Ibag) * 100. WBCs were counted using a hematology analyzer (Horiba 80XL).

Results: Patients maintained a stable baseline cloudiness of 2-5% (Fig 1). A peritonitis episode (subject PDMET0002) increased the cloudiness to 40%, which is 32 percentage points over the patient’s peritonitis-free baseline. One suspected peritonitis sample (albeit WBCs <100 cells/mL) showed slightly higher cloudiness than non-peritonitis samples (Fig 2).

Conclusions: Our smartphone app can distinguish peritonitis from normal PDE samples. Smartphone-enabled detection of cloudiness in PDE samples using light transmission is possible and has the potential to easily monitor and diagnose patients at risk for peritonitis. Studies to define diagnostic performance in a large patient cohort are underway.

Funding: Commercial Support - AWAK Technologies Pte Ltd
PO0965
Remote Monitoring of Patients with Automated Peritoneal Dialysis May Improve Clinical Outcomes: Analysis by Competing-Risk Regression Models
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Background: Current information technologies allow remote monitoring (RM) of patients on automatic peritoneal dialysis (APD) and the adoption of proactive behaviors to prevent complications and improve treatment quality. We analyzed the effect of RM-APD on survival and preventable complications through a controlled clinical trial.

Methods: In a two-branched cluster RCT, hospitals with >100 prevalent, >50 new patients per year, and >5 years APD experience were randomly assigned to perform RM-APD or conventional APD with equivalent APD-equipment in adults beginning APD. The primary outcome was a composite index (CI) of death, first adverse event (AE) or first hospitalization. Secondary outcomes were the same variables considered individually and for their specific causes. All-cause and cardiovascular disease (CVD) mortality risk and AEs were analyzed with competing-risk regression with transplantation as competing risk.

Results: Eleven hospitals per arm were included and 815 patients were followed-up by at least one year. 417 using RM-APD and 398 on APD. Patients in hospitals using APD reached earlier the CI as well as its individual components. Patients with APD as compared to RM-APD were older, more inflamed, and had higher all-cause and CVD mortality. In competing risk analysis, after adjusting for age, sex, presence of smoking, hypertension, CVD and diabetes, APD as compared with RM-APD associated with higher subdistribution hazard ratio (sHR) for all-cause mortality (sHR 1.79, 95%CI (1.15-2.81); p=0.01), CVD-related mortality (sHR 2.21, 95%CI (1.07-4.58); p=0.03), and AE (sHR 1.74, 95%CI (1.34-2.25); p=0.001).

Conclusions: Use of RM-APD may improve survival and prolong the time to first AE and hospitalization in comparison with APD, suggesting that RM-APD may improve clinical outcomes in APD patients.

Funding: Commercial Support - Baxter

PO0966
Peritoneal Dialysis Discontinuation: Trends and Risk Factors
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Background: Increasing use of dialysis home modalities among ESRD patients is a Centers for Medicare and Medicaid Services priority. This can be accomplished by increasing use of home dialysis among incident patients or by reducing PD discontinuation. We explore trends in PD persistence and risk factors associated with PD discontinuation.

Methods: We identified incident ESRD patients from 2008 to 2018 who received peritoneal dialysis in their third month of ESRD treatment. We used data from CROWNWeb and Medicare claims to determine the patient’s modality 1, 2, and 3 years after initiation of ESRD treatment. We summarize trends in share of incident PD patients who were treated with PD at each follow up and describe differences by patient and facility characteristics.

Results: From 2008 to 2017, approximately 70 percent of incident PD patients remained on PD after 1 year of dialysis, 50 percent after 2 years, and 30 percent after 3 years of dialysis (figure 1). Over these years the percentage of incident PD patients treated with PD after two years rose from 47.9 to 52.3 percent. The rate of two-year PD persistence has declined modestly since a peak of 53.1 percent in 2013. PD patients treated at DaVita facilities were more likely than those treated at FMC or independent facilities to remain on PD after two years. PD patients treated at facilities with a higher share of PD patients were more likely to remain on PD after two years. Among incident PD patients, the rate of peritonitis during the first year of dialysis declined from 33.5 to 21.7 between 2010 and 2018. Peritonitis was more common among dual eligible patients, Black and American Indian/Alaska Native patients, and overweight or obese patients.

Conclusions: Differences in PD discontinuation and peritonitis incidence across patient and facility subgroups represent opportunities for future quality improvement efforts.

Funding: Other U.S. Government Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.
PO0968
Contemporary Incidence of Peritoneal Dialysis Attrition and Variability Therein Among Age Strata
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Background: With an increasing percentage of patients performing dialysis in the home setting, quality measurement systems should increase focus on home dialysis outcomes. Considering the central role of peritoneal dialysis (PD) in home dialysis, an important and readily estimable measure is the duration of PD before initiation of hemodialysis. We estimated the cumulative incidence of attrition due to initiation of hemodialysis among patients who recently initiated PD in the United States and assessed variability of incidence among age strata.

Methods: We analyzed United States Renal Data System Standard Analysis Files. We identified all patients who initiated PD in the home setting between January 1, 2011, and September 30, 2018, and within one year after diagnosis of end stage kidney disease (ESKD). We classified patients into cohorts of age 18-44, 45-64, 65-74, and ≥75 years. Overall and within age strata, we estimated the 5-year cumulative incidence of conversion to hemodialysis, with accounting for the competing risks of death and kidney transplantation.

Results: The cohort included 111,464 patients who initiated PD. The cumulative incidence of conversion to hemodialysis was 22.4% at 1 year, 33.9% at 2 years, 41.4% at 3 years, 46.3% at 4 years, and 49.4% at 5 years (figure). During those 5 years, 25.4% of patients died while receiving PD and 12.8% received a kidney transplant, thereby resulting in only 12.4% of patients still performing PD after 5 years. Among patients aged 18-44 years, 1-year (5-year) cumulative incidence of conversion to hemodialysis was 23.3% (51.1%); corresponding estimates were 22.3% (52.0%) among patients aged 45-64 years (48.3%), 21.9% among patients aged 65-74 years, and 22.5% (41.6%) among patients aged ≥75 years.

Conclusions: Regardless of age, between 22% and 23% of patients who initiated PD during the first year of ESKD transferred to hemodialysis within one year.

Funding: NIDDK Support

PO0970
Identifying Patients on Peritoneal Dialysis at High Risk of Transfer to Hemodialysis Using a Modified Surprise Question
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Background: Transfer from peritoneal dialysis (PD) to hemodialysis (HD) is associated with poor outcomes. Available prediction models of modality transfer are limited to the incident PD population. Simple predictive tools are needed to help guide risk stratification and subsequent clinical interventions to avoid unwanted modality transfer. We report on the correlates of nurse prediction of high risk using the question “Would you be surprised if this patient transfers to HD in the next 6 months?” (PD Surprise Question [PDSQ]).

Methods: This observational study included 1362 adults on PD receiving care at 35 centers in 3 states in the US, managed by a non-profit dialysis organization. A ‘no’ response to the PDSQ indicated high risk. Using multivariable logistic regression with backward elimination, we evaluated characteristics associated with being identified as high risk, including socio-demographic variables, BMI, primary kidney disease, vintage, comorbid conditions, renal and dialysate clearances, serum albumin, sodium, phosphorus, potassium, nPNA, last 3 months peritonitis and hospitalization, and insurance type. We used multiple imputations to handle missing data.

Results: Responses were obtained from 95/112 (85%) nurses for 1193/1362 (88%) patients. Mean age was 59 (SD: 16) years, 41% were female, median ERSD vintage 37 (IQR: 11 – 44) months and 46% had diabetes. 198 (17%) patients were identified as high risk. In the final model, patients were more likely to be identified as high risk if they were hospitalized in the last 3 months (odds ratio [OR]: 1.30, 95% confidence interval [CI] 1.30-1.74, p=0.0002). Considering the higher serum sodium serum level for 1 meq/L: OR: 0.95, 95% CI 0.90-1.00, p=0.032), being married (OR: 0.76 95%CI 0.52-1.00, p=0.029), and longer PD vintage (for 1 month: OR: 0.99, 95%CI 0.98-1.00, p=0.013) were associated with lower odds of being identified as high risk.

Conclusions: The PD surprise question is a simple tool to assess the risk of transfer from PD to HD. Identified correlates of risk are consistent with high risk factors from the literature for transfer to HD. We are currently observing outcomes of included patients to examine the performance of the PDSQ to predict transfer to HD.

Funding: Commercial Support - Fresenius Medical Care North America
**PO0971**

**Machine Learning-Driven Prediction of Peritoneal Dialysis Technique Failure**

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**Background:** Despite increased focus on starting and keeping dialysis patients on home therapy, Peritoneal Dialysis (PD) and Home Hemodialysis (HHHD) rates are lower than desired. Two areas of opportunity are 1) keeping PD patients healthy so they can remain on PD longer and 2) transitioning PD patients to HHHD when appropriate. To identify patients at risk of leaving PD in the short- (1-3 month) and long-term (3-6 month) timeframes, two machine learning (ML) models were developed. Along with risk scores, these models identify the factors driving increased risk to aid in prolonging time on PD while also allowing adequate notice to prepare for permanent access placement and HHHD education.

**Methods:** Data were extracted for PD patients (n=53022) from 2016-2019; patients contributed one set of observations for each month they were on PD (n=823892 patient months). PD failure was defined as the first disconnection from PD lasting over 30 days, and was coded as ‘1’ if the patient changed modality in the next 1-3 or 3-6 months for the short- and long-term models, respectively. All other observations were coded as ‘0,’ including censored events such as transplantation, loss to follow-up, or death. Two XGBoost ML models were trained using 80% of the dataset, with 20% used for evaluating model performance using 237 variables, derived from laboratory measurements, infection and hospitalization history, and other relevant clinical parameters.

**Results:** Evaluation of model performance on withheld data showed an area under the curve of 0.75 and 0.67 for the short- and long-term models, respectively. Patients were classified as High, Medium, or Low risk for each of their short- and long-term predictions. In the short-term model, one group of patients was identified with high risk of dropping in the first 3 months, a rate almost 5 times higher than average and 12 times higher than low risk patients. For long-term predictions, 14% of high risk patients dropped in the next 3-6 months, 6% of medium risk, and 2% of low risk.

**Conclusion:** The two ML models showed good discrimination between patient risk categories for both short- and long-term timeframes. Further work is underway to gauge the clinical utility of these tools, these tools offer the potential to improve care of “failing” PD patients, reduce morbidity of transitions, and increase optimal starts with dialysis technique failure.

**Funding:** Support - Fresenius Medical Care

**PO0972**

**Technique Failure in the Dominican Republic National Peritoneal Dialysis Program**

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**Background:** Technique failure is a critical concern in peritoneal dialysis (PD), and it’s associated with significant risk of patient lost. Technique failure is defined as transfer to HD 30 days after initiation of therapy or death within 30 days of transfer to HD.

**Methods:** This is a retrospective multicenter observational cohort study of incident Peritoneal Dialysis patients conducted between January 1st 2016 to December 31st 2020. Competing risk events were death and kidney transplantation, and patients were censored for recovery of kidney function, withdrawal or suspension of the therapy, and loss of a caregiver. Disease characteristics and baseline demographics were included. Data are expressed as mean ± standard deviation for continuous variables and as frequency counts and percentages for categorical variables. Incidence rates were performed for transfer to HD and finally, logistic regression analysis between the inferential type variables to determine the risk between having a history of diabetes mellitus and the variables of death and transfer to HD were calculated using an Odds Ratio analysis with 95% confidence intervals for parameters B.

**Results:** A total of 2326 patients were included, 59% men; the mean age was 57 ± 16 years, 53% had a diagnosis of Diabetes Mellitus (DM) and 65% had a basic educational level. 151 patients were censored (11%). Risk events were 1096 of which death accounts for 1084 (74%) and transplantation (0.8%). At the end of the first year the cumulative incidence risk to HD transfer was 1%, the second year 4%, the third year 6%, the fourth 11%, and the fifth 16%. Based on the regression analysis between the variables of interest and the patients with a history of DM, there is a higher risk of death (p<0.001; OR: 2.123; CI 95% 1.781-2.532), however, for transfer to HD, no statistical significance was found (p=0.39; OR 1.14; CI 95% 0.838-1.564). The most frequent reason for technique failure was psychosocial and medical conditions 44%, followed by catheter malfunction 30%, peritonitis 13% and ultrafiltration failure 13%.

**Conclusions:** The technique failure rate is similar to the reported in RTS Colombian PD Program, but being higher than the mean of Latin American countries reports. Still, improvement needs to be done in the catheter implant technique and mortality rates.

**PO0973**

**Nurse-Based Educational Interventions in Patients with Peritoneal Dialysis: A Systematic Review and Meta-Analysis**

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**Background:** Peritoneal dialysis (PD) is a major renal replacement therapy modality for patients with end-stage renal disease (ESRD) worldwide. As poor patient self-care could lead to serious complications, including peritonitis, exit-site infection, technique failure, and death; several nurse-based educational interventions have been introduced. However, these interventions varied and have been supported by small-scale studies so the effectiveness of nurse-based educational interventions on clinical outcomes of PD patients have been inconclusive.

**Methods:** We performed a systematic search using PubMed, Embase, and CENTRAL. Selection criteria included Randomized Controlled Trials (RCTs) relevant to nurse-based education interventions in ESRD patients with PD in the English language up to February 2020. The meta-analyses were conducted using a random-effects model to evaluate the summary outcomes of peritonitis, PD-related infection, mortality, transfer to hemodialysis, and quality of life (QOL).

**Results:** Of 7,240 potential studies, 61 theme-related abstracts were selected for further full-text articles screening against eligibility criteria. Ten studies (1,404 PD patients in seven countries) were included in the systematic review. Eight studies (1,363 PD patients in five countries) were included in the meta-analysis. Sleep QOL in the intervention group was significantly higher than control (mean difference 12.76, 95% CI 5.26–20.27). There was no difference between intervention and control groups on peritonitis, PD-related infection, transfer to hemodialysis, and overall QOL.

**Conclusions:** Despite increased focus on starting and keeping dialysis patients on PD, Peritoneal Dialysis catheters are felt to require a healing time prior to initial use. Concern for increased risk of leak, has led many to use a supine intermittent low volume exchanges (> 72 hours) without regard to maintaining a supine position. Higher volume dialysis with earlier initiation should allow for better PD clearances when clinically warranted and more salt and water removal compared to supine intermittent low volume exchanges. Two areas of opportunity are 1) keeping PD patients healthy so they can remain on PD longer and 2) transitioning PD patients to HHHD when appropriate. To determine the risk between having a history of diabetes mellitus and the variables of death and transfer to HD were calculated using an Odds Ratio analysis with 95% confidence intervals for parameters B.

**Quality of Sleep**

**PO0974**

**Immediate Start PD: A Single-Center Experience**

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**Background:** Peritoneal Dialysis catheters are felt to require a healing time prior to initial use. Concern for increased risk of leak, has led many to use a supine intermittent low volume exchanges (<1000mL) initially for earlier start peritoneal dialysis. We undertook a study to prospectively monitor and track peritoneal dialysis complications when catheter use was early (prior to 14 days post placement) and the nephrologist chose to start with higher volume dialysate (>1000mL) without regard to maintaining a supine position. Higher volume dialysis with earlier initiation should allow for better PD clearances when clinically warranted and more salt and water removal compared to supine intermittent low volume exchanges.

**Methods:** In this single center prospective observational study, peritoneal dialysis catheters were placed laparoscopically ensuring tunneling through the abdominal rectus muscle with the deep cuff placed just within or below the rectus abdominal muscle. Purse strings sutures were only used at the surgeons’ discretion. Surgeons did undergo consistent supervision from two experienced surgeons prior to the study. Patients were included in the study if the nephrologist felt early start dialysis was indicated. Prescriptions were at the discretion of the nephrologist.

**Results:** Since January 2021, 23 PD catheters have been placed using this technique with only one adverse event: 8 patients (35%) initiated PD 24 – 72 hours post placement and 15 patients (65%) started dialysis between 73 hours and 2 weeks post catheter placement. All patients first exchanges were 1000 mL, and volumes were increased rapidly at the discretion of the nephrologist as patient condition warranted. In these 23 patients, 1 patient experienced a perforation and leak, which resolved with rest. That patient was in the > 72 hour group. No other catheter complications were noted.
Converting ESKD Patients on Peritoneal Dialysis to Hemodialysis Post Cardiac Surgery: A Necessity or Comfort
Elias Basal,1 Milad Matta,2 Aimen Liaqat,1 Adam Fawaz,3 Georges Nakhoul,1,2 Joost C. Taliercio,1,2 Juan C. Calle,2,3 Serge C. Harb,1 Haytham Elgharably,1 Susana Arrigain,1 Jesse D. Schold,2 Remy Daou,1 Ali Mehdi,2,3 Cleveland Clinic, Ohio; 2Cleveland Clinic Glickman Urological and Kidney Institute, Cleveland, OH; 3Université Saint-Joseph, Beirut, Lebanon.

Background: End-stage kidney disease (ESKD) patients on peritoneal dialysis (PD) undergoing cardiac surgery are sometimes converted to hemodialysis (HD) post-surgery. The reasons for this conversion are not well defined in the literature. We sought to examine the reasons cited for converting PD patients to HD post operatively after undergoing major cardiac surgery.

Methods: We examined ESKD patients on PD undergoing cardiac surgery from 2009-2019 using an electronic health records (EHR)-based Cardio-Thoracic Surgery (CTS) registry at the Cleveland Clinic. We identified PD patients who were converted to HD perioperatively. We reviewed the EHR to identify the main causes for conversion.

Results: 62 ESKD patients on PD undergoing major cardiac surgery were identified. 16 patients, representing more than a quarter, were converted to HD post operatively. Out of those converted, 31.25% were converted for absolute indications (18.75% for PD catheter malfunction, 25% for gait difficulties, 25% for concern of pericardio-peritoneal communication). 68.75% were converted for less clear and relative indications (25% based on clinician preference, 43.75% for hemodynamic instability or requiring vasopressors). Results are displayed in (Table 1).

Conclusions: A small percentage of PD patients are converted to HD for absolute indications. Most patients are converted based on relative indications including lack of familiarity with PD and hemodynamic instability. As the number of ESKD patients on PD is expected to increase, a better understanding of the outcomes of PD patients post cardiac surgery is needed. In addition, more education is urgently needed to increase the comfort of practitioners managing PD patients in special situations that might be amenable to prescription alterations without premature transition to hemodialysis.

Table 1

<table>
<thead>
<tr>
<th>Reason Cited</th>
<th>Relative Indications (%)</th>
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<tr>
<td>Absolute Indications</td>
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<tr>
<td>Fluid accumulation</td>
<td>38.75%</td>
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<tr>
<td>Gastrointestinal</td>
<td>25%</td>
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<tr>
<td>Anemia</td>
<td>10%</td>
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<tr>
<td>Hypertension</td>
<td>10%</td>
</tr>
<tr>
<td>Relative Indications</td>
<td></td>
</tr>
<tr>
<td>Functional status</td>
<td>25%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18.75%</td>
</tr>
<tr>
<td>Other</td>
<td>12.5%</td>
</tr>
</tbody>
</table>

PO0975

Peritoneal Dialysis and QoL
Arrigain,1 Jesse Taliercio,2,1 Gloria Perez-Navarro,3 Rafael Valdez-Ortiz,1 Hospital General de Mexico Dr Eduardo Liceaga, Ciudad de Mexico, Mexico.

Introduction: For patients on Peritoneal Dialysis (PD), it is reasonable to expect a correlation between treatment efficacy and QoL. Residual kidney function, patient age, residual urea and creatinine levels, albumin were evaluated to assess their importance in determining QoL.

Methods: 91 patients on IAPD were included in this study. QoL was assessed using the EQ-5D-5L found to correlate with residual uresis (r -0.052, p 0.612). Questionnaires: Peritoneal Dialysis PO0975 was defined as less than 16hrs of treatment per day. Clinical, biochemical data were collected. The renewed interest in home dialysis requires a translational uremic large animal model to evaluate innovations in peritoneal dialysis. Ideally, toxin plasma levels should be comparable to those in dialysis patients, without requiring maintenance dialysis for survival. To this end, we developed a pig model with stable moderate chronic kidney disease.

Methods: CKD was induced in five female pigs by bilateral subtotal renal artery embolization aiming for embolization of ~85-90% of total kidney tissue. Temporary aggravation of uremia was induced with gentamicin (10 mg/kg twice daily for 7 days). We hypothesized this approach would lead to stable CKD without the need for maintenance dialysis. Peritoneal transport was assessed with a standard peritoneal permeability assessment.

Results: After embolization, urea and creatinine levels increased from 1.6±0.2 to 7.5±1.0 mM and 103±12 to 338±20 µM, respectively, followed by stabilization within 2 weeks to 2.5±1.0 mM and 174±25 µM, respectively. GFR (iohexol clearance) decreased from 49±7 mL/min to 28±5 mL/min. Gentamicin induced temporary acute-on-chronic kidney injury with peak urea and creatinine concentrations of 17±6±1 mM and 932±504 µM, respectively (Figure 1), while potassium (range 4.1-4.7 mM) and phosphate (range 2.3-2.7 mM) remained stable. Peak indoxyl sulfate and hippuric acid levels were 10.5 ± 0.85 mg/L and 75.3 ± 81.5 mg/L, respectively. Peritoneal dialysis, although complicated by peritonitis, could be successfully applied. Peritoneal transport assessment showed a low transport status (D/P creatinine (4h): 0.45±0.12) with an MTAC of 9.6±3.0, 4.6±2.5, 3.4±2.2 mL/min for urea, creatinine, and phosphate respectively.

Conclusions: We have established a pig model with stable moderate CKD without the need for maintenance dialysis. Temporary-on-demand acute-on-chronic kidney injury, resulting in uremic solute levels representative for ESKD, allows evaluation of novel dialysis methods.

Figure 1. Urea (left) and creatinine (right) plasma levels after administration of gentamicin (day 0). Mean ± SD, n=10 administrations in n=5 pigs.

PO0976

Effect of Low-Dose PD in Elderly Population on Protein Energy Wasting, Functionality, and Quality of Life
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Background: Elder population currently involves 55% of those who initiate dialysis. Some of them, including fungal peritonitis, requires PD catheter removal which highlights the importance of prompt diagnosis. IAPD in this elder population does not mean suboptimal dialysis: there are found favorable results in regard to biochemical parameters; FS and Qol, scores maintained despite the dialysis vintage. Of notice the group of 75yrs and older are more likely to be affected in a negative way by prescription of dialysis.

Conclusions: PO0976

Recurrent Abdominal Pain in a Patient on Peritoneal Dialysis
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Introduction: Abdominal pain can have many differentials in patients on peritoneal dialysis (PD). Some of them, including fungal peritonitis, requires PD catheter removal and a change in dialysis modalities. Here we present a case of recurrent abdominal pain in a patient on peritoneal dialysis which highlights the importance of prompt diagnosis.

Key: - TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Case Description: A 55-year-old female with history of ESKD due to diabetic kidney disease, CAD s/p CABG, and hypertension presented with a 1 day history of cloudy effluent. She had no prior peritonitis episodes. Vital signs were stable and exam was notable for a soft non-tender abdomen and clean and dry exit site without discharge or granulation tissue. Effluent was hazy in appearance. Administration of empiric vancomycin and gentamicin was initiated, varying in clearing of effluent within 24 hours. Effluent leukocyte count was 204 cells/µl with 58% neutrophils. Intrapertitoneal vancomycin was continued for 3 days due to intermittent low troughs. Further history revealed intermittent mask use while performing exchanges. After completion of treatment, repeat cell count and culture were repeated 1 month later during evaluation of abdominal pain eventually found to be due to constipation. Leukocyte count was 6 cells/µl, but culture again grew *Micrococcus sp*. After culture was repeated once more and remained persistently positive, repeat treatment to eradicate was attempted with 2 more weeks of treatment, but culture remained positive. Eventually the catheter was removed due to a change in living situation. After 5 months of hemodialysis, peritoneal catheter was removed. She had been having intermittent abdominal pain with PD effluent sometimes showing high white count for which she got multiple antibiotic courses for either presumed or culture positive bacterial peritonitis. She had also grown positive fungus culture about 18 months ago with Candida albicans and Streptococcus which went unnoticed.

Discussion: Fungal peritonitis can be catastrophic for patients on PD. Treatment involves prompt catheter removal and systemic antifungal treatment. Given its dire consequences, prevention is paramount. The ISPD recommends using anti-fungal prophylaxis when PD patients receive antibiotic courses. Risk factors include previous bacterial peritonitis and antibiotic use. This case demonstrates the need to follow cultures as fungal growth is slow and can take weeks. It is important to have a high index of suspicion for a fungal organism when cultures are negative. This patient received antibiotics on several occasions but only developed fungal peritonitis on 2 occasions which raises concerns on antifungal prophylaxis. Further studies are indicated to determine number needed to treat to decide on need for antifungal prophylaxis.

PO0979
Micrococcus Peritonitis Complicating Peritoneal Dialysis
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Introduction: Peritonitis is one of the most common and consequential complications of peritoneal dialysis. *Micrococcus sp* are catalase-positive, coagulase-negative, gram-positive cocci that are increasingly recognized as opportunistic pathogens in patients with immunocompromise or indwelling catheters. These bacteria have been rarely implicated as causative in peritonitis. We present a case of peritonitis due to *Micrococcus sp* and review the pertinent literature.

Case Description: A 78-year-old man with ESKD due to diabetic nephropathy, transitioned five weeks prior from HD to PD, presented with newly cloudy PD fluid. His past medical history included hypertension, coronary artery disease, and monoclonal gammopathy of undetermined significance. He reported a newly cloudy white initial drain on PD for 5 days. Peritoneal fluid was cloudy (figure 1a) with 101 white blood cells (4% neutrophils); gram stain and culture were negative. Triglycerides were 96 and 62 mg/dL in the PD fluid and serum, respectively. Etiologic work-up was negative for malignancy, pancreatitis, cirtosis, trauma and tuberculosis. Cloudy nature of the PD fluid resolved within a day and the cloudy fluid persisted for the following week. After disease progression, the cloudy fluid reduced further.

Discussion: This patient had the onset of cloudy PD fluid 5 weeks after initiating PD, which resolved with cessation and reinstitution of his long-term nifedipine. The mechanism of calcium channel blockers (CCB) related cloudy ascites is not well established. Some have suggested it may be related to the lipophilic nature of CCB. Patients on PD with higher peritoneal membrane transport may be at higher risk. Genetic factors may predispose to this phenomenon. Nephrologists should be aware of this rare complication of CCB use in PD patients. More research is needed to better understand the underlying pathophysiology of this rare condition.

PO0981
Chylous Peritoneal Fluid in a Patient on Peritoneal Dialysis Taking Nifedipine
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Introduction: Chylous fluid in peritoneal dialysis (PD) patients may appear with lymphatic system disruption. This can be due to lymphatic obstruction, exudation through vessels, or via a lymphoperitoneal fistula.

Case Description: A 78-year-old man with ESKD due to diabetic nephropathy, transitioned five weeks prior from HD to PD, presented with newly cloudy PD fluid. His past medical history included hypertension, coronary artery disease, and monoclonal gammopathy of undetermined significance. He reported a newly cloudy white initial drain on PD for 5 days. Peritoneal fluid was cloudy (figure 1a) with 101 white blood cells (4% neutrophils); gram stain and culture were negative. Triglycerides were 96 and 62 mg/dL in the PD fluid and serum, respectively. Etiologic work-up was negative for malignancy, pancreatitis, cirrhosis, trauma and tuberculosis. Cloudy nature of the PD fluid resolved within a day and the cloudy fluid persisted for the following week. After disease progression, the cloudy fluid reduced further.

Discussion: This patient had the onset of cloudy PD fluid 5 weeks after initiating PD, which resolved with cessation and reinstitution of his long-term nifedipine. The mechanism of calcium channel blockers (CCB) related cloudy ascites is not well established. Some have suggested it may be related to the lipophilic nature of CCB. Patients on PD with higher peritoneal membrane transport may be at higher risk. Genetic factors may predispose to this phenomenon. Nephrologists should be aware of this rare complication of CCB use in PD patients. More research is needed to better understand the underlying pathophysiology of this rare condition.

PO0980
Cutaneous Oxalosis in a Patient on Peritoneal Dialysis
Stephanie Torres Rodriguez, Hunter Pyle, Audrey Rutherford, Arturo R. Dominguez, Shani Shastri. The University of Texas Southwestern Medical Center, Dallas, TX.

Introduction: Oxalosis is the systemic deposition of calcium oxalate in multiple tissues and can be of primary or secondary etiology. Skin manifestations due to secondary hyperoxaluria (SH) attributable to renal insufficiency are rare. We present a case of cutaneous oxalosis in a patient with end stage renal disease (ESRD) receiving peritoneal dialysis (PD).

Case Description: A 45-year-old female with ESRD due to lupus nephritis (LN) on PD for 15 years presented with hypertensive encephalopathy. Dermatological evaluation revealed pseudoeutectic hyperpigmented patches overlying firm, non-tender, subcutaneous nodules and plaques on bilateral lower extremities (Figure 1) and upper arms and firm nodules overlying the joints of her hands (Figure 2). With history of lupus, cutaneous findings were concerning for dystrophic calcinosis cutis. Skin biopsy showed radially arranged yellow-brown rhomboid crystals in the subcutis and deep dermis surrounded by histiocytes consistent with cutaneous oxalosis (Figure 3). Additional history revealed daily intake of Vitamin C 1g for past year and no prior gastrointestinal surgeries or chronic diarrhea. Non-obstructive bilateral nephrolithiasis were seen on imaging in 2020 but absent previously.

Discussion: Absence of early-age nephrolithiasis, negative family history & renal biopsy findings are inconsistent with primary hyperoxaluria (PH). SH is a result of excessive oxalate accumulation from increased intake, increased reabsorption due to small bowel disease, or decreased excretion in renal failure (retention oxalosis). Although dialysis patients may have high serum oxalate, clinical calcifications are rare. We speculate vitamin C supplementation and ESRD status contributed to the production of these deposits in our patient. Ascorbic acid is metabolized to oxalate; in long term dialysis patients doses of 500 mg daily may raise plasma oxalate by 50% to 100%. Management includes lowering serum calcium and oxalate levels by eliminating Vitamin C supplements or reducing dose < 100 mg daily, limiting dietary oxalate, increasing dialysis clearance and lowering dialysate calcium concentration if needed.
PO0982

Severe Bleeding and Deep Inferior Epigastric Pseudoaneurysm After PD Catheter Removal
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Introduction: In this case, the removal of a PD catheter with deep cuff calcification results in pseudoaneurysm formation with hemorrhage and hospitalization.

Case Description: A 24-year-old woman with end-stage kidney disease was switched from PD to HD due to worsening uremia and PD catheter removal was organized. At the time of catheter removal heavy calcification around the deep Dacron cuff was seen, creating a pseudoaneurysm where urgent angiographic embolization to stop the bleeding was needed (Fig. 1). Intimate relationship between DIEP vessel and Dacron cuff was felt to be secondary to heavy calcification of these structures that developed during her time on PD (Table 1). The patient required an urgent transfusion and was admitted to hospital for monitoring. She was discharged the following day in stable condition.

Discussion: This is an important learning case in PD catheter removal and highlights the following: - Poorly controlled bone mineral disease may lead to excessive heavy calcification of the deep Dacron cuff and DIEP vessels. - When heavy calcification of the PD cuff is seen, catheter removal should be done in settings equipped with interventional radiology support in the event of complication.

Calcium-phosphate balance while on PD

Enter Cell Value

A 24-year-old woman with end-stage kidney disease was switched to hemodialysis. She was admitted to hospital for monitoring. She was discharged the following day in stable condition.

Discussion: This is an important learning case in PD catheter removal and highlights the following: - Poorly controlled bone mineral disease may lead to excessive heavy calcification of the deep Dacron cuff and DIEP vessels. - When heavy calcification of the PD cuff is seen, catheter removal should be done in settings equipped with interventional radiology support in the event of complication.

PO0983

A Case of Abdominal Wall Abscess Caused by Aeromonas hydrophila in Prior Peritoneal Catheter Site in an Immunocompromised Patient
Post Kidney Transplant
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Introduction: Aeromonas hydrophila is a gram-negative rod-shaped bacterium found in aquatic ecosystems; it has been identified as the causative organism of different opportunistic infections in the immunocompromised and there is growing evidence of infection in the immunocompetent. This pathogen has been implicated in acute gastroenteritis, soft tissue infections, meningitis, peritonitis and sepsis among others.

Case Description: We report a case of a 56 year old woman with end stage kidney disease previously on peritoneal dialysis (PD) with subsequent live donor kidney transplant on immunosuppression, who presented with right lower quadrant abdominal cellulitis and deep abscess around the catheter site. Post transplant, her PD catheter was removed, however, the catheter site never healed completely. Although she did have multiple superficial skin infections in the past, those resolved with antibiotics. But this specific cellulitis, did not improve despite multiple antibiotic regimens, and further imaging studies revealed she had developed an abscess. The abscess was managed by surgical incision and drainage with debridement of the skin, subcutaneous tissue, fascia, and muscles around the whole catheter tract. Aeromonas hydrophila was found as the causative organism.

Discussion: To our knowledge, this is the first case of an A. hydrophila abscess associated with a peritoneal dialysis catheter. Firm association between aeromonads and the use of intravenous indwelling devices has already been demonstrated. We hypothesize that her deep seeded infection could be associated with the intrinsic ability of A. hydrophila to form biofilms upon detecting a suitable surface, making them more virulent. The formation of biofilm has been associated with exponential growth as the source of pathogenicity of this bacteria in pisciculture studies. This characteristic could be one of the factors contributing to reported cases of peritonitis and intravenous hemosidalization catheters by A. hydrophila. Further elucidation of A. hydrophila virulence factors in humans can provide insight on prevention of PD catheter associated infections by A. hydrophila.

PO0984

Mesenchymal Stem Cell Exosomes Protect Mouse Peritoneal Injury Induced by Human Peritonitis Dialysis Effluent
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Background: Peritoneal fibrosis is a severe complication of peritoneal dialysis, but there are few effective therapies for it. The purpose of this study was to investigate the protective effect of exosomes secreted by mouse bone marrow mesenchymal stem cells (MSC) on peritoneal injury and to reveal the mechanism.

Methods: Forty-two male C57BL/6 mice were randomly divided into a normal group, a control group (2.5% glucose dialysate), a peritonitis-effluent (Peritoneal infection and dialysate group) and a peritonitis-effluent+exosome group, and a high glucose dialysate+exosome group. The mouse model of peritoneal injury was constructed by intraperitoneal injection of human peritonitis dialysis effluent continuously for 42 days. The mice in the exosome treatment group received intraperitoneal injection of MSC-exosomes twice. The level of peritoneal structural and functional damage was detected. The effect of MSC-exosomes was validated in vitro.

Results: Peritoneal transport and structure was significantly impaired in the peritonitis-effluent group and the high glucose dialysate group after 42 days, and was significantly higher than control group. The results suggested that human peritonitis dialysis effluent could be used to construct a mouse model of peritoneal injury. Masson staining showed that fibrosis degree of exosome treatment group was significantly less than peritonitis-effluent group. Immunohistochemical analysis showed that expressions of mesothelial markers E-cadherin and ZO-1, neutrophil granulocytes (MOPO) and macrophages (F4/80), and fibrosis markers (collagen La-SMA) in exosome treatment group were significantly lower than peritonitis-effluent group. Peritoneal ultrafiltration function of exosome treatment group was significantly improved than peritonitis-effluent group. In vitro experiments showed that exosomes could down-regulate the secretion of IL-1β, IL-6 and TGF-β1 by peritoneal mesothelial cells stimulated by high glucose dialysate, maintain expression of mesothelial cell marker (E-cadherin), and inhibit mesenchymal marker (a-SMA), suggesting that exosomes could inhibit the transdifferentiation of peritoneal mesenchymal cell-mesenchymal cells (MMT).

Conclusions: MSC-exosomes can alleviate peritoneal fibrosis by inhibiting peritoneal mesothelial cell-mesenchymal cell transdifferentiation.
PO0985

Dual Therapy with JAK1/2 Inhibitor and Losartan Attenuates Dialyse-Induced Angiogenesis in Polycystic Rats

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Background: Long term peritoneal dialysis (PD) is limited by reduced efficacy over time. Early peritoneal membrane (PM) injury is characterized by inflammation which progresses to hypervascularity and fibrosis. JAK-STAT signaling mediates inflammatory pathways, including angiotensin signaling. Our previous study showed dual therapy with JAK1/2 inhibitor (JAK1/2i) and an ARB maintains PM structure and function in rats with polycystic kidneys (PCK) chronically infused with 4.25% Dianzel x 16 wks. By using VEGF-R2 as an endothelial marker, we further investigated if this dual therapy can attenuate chronic dialysate infusion induced hypervascularity in this rat model.

Methods: PCK rats were used. Dialysate infusions were performed BID via an implanted subcutaneous port in the neck tunneled to the intraperitoneal cavity. The following treatments were administered: (1) No surgery/infusions; (2) 4.25% Dianzel; (3) 4.25% Dianzel + JAK1/2i (5mg/kg BID); (4) 4.25% Dianzel + Losartan (5mg/kg BID); and (5) 4.25% Dianzel + Losartan + JAK1/2i (5mg/kg BID each). Partial peritoneal was used for immunohistochemical staining of VEGF-R2, which was digitally quantified by using Qu Path program. Data were analyzed by one-way ANOVA followed by Tukey test. Results are mean ± SEM.

Results: VEGF-R2 staining was significantly elevated after 16 weeks of infusion of 4.25% Dianzel alone. JAK1/2i significantly reduced VEGF-R2 expression; losartan tended to reduce VEGF-R2, but this did not reach significance. Dual therapy with JAK1/2i and losartan resulted in the greatest reduction of VEGF-R2.

Conclusions: Long-term JAK1/2i, or JAK1/2i plus losartan intraperitoneal treatment reduces angiogenesis. Angiotensin inhibition is advocated to maintain residual renal function, by adding JAK1/2i, the combination also protects peritoneal structure/function by reducing angiogenesis.

PO0986

The Effect of Far-Infrared Therapy on the Peritoneal Expression of Glucose Degradation Products in Diabetic Patients on Peritoneal Dialysis

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Background: Peritoneal dialysis (PD) is a treatment modality for end-stage renal disease (ESRD) patients. Dextrose is a common osmotic agent used in PD solutions and its absorption may exacerbate diabetes mellitus. PD solutions also contain glucose degradation products (GDPs) that may lead to encapsulating peritoneal sclerosis (EPS). A previous study showed that far-infrared (FIR) therapy improved a patient’s gastrointestinal symptoms due to EPS. Due to limited literature, this study aims to investigate dialysate GDPs and peritoneal function in diabetic patients on PD.

Methods: A prospective analysis conducted in a single center. The participants were recruited from the peritoneal dialysis outpatient department from November 25, 2016 to September 5, 2018. We included the patients who met the following criteria: (1) ESRD patients aged 20-90 years without receiving FIR therapy within 12 months; (2) receiving continuous ambulatory peritoneal dialysis or automated peritoneal dialysis; (3) no history of peritonitis, cerebrovascular accident, myocardial infarction, or receiving any cardiovascular intervention in the past 3 months. Patients were allocated to two groups based on their underlying DM history. Both groups of PD patients received FIR therapy for 6 months. We collected the last daily bag of peritoneal dialysate and measured the dialysate concentration of GDPs and clinical data in PD patients pre- and post-FIR therapy.

Results: Thirty-one PD patients were enrolled and underwent 40 min of FIR therapy twice daily for six months. We demonstrated the effect of FIR therapy on the following: (1) decrease of methylglyoxal (p = 0.02), furfural (p = 0.05), and 5-hydroxymethylfurfural (p = 0.03), (2) increase of D/D0 glucose ratio (p = 0.03), and (3) decrease of potassium levels (p = 0.008) in both DM and non-DM patients, as well as (4) maintenance and increase of peritoneal K/ V in DM and non-DM patients, respectively (p = 0.03). FIR therapy is a non-invasive intervention that can decrease dialysate GDPs in PD patients by improving peritoneal transport rate and solute removal clearance, while also maintaining dialysis adequacy.

Conclusions: In conclusion, our study demonstrated that FIR therapy can decrease patients’ dialysate GDPs by improving peritoneal transport rate and solute removal clearance, while also maintaining dialysis adequacy.

PO0987

Cumulative Dialysate Glucose Exposure Is a Risk Factor for Peritoneal Sclerosis in Pediatric Peritoneal Dialysis Patients Using Neutral-PH Fluids

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Background: The benefits of neutral-pH fluids for preventing peritoneal dialysis (PD)-related peritoneal sclerosis have been established, however, advanced peritoneal sclerosis still has been described in pediatric PD patients using neutral-pH fluids (Kidney Int 2018). The factors associated with peritoneal pathological changes after long-term use of neutral-pH fluids have not been elucidated.

Methods: Pediatric PD patients using only conventional acidic fluids (conventional group) and those using only neutral-pH fluids (neutral-pH group, n=33) for more than one year were analyzed. Propensity score matching was performed to compare the peritoneal pathological changes between groups. Clinical risk factors including PD duration and cumulative dialysate glucose exposure for peritoneal pathological changes in the neutral-pH group were analyzed using generalized linear model. Furthermore, immunohistochemistry studies were performed on vascular endothelial growth factor-α (VEGF-α), cytookeratin; an epithelial marker, and α-smooth muscle actin (α-SMA); a myofibroblastic marker of epithelial-mesenchymal transition (EMT).

Conclusions: The neutral-pH fluids showed less deteriorations of the peritoneal membrane than acidic fluids except for increased angiogenesis. Cumulative dialysate glucose exposure was an independent risk factor for increased thickness of the submesothelial compact zone (OR, 1; 95%CI, 1.001-1.007) and submesothelial microvesSEL density (OR, 1; 95%CI, 1.003-1.005).

CVD-related mortality risk and tendency towards reduced technique survival when analyzed with adjusted competing-risk regression models. Funding: Commercial Support - Baxter Renal Care Services; Baxter Healthcare Corporation.
PO0989
Multifrequency Bioimpedance Is a Useful Adjunct to Control Fluid Overload in PD Patients
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Background: Fluid overload is a well recognized phenomenon in many peritoneal dialysis (PD) patients, but a balance between reduction of dry weight and preservation of residual renal function (RRF) is mandatory. We hypothesize that, to achieve an ideal dry weight, adjustment by multifrequency bioimpedance (MF-BIA) guide offers less adverse effect on residual renal function than that by clinical judgment alone.

Methods: The hydration status of various body compartments were measured using a MF-BIA device (Inbody 720, Biospace). The normalized hydration score was defined as extracellular water (ECW)/total body water (TBW). All patients were evaluated monthly for 6 months. The dry weight of study group was adjusted according to MF-BIA to avoid dehydration, and the dry weight of control group was determined clinically. Ambulatory blood pressure, anti-hypertension medication dosage, serum biochemical parameters, and RRF were recorded monthly. IL-6 and hs-CRP will be checked before and after the study.

Results: 93 stable PD patients (48 in study and 45 in control group) completed the study. ECW/TBW ratio was higher in PD patients than sex- and age- matched healthy subjects. (Figure 1). In PD patient, the ratio of ECW/TBW was positive correlated to age (r = 0.334), peritoneal D/P ratio (r = 0.318), systolic BP (r = 0.526) and negative correlated to urine volume (r = -0.526), serum albumin (r = -0.658). After 6 months intervention, study group decreased 1.2 kg and control group gained 0.2 kg. The study group had a better systolic and diastolic BP control and a higher serum albumin (3.75 ± 0.61 vs 3.48 ± 0.68 g/dl, p = 0.047). The RRF has no difference between two groups.

Conclusions: Our results showed that correction of fluid overload would improve blood pressure control. Being an objective tool to assess hydration status of various body compartments, MF-BIA is a useful adjunct to correct fluid overload without the loss of RRF in our short-term study.

PO0990
Associations Between Loop Diuretic Use and Outcomes Among Patients Treated with Peritoneal Dialysis
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Background: Among hemodialysis patients, an active loop diuretic prescription at the time of dialysis initiation is associated with a lower hospitalization rate and other favorable outcomes, compared to no prescription. Whether this finding extends to patients initiating peritoneal dialysis (PD) is not known.

Methods: Data used for this retrospective study comprised electronic health records and US Renal Data System claims data merged through direct linkage. Included patients initiated PD at a large dialysis organization between 01 Jan 2006 and 30 June 2014, were nonoliguric at dialysis start (24-hour urine collection >200 cc), and had Medicare insurance. Exposure was determined on the basis of an active, filled supply for a loop diuretic spanning day 90 of PD. Outcomes were considered from day 91 of PD through the time of dialysis initiation is associated with a lower hospitalization rate and other favorable outcomes, compared to no prescription. Whether this finding extends to patients initiating peritoneal dialysis (PD) is not known.

Results: Among patients initiating PD with a loop diuretic prescription (N=792), the hospitalization rate during follow-up was 1.77 admissions/patient-year (pt-yr), compared to 1.75 pt-yr for those without (N=1363), corresponding to an adjusted incidence rate ratio (aIRR) of 1.05 (95% confidence interval [CI] 0.97-1.15). Mortality was likewise comparable between groups, with crude rates of 0.21 and 0.18 deaths/pt-yr, respectively (aIRR 1.05, 95% CI 0.82-1.35). No substantial differences were observed between exposure groups with respect to serum potassium, renal K/V, or time to transition to hemodialysis.

Conclusions: Among patients initiating PD, no beneficial associations were observed between loop diuretic use and any of the outcomes examined.
Identifying Peritoneal Dialysis (PD)-Associated Peritonitis Using Medicare Claims

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Background: Medicare fee-for-service (FFS) claims offer a population-based approach to PD-associated peritonitis that may offer valuable insights into predictors, trends and preferred practices.

Methods: We used United States Renal Data System (USRDS) standard analysis files for claims (inpatient, outpatient and physician-supplier), eligibility, modality and demographic information. The sample consisted of PD patient-months from 2013 through 2017 characterized by Medicare FFS coverage and paid claims for dialysis or hospital services. We identified ICD-9 and ICD-10 diagnosis codes for peritonitis, including those that do not clearly distinguish peritonitis from catheter infections/inflammation (“catheter codes”). A new peritonitis episode was defined as a peritonitis claim >30 days from any prior peritonitis claim or 30 days from the initial peritonitis claim for a prior episode.

Results: The sample included 88,396 adult patients (128,000 observed patient-years), yielding 510,000 peritonitis claims and 75,000 peritonitis episodes. Coding was heterogeneous with no single diagnosis code present on the majority of claims. Peritonitis episodes were inferred from aggregated claims (mean 6.3, median 2). Half of episodes were exclusively outpatient, 7% exclusively inpatient, and 16% exclusively comprised of catheter code claims. The overall peritonitis rate was 0.59 and 0.49 episodes per patient-year with and without inclusion of catheter codes respectively. Peritonitis rates declined by 4%/year from 2013-2017, and varied by age, race (Black < White = Asian), and ESKD vintage.

Conclusions: Coding heterogeneity indicates a lack of standardization and need for clearer coding guidance. We found differences between races, ages, and patient vintages, and declining rates from 2013-2017. These rates are 2-fold higher than reported in US-PDOPPS by Perl et al (AJKD 2020) which is not restricted to Medicare. Claims are an important data source for peritonitis, but more work is needed to validate these rates.

Funding: Other NIH Support - Agency for Healthcare Research and Quality

PO0994

Protective Association Found Between Peritoneal Dialysis Patients Prescribed Home Antibiotics Kits and In-Center Hemodialysis Transition

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Background: Peritonitis is a complication of peritoneal dialysis (PD) and is likely associated with technique failure. To decrease time to peritonitis treatment, Fresenius Kidney Care (FKC) clinicians can prescribe broad-spectrum intraperitoneal and oral antibiotic kits. Kits are self-administered by home PD patients for suspected wet contamination or peritonitis per algorithm. The study purpose is to assess hemodialysis (HD) transition as well as peritonitis among PD patients receiving a home antibiotic kit.

Methods: This retrospective cohort study identified FKC PD patients prescribed home antibiotic kits between June 1, 2019 and June 30, 2020. Home FKC PD patients not receiving kit during same period composed the control pool. Patients are matched in a 1:4 ratio on clinical and demographic data using propensity scores. Patients were followed up to 6 months for transition to HD and first peritonitis event. Outcomes were analyzed with weighted competing risk Cox Proportional Hazards Models.

Results: 2,888 treatment and 10,613 controls were studied. Of the 2,888 treatment patients and weighted 1,921.2 matched controls, 11.9% and 13.5% transitioned to HD, respectively. A 0.88 hazard ratio (p=0.0448) determined treatment group is 12% less likely to transition to HD at any point during follow-up period. 10.4% treatment patients and 8.5% controls have at least one peritonitis event. The treatment group is 23% more likely to have a Peritonitis event (p=0.0019).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: The study identified a protective association in HD attrition for home PD patients receiving peritonitis kits despite a positive association between patients receiving the kits and peritonitis. This finding may reflect residual confounding factors such as clinicians prescribing kits for patients at higher risk of peritonitis for uncontrolled or unmeasurable factors since kits do not prevent peritonitis but increase uniformity of treatment. The findings justify need for further research including prospectively randomized studies.

Funding: Commercial Support - Fresenius Medical Care

PO0995

Assessing Physician Clinic Practices and Competencies in Performing Peritoneal Dialysis Catheter Flushes During the 10-Day Global Period

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Background: Early flushing of peritoneal dialysis (PD) catheters theoretically reduces the incidence of catheter obstruction by decreasing formation of fibrin strands or blood clots. Early flushing also enables timely identification of catheter dysfunction, creating an opportunity to revise the catheter prior to scheduled training and initiation of therapy. It is unknown how frequently PD access providers perform flushes in their clinics, but Centers for Medicare & Medicaid Services (CMS) has indicated that services performed within 10 days following catheter placement (global period) are the responsibility of PD access providers. Therefore, under existing regulations, dialysis organizations generally defer to access providers to perform catheter flushes during this global period. The purpose of this study is to assess current practices of PD access provider clinics (surgeon, interventional nephrologist or radiologist) in performing catheter flushes.

Methods: PD access providers placing catheters for a large dialysis organization in the southwestern United States during 2020 were surveyed. The 3-question survey asked: 1) PD access provider specialty, 2) if the clinic performed catheter flushes, and 3) the background of the staff person assisting the physician with clinic procedures. Responses were acquired by direct or telephone contact with the physician or clinic staff.

Results: Survey responses were obtained for all 201 providers who placed PD catheters during 2020 (Table).

Conclusions: Significantly, none of the PD access provider clinics elected to perform catheter flushes. This lack of service may indicate a lack of expertise or readily accessible supplies. While PD nurses are trained and equipped by dialysis organizations to competently perform catheter flushes, current regulations generally prevent them from providing these services during the global period. The study supports a re-examination of the CMS policy, suggesting a need for more flexibility for dialysis organizations to provide these services during the global period for patient safety and optimal patient outcomes.

Funding: Commercial Support - DaVita, Inc.

PO0996

Peritoneal Dialysis Catheter Flushing Leading to Syncope from Vagal Nerve Stimulation

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Introduction: Peritoneal dialysis is the most common form of home dialysis. Complications can arise however any time the peritoneum is invaded such as during surgery. The patient is a 37-year-old male on PD secondary to developing progressive IgA nephropathy. The patient suffered from an inguinal hernia which required open repair with mesh placement. This required the patient to be subsequently bridged with HD.

Case Description: After 6 weeks the patient was in the process of beginning to transition back to PD dialysis. The patient underwent flushing of his peritoneal catheter and subsequently developed hypotension, diaphoresis and near syncope. This process continued every time the patient’s peritoneal catheter was flushed. 500 mL’s of 2.5% warm dyesaltate was also attempted to fill the patient resulting in the same near syncopal episode. There was no problem with aspiration of the catheter. There was no resistance involved in suction or flushing. KUB was obtained showing the catheter placed in the left lower pelvis as well as a significant amount of stool burden. Despite aggressive regimen of laxatives the patient continued to suffer from hypotension and near syncope with catheter flushing. The patient was referred for surgery for catheter repositioning. Operative report identified that the tip of the catheter was caught in anterior abdominal adhesions. The catheter was repositioned to the right lower pelvis. After 2 weeks the patient was able to tolerate flushing of his dialysis catheter with progressively increasing fill volumes to the point that he was able to be completely converted back to peritoneal dialysis.

Discussion: It was theorized that catheter tip was uniquely positioned leading to vagal nerve stimulation when liquid was infused through the catheter. This case illustrates a unique complication of catheter malposition and adhesions resulting in near syncope secondary to vagal nerve stimulation. With repositioning of the patient’s catheter the symptoms completely resolved.

Funding: Commercial Support - Fresenius Medical Care

PO0997

Pharmacokinetics of Intraperitoneal Vancomycin in Patients on Automated Peritoneal Dialysis

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Background: It is unclear if the pharmacokinetics of vancomycin is the same during automated peritoneal dialysis (APD) where cycler exchanges may affect the systemic, peritoneal, and urinary disposition of drug.

Methods: This was a prospective pharmacokinetic study in peritonitis-negative patients on APD. A single dose of vancomycin (20 mg/kg) was administered through the peritoneum and allowed to dwell for at least 15 hours. Patients underwent four drug-free exchanges following the initial dwell period. Plasma, dialysate and urine were collected over the course of 7 days for pharmacokinetic analysis. A non-compartmental analysis was used to estimate vancomycin pharmacokinetic parameters.

Results: Four patients enrolled and completed the study with no adverse events. Three patients had residual renal function. Following a median (range) dwell of 14.6 (14.2 – 17.6 hours), the mean (± SD) observed maximum plasma concentration was 28.7 ± 4.9 mg/L with a mean (± SD) bioavailability of 98.5 ± 1.4% prior to starting the cycler. The overall mean plasma clearance estimated from study start to completion was 7.3 ± 1.2 mL/min. In patients with residual renal function, the mean (± SD) vancomycin renal clearance was 3.1 ± 1.5 mL/min.

Conclusions: Despite the small sample size, this pilot study suggests that the dwell time has important implications for systemic vancomycin exposure, time to therapeutic plasma concentration, and dosing. Dose is driven by dwell time while the cycler determines the dosing interval. Rapid exchanges from APD will determine the frequency of dosing rather than the adequacy of absorption when vancomycin is given in the peritoneum.

Funding: Other NIH Support - Edwin Lam was supported by an NIH T32 training grant (GM008562) at the time of study conduct.

Discussion: It was theorized that catheter tip was uniquely positioned leading to vagal nerve stimulation when liquid was infused through the catheter. This case illustrates a unique complication of catheter malposition and adhesions resulting in near syncope secondary to vagal nerve stimulation. With repositioning of the patient’s catheter the symptoms completely resolved.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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PO0998

Effect of Velphoro on Serum Phosphate and Albumin in Peritoneal Dialysis Patients
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Background: Hyperphosphatemia is common in patients on peritoneal dialysis (PD). Restricting phosphorus in the diet often leads to a decrease in protein intake, which may result in hypoalbuminemia. Hypoalbuminemia is associated with an increased risk of morbidity and mortality in PD patients. In observational studies, saccharin cocohydroxide (SO), an iron-based phosphate binder, was associated with improved phosphate control and higher serum albumin in hemodialysis patients. Whether SO improves phosphate control and nutritional status in PD patients is unknown.

Methods: We performed a prospective, open-label, 6-month, pilot study of 17 adult PD patients from the Denver Metro Area. Patients had to use automated peritoneal dialysis for at least 3 months, have a serum albumin ≥ 3.8 g/dL, and have serum phosphate ≥ 5.5 mg/dL or ≤ 5.5 mg/dL on a binder other than SO. Patients currently on phosphate binders underwent a 2-week washout period. Participants were started on SO at a dose of 1 tablet daily with meals. Serum phosphate was checked monthly and the dose of SO was titrated to a goal serum phosphate of < 5.5 mg/dL. The primary outcome was change in serum phosphate and serum albumin over 6 months.

Results: The mean (SD) age and dialysis vintage was 55 ± 13 years and 3.8 ± 2.7 years, respectively. The majority of patients were male (65%), white (82.4%) and non-Hispanic (64.7%). 88% of patients were on a phosphate binder at baseline and the majority were on sevelamer (73%). Twelve patients completed the study. Two patients withdrew due to side effects (diarrhea), 1 patient changed to hemodialysis and 2 patients died (unrelated to the study). Mild diarrhea and change in stool color were the most frequently reported side effects. Results are shown in Table 1. Serum phosphate decreased significantly from baseline but there was no significant change in serum albumin. Phosphate binder pill burden significantly decreased.

Conclusions: Serum phosphate decreased significantly with fewer phosphate binder pills/day after switching to SO. There was no change in serum albumin.

Funding: Commercial Support - Fresenius Renal Therapies

PO0999

Prognostic Significance of Plasma Vaspin and Adiponectin Levels in Peritoneal Dialysis Patients
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Background: Adiponectin and vaspin are key adipokines that play important roles in the physiology of adipose tissue and contribute to the pathogenesis of metabolic disturbance in chronic kidney disease (CKD). We explored the prognostic role of plasma adiponectin and vaspin levels in peritoneal dialysis (PD) patients—a population that metabolic syndrome, obesity, and cachexia are all common.

Methods: We measured plasma adiponectin and vaspin levels in a cohort of new PD patients and analyzed their relation with patient survival.

Results: We studied 152 patients. Their mean age was 58.38 ± 11.67 years; 102 (67.1%) were men, 92 (60.5%) were diabetic. The median plasma adiponectin level was 31.98 (Interquartile range [IQR]: 16.81-49.49) mg/mL; median vaspin level was 0.18 (IQR: 0.01-0.32) ng/mL. There was no significant correlation between plasma adiponectin and vaspin levels. Plasma adiponectin level had modest correlations with Charlson's score (r = 0.174, p = 0.039), triceps skin fold (r = -0.269, p = 0.001), and mass transfer area coefficient of peritoneum (r = 0.211; p = 0.015). In contrast, plasma vaspin level correlated with carotid-to-femoral pulse wave velocity (r = -0.240, p = 0.005), triceps skin fold (r = 0.198, p = 0.018), and extracellular to Intracellular fluid volume ratio (r = -0.170, p = 0.047). After adjusting for clinical confounders, plasma adiponectin and vaspin levels significantly predicted patient survival (adjusted hazard ratio [AHR] of adiponectin 1.018, 95% confidence interval [CI] 1.004-1.031; p = 0.010; AHR of vaspin 1.018, 95%CI 1.008-1.029; p = 0.001).

Conclusions: Plasma adiponectin level also correlated with peritoneal transport status, while plasma vaspin level correlated with the severity of fluid overload and atherosclerosis. Plasma levels of both adiponectin and vaspin are independent predictors of patient survival. Our results suggest that adiponectin and vaspin are involved in different pathways of metabolic disturbance in uremia.

PO1000

The Impact of Peritoneal and Urine Protein Losses on Nutritional Status in Peritoneal Dialysis Patients

Background: The etiology of malnutrition in peritoneal dialysis (PD) patients is multifactorial, but the peritoneal protein losses (PPL) and proteinuria may be important contributing factors. We aimed to evaluate if the total protein losses (into urine and dialysate) in PD patients have an impact on their nutritional status.

Methods: A retrospective observational study of PD patients over the first year in PD. Demographic, clinical, and analytical data were collected at baseline (time of PD initiation), 6 and 12 months later. Nutritional status was assessed using normalized protein catabolic rate (nPCR), body mass index (BMI), lean body mass (LBMI), and body fat mass (BFM). The total amount of 24h urine and dialysate protein losses (ProtUrDial) and delta (Δ) values (difference between the end of follow-up period and baseline) of continuous variables were also calculated.

Results: Twenty patients were enrolled (55.8±10.8 years; 65% male). Except for serum albumin (AaB), which changed significantly from the baseline to the end of the follow-up period (p=0.001), there were no differences in protein loss into dia lyse (ProtDial), proteinuria (ProtUrine), nPCR, BMI, LBMI, and BFM over time. In the 3 time points there was a significant positive correlation between ProtUrine and nPCR (r=0.563, p=0.01; r=0.584, p=0.031; r=0.611, p=0.004, respectively). At the end of the follow-up period, we verified a negative correlation between AaB and ProtUrDial (r=-0.420, p=0.033). There was no correlation between ProtDial and nutritional parameters status, however, there was a positive correlation between ΔProtUrine and ΔBMI (r=0.492; p=0.028). Regarding ΔProtUrDial, we verified a negative correlation with ΔBMI (r=-0.664; p=0.026) and, although not significant, a positive correlation with Δ%BFM (r=0.573; p=0.066).

Conclusions: The PPL has already been linked to malnutrition in PD patients. However, we found that the total amount of protein losses daily (into urine and dialysate), and not each one individually, seems to influence the nutritional status of PD patients. Besides, proteinuria appeared to have a greater impact on nutritional changes than peritoneal losses. However, more studies with larger samples are needed to clarify this association.

Funding: Clinical Revenue Support
Peritoneal Dialysis

PO1002
Psychosocial Impact of COVID-19 Pandemic on Patients with ESKD on Peritoneal Dialysis

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Introduction: Increased intra-abdominal pressure is a well-recognized non-infectious complication of peritoneal dialysis (PD) resulting from instillation of dialysate fluid into the peritoneal cavity. Peritoneal-pleural communication causing hydrothorax is well-described in the literature, but cases of peritoneal-pleuromedial communication are scarce.

Case Description: A 36-year old Caucasian man with end-stage kidney disease secondary to calcineurin inhibitor nephrotoxicity and BK virus nephropathy transitioned to continuous cyclic peritoneal dialysis (CCPD) after one year of intermittent hemodialysis (iHD). He presented to our institution nine months after starting CCPD primarily because of complications related to prior heart transplantation. He underwent cardiac surgery and did not have any problem with his CCPD in the immediate post-operative period and was discharged. One month later, however, he presented with increased serum drainage from his sternal incision site and reduced ultrafiltration. A chest CT scan revealed a partially loculated anterior chest wall subcutaneous fluid collection. He was taken to the operating room and was found to have a peritoneal-pleural-medial communication. He was successfully managed with “low-pressure” PD by using reduced fill volumes for all his exchanges, which also allowed optimal healing of the muscle flap closing the communication. Transition to iHD was considered, but he had no vascular access options because of multiple prior thromboses. He was able to subsequently return to his outpatient PD in four months after his surgery by doing very gentle up titration of his fill volumes. Unfortunately, one and a half months after his last hospitalization, he succumbed to septic shock secondary to trans-lumbar PICC-associated Candida glabrata fungemia.

Discussion: A peritoneal-pleural-medial communication should be suspected in an otherwise asymptomatic patient on PD with reduced ultrafiltration who underwent any form of chest surgery. Clinical suspicion can be confirmed either through CT peritoneography or intraoperatively. Management with a trial of “low-pressure” PD is feasible and can be successful, particularly if iHD is not an option. A multi-disciplinary approach involving our surgical colleagues is also crucial to ensure appropriate patient care.

PO1003
Peritoneal-Mediastinal Communication Complication in Peritoneal Dialysis

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Introduction: The mortality rate from COVID-19 is remarkably high in elderly patients and those with chronic conditions. Increases in physical and mental stress among patients with chronic conditions, especially end-stage kidney disease, were expected to have a notable increase in response to the COVID-19 pandemic. This study reports that the psychosocial impact of the COVID-19 pandemic on patients receiving peritoneal dialysis is significant.

Methods: During the pandemic, we surveyed the mental health of patients with end-stage kidney disease on peritoneal dialysis at a single center. Depression using with BDI scoring was evaluated and then compared in peritoneal dialysis patients between before and the pandemic declaration. We also surveyed patient satisfaction with the self-care services associated with peritoneal dialysis under the pandemic period.

Results: One-third of the survey respondents (n=176) were moderately to extremely worried about their physical health being impacted by the pandemic, while 20% moderately to extremely worried about their mental and emotional health being impacted. About half of participant reported feeling that they were unable to handle their personal problems and that things were out of their control. However, most felt that they could retain control over the important things and overcome their difficulties. Despite COVID-19 pandemic, no significant changes in depression scores were apparent between before and during the pandemic. Most participants were satisfied with the in-home self-care services delivered by either telephone or remote monitoring.

Conclusions: Many participants reported that they were afraid of COVID-19, but most patients with PD felt that they could overcome the crisis. The COVID-19 pandemic did not affect the depression of patients receiving peritoneal dialysis.

PO1004
Sweet Pleural Effusion in a Peritoneal Dialysis Patient

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Introduction: Pleural Effusions are frequently seen in dialysis patients with an incidence as high as 80%, with a variety of possible differential etiologies.

Case Description: A 62-year-old female with HFpEF, DM and ESRD due to biopsy proven diabetic nephropathy recently started on nightly continuous cyclic PD with a prescription of 4 exchanges of 2.5% Dextrose solution with 2 liters fill volumes with a dwell time of 1840 min for a total time of 8.5 hrs with no day dwells presented with dyspnea. She had missed 2 sessions of dialysis and noted increasing weight as declining ultrafiltration volumes. On exam tachypneic on 4L of oxygen and saturating 100%, a dwell time of 1h40 min for a total time of 8.5 hrs with no day dwells presented with prescription of 4 exchanges of 2.5% Dextrose solution with 2 liters fill volumes with a dwell time of 1840 min for a total time of 8.5 hrs with no day dwells presented with dyspnea. She had missed 2 sessions of dialysis and noted increasing weight as declining ultrafiltration volumes. On exam tachypneic on 4L of oxygen and saturating 100%, had decreased breath sounds on the right primary pulmonary lobe or lower extremity.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

PO1005
Progression of Left Ventricular Mass Index After Peritoneal Dialysis Initiation: A Potential Killer

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Background: Left ventricular hypertrophy (LVH), defined by the left ventricular mass index (LVMI), is highly prevalent in dialysis patients. LVMI has been widely accepted as a strong predictor of cardiovascular events. However, the dynamic changes of LVMI are rarely discussed, especially among peritoneal dialysis (PD) patients. The study aimed to investigate the prognostic significance of LVMI-progression in PD patients, and explore risk factors for LVMI-progression.

Methods: It was designed as a prospective, observational study. Incident PD patients between February 2008 and July 2018 were recruited. Echocardiography was performed yearly to collect LVMI and evaluate its progression. Participants were divided into two subgroups: group with LVMI-progression and group without LVMI-progression. The end points include all-cause mortality, cardiovascular mortality and cardiovascular events. Cox regression models were performed to identify the associations between LVMI-progression and these endpoints. Multivariate logistic regression was conducted to identify factors associated with LVMI-progression.

Results: A total of 216 PD patients (130 men,60.2%) with a mean age of 54.3±16.7 years were recruited. LVMI-progression was identified in 65 patients (30%) after PD initiation. The cohort was followed for a median duration of 65.9 months. Multivariable Cox regression analysis revealed that LVMI-progression was an independent predictor of all-cause mortality (HR, 2.111; 95% CI, 1.485–3.881; p = 0.016), cardiovascular mortality (HR, 2.785; 95% CI, 1.581–4.741; p = 0.023), and cardiovascular events (HR, 1.869; 95% CI, 1.016–3.439; p = 0.044). Multivariable logistic regression showed that hemoglobin (OR, 0.967; 95% CI, 0.939–0.996; p = 0.027), ferritin (OR, 0.995; 95% CI, 0.992–0.999; p = 0.007) and mean arterial pressure (MAP) (OR, 1.048; 95% CI, 1.001–1.097; p = 0.043) were significantly associated with LVMI-progression.

Conclusions: LVMI-progression after PD initiation was independently associated with all-cause mortality and cardiovascular outcomes in PD patients. The dynamic monitoring of LVMI might therefore help identify high-risk patients early. Further studies are needed to clarify whether treatment interventions for factors such as anemia could improve patient outcomes.

PO1006
Estimation of Residual Kidney Function with Serum Levels of β2-Microglobulin in Peritoneal Dialysis

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Background: Residual kidney function (RKF) is defined as the kidney function in patients with end-stage renal disease (ESRD) who are receiving dialysis. The ideal method to evaluate and measure RKF is still uncertain and the estimated glomerular filtration rate (eGFR) and urea clearance may over- and underestimate RKF, respectively. β2-microglobulin (β2M) is an 11818 Da protein freely filtered and metabolized in kidney...
PO1007

A Rare Case of Roseomomas gilardii Peritonitis in a Peritoneal Dialysis Patient

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Introduction: We report a case of Roseomonas gilardii peritonitis in a continuous ambulatory peritoneal dialysis patient.

Case Description: A 71-year-old woman with end stage renal disease (ESRD) on continuous ambulatory peritoneal dialysis (CAPD) for 5 years presented with cloudy effluent without abdominal pain or fever. Laboratory studies revealed a fluid cell count of 800 wbc/mm³ with 87% neutrophils. She was started on empiric antibiotic therapy with intraperitoneal vancomycin and cefazolin. Effluent remained cloudy with elevated WBC despite a 2-week course of antibiotics. Eventually culture grew Roseomonas gilardii, a slow growing gram-negative bacillus sensitive to amoxicillin. Her antibiotic was changed to IP gentamycin and her effluent cleared by day three. Gentamycin is a slow growing gram-negative bacillus sensitive to aminoglycosides. Her antibiotic was changed to IP gentamycin and her effluent cleared by day three.

Discussion: Peritoneal dialysis peritonitis is known to be caused mainly by gram positive and occasionally gram-negative organisms, the usual culprits being pseudomonas, klebsiella etc. Roseomonas has recently been implicated as a rare cause of bacterial peritonitis with only six reports between 1997 till date. It was first described in 1993 as a cause of bacteremia in humans. Roseomonas gilardii is a pink-pigmented, oxidized, gram-negative cocacobacillus genus of Roseomonas associated with contaminated water source and soil. Our patient was unaware of being in contact with contaminated water or soil however this could not be ruled out as she did endorse having plants. Of the six cases reported, ours is the third case of R. gilardii reported till date. Although the incidence of peritoneal dialysis peritonitis caused by Roseomonas gilardii is rare, it is causative agent to be considered by physicians and laboratory staff in the differential diagnosis of refractory bacterial peritonitis in peritoneal dialysis patients. It also serves as a point to emphasize when educating PD patients on the hand-washing techniques and ensuring sterility of water source used for this.

PO1008

Unusual Cause of Recurrent Shortness of Breath in a Peritoneal Dialysis Patient

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Introduction: Pleuropertitoneal leak (PLL) is an unusual cause of recurrent pleural effusion in patients on peritoneal dialysis (PD). It is a rare complication and occur in less than 2% of cases. Diagnosis is challenging and requires high clinical suspicion and awareness of this life threatening complication. Pleural fluid to serum glucose ratio of >30 mg/dl is highly specific for detecting leak of high glucose dialysate into pleural cavity, however this needs to be interpreted in relation with the last dialysis session.

Case Description: A 72 year-old-female with history of end stage renal disease due to biopsy proven focal segmental glomerular sclerosis thought to be secondary to obesity started on CCPD one-month prior presented with worsening shortness of breath of 1 week duration. Workup was unremarkable except for chest-X-ray that showed right side pleural effusion. A non-contrast CT chest did not show a diaphragmatic defect. She continued to have worsening SDB prompting an emergent thoracentesis that drained 1.6 L transudate pleural fluid. Pleural fluid to serum glucose gradient was normal at 5 mg/dl but pleural fluid to serum glucose ratio was >1. However, last PD session was 2 days prior to thoracentesis, which could explain this lower ratio. Due to inconclusive results, it was decided to instill 30 ml of pleurolytic solution into the pleural cavity. It showed interval re-accumulation of high-density pleural effusion, suggesting trans-diaphragmatic communication. Cardiothoracic surgery was consulted for repair of diaphragmatic defect; however, patient opted for hemodialysis instead.

Discussion: It is important to maintain high clinical index of suspicion in PD patients presenting with hydrothorax. Although high pleural fluid to serum glucose gradient is specific for PLL, pleural to serum glucose ratio >1 is another index that should be considered in addition to post-gastrogafin imaging or technetium 99m peritoneal scintigraphy, especially if the diagnosis was not recent and could potentially alter the biochemical assay results as happened in our case. Most cases of PLL occur soon after PD initiation, common on right side. For those who wish to continue PD, surgical repair is often required while transitioning to HD temporarily or doing low volume recurrent PD. Some case series have noted the defect to close spontaneously after holding PD.

PO1009

The Association Between Lower Serum Potassium Level and Increased Cardiovascular Death Among Patients Undergoing Peritoneal Dialysis

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Background In patients undergoing peritoneal dialysis (PD), lower serum potassium concentration has been related to low nutrition status and suggested as a risk factor for all-cause and cardiovascular mortality. However, the risk of lower serum potassium concentration for cardiovascular death in patients using renin-angiotensin system (RAS) inhibitors or β-blockers is not clear. This study investigated the relationship between lower serum potassium concentration and cardiovascular death among Japanese patients undergoing PD.

Methods: We retrospectively included the 549 patients from our previous multicenter cohort study (Fukuoka Peritoneal Dialysis Database Study). The participants who had undergone PD for at least 90 days were registered from 1 January 2006 to 31 December 2016 and followed until they were transferred to hemodialysis, received a kidney transplantation, died during PD, or were lost to follow-up, or until 31 December 2017. The patients were divided into three groups according to the baseline serum potassium concentration: T1 (≤ 4.0, 4.0 < T2 ≤ 4.5, T3 > 4.5 mEq/L). We estimated the relationship between serum potassium concentration and cardiovascular mortality using a Cox proportional hazards model.

Results: During the median observation period of 2.3 years, 111 patients died of any cause, and 38 died of cardiovascular. After multivariable adjustment in the Cox proportional hazard model, lower serum potassium concentration was shown to be an independent risk factor for cardiovascular death; (hazard ratio 95% confidence intervals) T2 and T1 vs. T3 were 2.21 (1.77–2.67) and 2.67 (1.91–3.70), respectively. Stratified-analysis according to the use of RAS inhibitors, β-blockers, or a combination of both drugs showed that this relation was not modified by the use of these drugs.

Conclusions: This study showed that lower serum potassium concentration was associated with increased cardiovascular mortality in PD patients. There was no difference in the risk of lower serum potassium concentration for cardiovascular death according to the use of the RAS inhibitors and/or β-blockers in PD patients.
PO1010

Higher Serum Total Cholesterol to High-Density Lipoprotein Cholesterol Ratio Was Associated with Increased Mortality Among Incident Peritoneal Dialysis Patients

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Background: A few studies have shown that serum total cholesterol to high-density lipoprotein cholesterol ratio (TC/HDLC) was a risk factor for cardiovascular mortality in the general populations. This study aimed to evaluate the association of TC/HDLC with mortality in incident peritoneal dialysis patients.

Methods: We enrolled Total of 6,30 incident peritoneal dialysis patients from 2008 to 2015 in a multi-center, prospective cohort study of Korea. Participants were stratified into quintiles according to the baseline TC, HDL-C, or TC/HDLC. The association between all-cause mortality and each lipid profile was evaluated using multivariate Cox regression analysis.

Results: During a median follow-up period of 70.3 ± 25.2 months, 185 deaths were recorded. The median TC/HDLC was 4.54 ± 2.51. Highest TC/HDLC group showed highest body mass index, percentage of diabetes, and serum albumin level. Multivariate analysis revealed that the highest quintile of the TC/HDLC (≥5.60) was associated with increased risk of all-cause mortality (hazard ratio 1.69, 95% confidence interval 1.04 to 2.76; P = 0.036), whereas neither of TC and HDL were associated with mortality. Increased serum TC/HDLC was also independent risk factor for mortality in the patients with old age over 50 years, non-diabetes, and any cardiovascular disease.

Conclusions: The single lipid marker of TC or HDL-C could not predict mortality in PD patients. However, non-traditional lipid profile such as increased serum TC/HDLC ratio was independently associated with an increased risk of all-cause mortality in PD patients.

PO1011

Peritoneal Dialysis Caregiver Scope and Functions: A Systematic Scoping Review

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Background: Caregivers play important roles in peritoneal dialysis (PD) care. Classifying PD self-care tasks is important for determining the PD caregiver roles. As the scope and functions of PD caregiver in published literature have been inconsistent, we aimed to systematically explore the variations of the term caregiver in high-quality PD studies.

Methods: We performed a systematic search using PubMed, Embase, and CENTRAL for randomized controlled trials and observational studies relevant to a caregiver in ESRD with PD studies.

Results: Of 2,514 potential studies relevant to a caregiver in ESRD patients with PD, 299 theme-related abstracts were selected for further full-text articles screening against eligibility criteria, and 111 were included in the systematic review (72,101 patients in 34 countries). In terms of word choice, “caregiver(s)” was used in 86.4%, “care-taker(s)” in 20.7%, and other words were used in 13.5% of included studies. Only 8.1% of studies gave the explicit definitions of those words. The most referred person is the parents (40.5%), followed by a spouse (37.8%), other family members (37.8%), children (34.2%), non-relative non-healthcare workers (25.2%), friends (20.7%), and healthcare workers (19.8%). The explanation of functions for each word comprises 41.4%, with the PD-related functions explained in p96% (p<0.001) in both in vivo models. Disturbed autophagy flux also observed in human vein samples collected during new AVF creation. In vitro model showed dysregulation of autophagy flux in disturbed flow, as compared to laminar flow.

Conclusions: Our in vivo and in vitro studies both demonstrated that autophagy response may play an important role in vessel remodeling in the setting of disturbed flow as seen in AVFs. Autophagy may be a potential target to improve AVF maturation.

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Underline represents presenting author.

PO1012

Autophagy Response and Arteriovenous Fistula Maturation

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Background: Arteriovenous fistula (AVF) are the preferred vascular access for hemodialysis. AVF creation results in disturbed blood flow within the AVF anastomosis. The objectives of this study were to: 1. Characterize autophagy flux after AVF creation, and during the remodeling process, 2. Use an in vitro model to evaluate autophagy status during the laminar and turbulent flow.

Methods: Femoral AVFs were created in male rats. Yorkshire pigs were used to create carotid artery-jugular vein AVF. Autophagy flux was evaluated after 1 hour and 7 days. AVF and contralateral vessels were harvested for histology and Western blot (WB). Autophagy-related proteins were analyzed in the AVF human vein samples. Effects of hemodynamic changes were investigated by utilizing an in vitro model. Human umbilical vein smooth muscle cells and endothelial cells were co-cultured in the vessel-like system under laminar or disturbed flow conditions. After 24 hours, cells were harvested for histology and WB.

Results: In the rat model impaired autophagy flux was observed in the vein 1 hour after AVF creation. At day 7 expression of ATG3 and ATG7 protein was significantly higher (p<0.003) in the AVF vein compared to contralateral control. Significant increases in p62 expression was detected in 7 days AVF vein (p<0.001) in both in vivo models. Disturbed autophagy flux also observed in human vein samples collected during new AVF creation. In vitro model showed dysregulation of autophagy flux in disturbed flow, as compared to laminar flow.

Conclusions: Our in vivo and in vitro studies both demonstrated that autophagy response may play an important role in vessel remodeling in the setting of disturbed flow as seen in AVFs. Autophagy may be a potential target to improve AVF maturation.

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Methods: An end-vein to side-artery AVF was surgically created in the femoral vessels of rats which had previously been subjected to uremia via subtotal nephrectomy. At 1 and 2 weeks after AVF formation the arterial and venous limbs of the AVF were harvested for the assessment of gene and protein expression and the assay of SA-β-Gal activity. Femoral veins and arteries from rats subjected to sham surgery were used as controls.

Results: At 1 week after AVF creation mRNA levels of senescence drivers p16 and p21 were markedly elevated in AVF veins compared to sham veins, as were p21 protein levels; the AVF artery also displayed elevated p21 protein levels at this time point. At 2 weeks, p21 protein was again upregulated in both the vein and artery of the AVF, and protein levels of an upstream mediator in the p21 senescence pathway, p53, were significantly increased in the AVF artery; p53 levels did not achieve significance (p=0.083) in the AVF vein at this time point. Upregulation of SASP factors was also observed in the AVF vein at 1 week: mRNA expression of PAI-1, IL-6, TNF-α and MCP-1 was robustly increased as compared to sham veins at 1 week after AVF creation. Additionally, miR21, which has been associated with vascular senescence, was markedly elevated in the AVF vein at 1 week post AVF placement. Finally, SA-β-Gal activity, an established marker of senescence, was significantly increased in both the artery and vein compared to their sham counterparts at both 1 and 2 weeks post AVF surgery.

Conclusions: Using established criteria, this study demonstrates that the rat femoral AVF in the setting of CKD has a senescence phenotype similar to the murine AVF-CKD model. These findings thus demonstrate the development of senescence in another species subjected to an AVF in the presence of uremia.

Funding: NIDDK Support

PO1014

The Adaptive Response of the Vein to CKD: A Transcriptomics Perspective

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Background: The impact of CKD on gene expression in the vascular wall remains unknown, particularly in veins, despite their fundamental role as conduits for hemodynamics.

Methods: In this study, we investigated the CKD fingerprint on the transcriptome of basilar veins by analyzing 48 pre-access veins from end-stage renal disease patients and 20 veins from non-CKD trauma donors by bulk RNA sequencing.

Results: We uncovered 16,893 differentially expressed genes (DEG) between CKD and control individuals (log Fold Change ≥1, FDR <0.05). The presence of kidney disease caused a noticeable decrease in transcriptional activity in veins, with the downregulation of ≥97% of DEG transcripts. These included 6,081 non-coding RNAs, 3,826 protein-coding genes, and the rest to minor RNA biotypes. Gene set enrichment analysis (GSEA) identified a suppression of pathways related to vascular maintenance, cell morphogenesis, cell metabolism, and microtubule-based cytoskeletal functions. Interestingly, the protein-coding genes upregulated in CKD veins belonged to processes related to gas transport and detoxification of oxidative stress byproducts.

Conclusions: In conclusion, we have uncovered a profound suppressive effect of CKD on the venous transcriptome, likely affecting basic cell functions such as metabolism, cell division, and migration. We also identified a transcriptomic signature of upregulated genes in response to oxidative stress which may play a fundamental role in cell survival in the CKD environment.

Funding: NIDDK Support, Other NIH Support - NHLBI, Veterans Affairs Support

PO1016

Inhibition of Phosphodiesterase Type 5A Prevents Pathological Cardiac Remodeling Following Arteriovenous Fistula Creation

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Background: Cardiac events are the most common etiology of mortality in hemodialysis patients. The gold standard of vascular access, the arteriovenous fistula (AVF), may adversely affect cardiac structural and functional remodeling leading to heart failure. We hypothesize that inhibition of cGMP catalysis with a selective phosphodiesterase type 5A (PDE5A) inhibitor, sildenafil, may induce more favorable cardiac remodeling following AVF creation.

Methods: Sildenafil was administered to 12-16 weeks old Sprague-Dawley rats two weeks prior to AVF creation and continued until sacrifice at 28 days. Cardiac structural and functional changes were evaluated by 1) 2D-echocardiography 2) measurement of collagen volume and oxidative stress and 3) evaluation of cardiomyocyte cytoskeletal-mitochondrial architecture.

Results: Sildenafil treatment significantly improve pathologic collagen degradation, reduces HNE4 expression, reverse desmin degradation and focal mitochondrial clustering following AVF creation, as compared to the control. We also observed a significant increase in cardiac output and stroke volume without reversing LV dilation which may suggest improvement in cardiac contractility.

Conclusions: PDE5A inhibition may provide a new treatment strategy for pathological cardiac remodeling following AVF creation.

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PO1017

Pre-Access Vein Transcriptomics as a Predictor of Arteriovenous Fistula Failure: A Machine Learning Approach

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Background: As the number of patients with end-stage renal disease continues to rise, the creation of a robust and efficient hemodialysis access is more important than ever. A mature arteriovenous fistula (AVF) is the preferred method for long-term hemodialysis. However, the nationwide maturation rate continues to be as low as 50-60%, and we currently lack an effective risk stratifying method to identify patients at higher risk of AVF failure.

Methods: To address this clinical need we developed a predictive model based on supervised machine learning from transcriptomics of the pre-access vein. Forty-eight pre-access veins obtained at the time of AVF creation (24 matured and 24 failed postoperatively) were randomly selected from the University of Miami Vascular Biorepository and submitted for bulk RNA sequencing. Both outcome groups were matched by age, sex, demographics, and baseline characteristics. The highest expressing genes (normalized gene expression counts >200) were used as input in KNNS, SVM, XGBoost, and other machine learning algorithms. Area under the curve (AUC) and receiver-operating characteristic (ROC) plots were used to compare the performance of the models relative to each other. The best performing algorithm, XGBoost, was optimized with the following hyperparameters [gamma=0.25, learning_rate=0.001, max_depth=4, reg_lambda=10, scale_pos_weight=3]. The SHapley Additive exPlanations (SHAP) analysis was then used to evaluate the highest contributing features to the XGBoost model.

Results: Ten highly predictive and abundantly expressed genes were identified using this methodology (RLIC, CLIC5, DNAL1, FOXO4, TIMMDC1, GALNT11, CDH13, KLHDC10, ZNF8, and DBT). Using these transcripts, the AUC in the logistic regression model is 97.6%.

Conclusions: In conclusion, this study has identified 10 potential pre-access gene predictors of postoperative AVF failure, which could be used clinically as a stratifying or risk management tool in vascular access patients.

Funding: NIDDK Support, Other NIH Support - NHLBI, Veterans Affairs Support

PO1018

Arteriovenous Fistula Non-Maturation: Does the Immune System Play a Role?

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Background: Arteriovenous fistula (AVF) non-maturation is a persistent problem, particularly among female and Black patients. The immune system promotes several vascular disease processes, but its contribution to AVF non-maturation has not been well-studied. We evaluated the association of serum panel reactive antibodies (PRA), a measure of immune system reactivity assessed in patients undergoing kidney transplant evaluation, with AVF non-maturation.

Methods: We identified 132 patients at our institution who underwent surgical AVF creation between 2010-2019 and had PRA testing within one year of AVF creation. Multivariable logistic regression was used to determine the association of patient demographic, clinical, and vascular factors with AVF maturation. Receiver operator characteristic (ROC) curves were generated to determine the predictive value of key variables on AVF non-maturation.

Results: AVF non-maturation was more common in females than males (44% vs 20%, p=0.003) and in Black than white patients (40% vs 13%, p=0.001). Class II PRA was higher in females than males (12% vs 4% vs 13%, p=0.02), but did not differ by race. In the multivariable model, AVF non-maturation was associated with class II PRA (adjusted odds ratio [aOR] 1.34 per absolute 10% increase; 95% confidence interval [CI], 1.04 to 1.82, p=0.02) and Black race (aOR 3.34, 95% CI, 1.02 to 10.89, p=0.03). An ROC curve using seven key variables (Table 1 and Figure 1) showed an area under the curve of 0.73 (95% CI, 0.63 to 0.82, p=0.0001).

Conclusions: The novel association of elevated class II PRA with AVF non-maturation suggests a role for the immune system in AVF maturation outcomes, especially for female patients.

Table 1. AOR of 7 key variables for AVF non-maturation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per 10 yr increase</td>
<td>1.09</td>
<td>0.98 to 1.21</td>
<td>0.14</td>
</tr>
<tr>
<td>Race, Black or African American</td>
<td>1.63</td>
<td>1.08 to 2.48</td>
<td>0.02</td>
</tr>
<tr>
<td>Preoperative arterial diameter, per 1 mm increase</td>
<td>0.80</td>
<td>0.60 to 1.06</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Figure 1. ROC curves.

PO1019

Functioning Tailor-Made 3D-Printed Vascular Graft for Hemodialysis: A Proof-of-Concept In Vivo Study

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Background: The two ends of arteriovenous graft (AVG) are anastomosed to the upper limb vessels by surgery for hemodialysis therapy. However, the size of upper limb vessels varies to a large extent among different individuals. With advances in three-dimensional (3D) printing technology, it is now possible to realize tailor-made AVG for personalized surgery. In this study, we aim to investigate the function of 3D-printed AVGs in vivo.

Methods: The computed tomography angiographic scan of the rabbit neck was performed before the surgery. According to the shape and size of neck vessels, an H-shape AVG was produced by the 3D printer and then sterilized. The 3D-printed AVG was trimmed and inserted in the rabbit’s common carotid artery and common jugular vein.

Results: The tailor-made 3D-printed AVGs can be implanted in the rabbit’s neck vessels with ease and function in vivo. The surgical procedure was quick, and no suture was required. The blood loss was minimal, and no hematoma was noted at least one week after the surgery. The blood flow velocity within the implanted AVG was 14.9 ± 3.7 cm/ sec.

Conclusions: Through the 3D printing technology, the AVG can be tailored to fit the specific vessel size. This kind of 3D-printed AVG is functioning in vivo, and our results realize personalized vascular implants. Further studies conducted in large animal models are warranted to validate our promising results.

Funding: Government Support - Non-U.S.
POI021
The Association of Transition-to-Dialysis Planning and Healthcare Resource Use and Mortality in Patients with ESRD
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Background: The onset of ESRD is associated with poor outcomes and high mortality, and the role of transition-to-dialysis planning is not well understood. We evaluated the association between dialysis transition planning factors such as nephrologist care, vascular access placement, and place of index dialysis, with inpatient (IP) stays, emergency department (ED) visits, and mortality.

Methods: This retrospective study used the Humana Research Database to identify 7,026 patients, 19-89 years of age, diagnosed with ESRD between 1/1/17 and 12/31/17, enrolled in a Medicare Advantage Prescription Drug plan, with ≥12 months of continuous enrollment pre- and post-index date (i.e., first evidence of ESRD). Patients with a kidney transplant indication, hospice election, or dialysis pre-index were excluded. Transition-to-dialysis planning was defined as optimal, partial, or unplanned (Table 1). IP stays, ED visits, and mortality were evaluated within 12 months post-index.

Results: The cohort was 41% female, 66% White, with an average age of 70 years. An optimally planned, partially planned, and unplanned transition to dialysis occurred for 15%, 34%, and 44% of the ESRD cohort, respectively. Among patients with pre-index CKD stages 3a and 3b, 64%, and 55%, respectively, had an unplanned dialysis transition. For patients with pre-index CKD stages 4 and 5, 68% and 84%, respectively, experienced planning prior to dialysis initiation. In adjusted models, patients with partially or optimally planned transition to dialysis were 57% to 72% less likely to die, 20% to 37% less likely to experience an IP stay, and 80% to 100% more likely to experience an ED visit than patients with an unplanned transition. Higher ED utilization with planned transition was attributed to longer time to mortality, allowing more time for healthcare utilization.

Conclusions: A planned transition to dialysis was associated with improved outcomes and lower mortality. Targeting care coordination for patients with CKD stages 3a/3b may help slow disease progression and ensure a planned, safer transition to dialysis.

Table 1. Transition-to-Dialysis Planning Definitions

<table>
<thead>
<tr>
<th>Planning Status</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimized</td>
<td>All necessary planning factors were met</td>
</tr>
<tr>
<td>Partial</td>
<td>At least one planning factor was not met</td>
</tr>
<tr>
<td>Unplanned</td>
<td>None of the planning factors were met</td>
</tr>
</tbody>
</table>

POI022
Prediction of Stenosis in Arteriovenous Fistula Using Video Image Analysis
Fansan Zhu,1 Lin-Chun Wang,1 Alhaji Cherif,2 Ohnmar Thwin,1 Lela Tisdale,1 Xia Tao,1 Paulo Panque Galuzio,1 Norbert Shihtaynberg,2 Dean C. Preddice,2 Peter Kotanko,1,3 1Renal Research Institute, New York, NY; 2Azura Vascular Care, New York, NY; 3Icahn School of Medicine at Mount Sinai, New York, NY.

Background: We developed a video image processing (VIP) technique with frequency domain analysis to predict stenosis in AVF. The study aimed to evaluate whether the degree of stenosis can be assessed using parameters from frequency domain signal analysis.

Methods: We employed VIP in 100 hemodialysis patients (age 63.3 ±14.1 years, 47 females) prior to endovascular arteriovenous fistula (AVF) interventions. A 1-minute video of the AVF area was recorded using a smartphone (Fig 1). We constructed time series based on pixel changes between two consecutive video frames (Fig 2-A) and used Fast Fourier Transform (FFT) to transform the time domain signals into the frequency domain (Fig 2-B). Parameters in the frequency domain included maximal (Max) and minimum (Min) amplitude, and frequency (FMax and FMin). M2 was calculated by the squared ratio of the Max-to-median magnitude. The degree of AVF stenosis (%ST) was determined by angiography, the access flow (AF) by thermodilution (HVT100; Transonic Systems Inc., Ithaca, NY, USA).

Results: Data from 98 patients were analyzed. %ST was categorized into three groups: 66% stenosis (n=8), 70-80% (n=76), and 90% (n=14). AF correlated with %ST. Max, FMax, and M2 were associated with %ST (Table 1). An algorithm was developed to predict degree of %ST based on patient characteristics and parameters of frequency domain analysis. In the respective three %ST groups the sensitivities to detect AVF stenoses were 88%, 86%, and 90%, and the specificities 99%, 82%, and 98% (Table 1).

Conclusions: VIP applied to videos taken with a smartphone may provide a contact-free method to estimate the degree of AVF stenosis. Validation studies in independent cohorts are needed to further assess the diagnostic capability of the proposed method.
Catheter-Related Bloodstream Infection Incidence and Associated Mortality Risk: Analysis of Merged USRDS, Medicare Claims

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Aaron Grossman,
Paul Chew,
Cormedic, Berkeley Heights, NJ, 
Antilitks Inc, Dover, MA.

Background: Despite policy and provider initiatives, nearly 80% of end-stage-renal-disease (ESRD) patients initiate hemodialysis (HD) with a central venous catheter (CVC). However, CVCs may elevate risk of catheter hub contamination resulting in catheter-related blood stream infections (CRBSIs) and potentially serious consequences. This analysis aims to estimate the incidence, risk, and associated mortality of CRBSIs among CVC-dependent HD patients in the US.

Methods: A propensity score matched case-control analysis of 2013-2017 linked data from the United States Renal Data System (USRDS), dialysis organizations (e.g., AVP Network), and Medicare claims was conducted. Occurrence of CRBSI and associated mortality among incident CVC-dependent HD patients between 2014-2016 with a 1-year pre- and a 1-year post-index were assessed. CRBSI case group index date was the first date of occurrence of any of the following post CVC insertion: ICD-9-CM 999.32, T902.11x; 999-31, T80218x and sepsis/bacteremia diagnosis within ±3 days of hospitalization; sepsis/bacteremia diagnosis without occurrence for pneumonia, gangrene, or urinary tract infections within ±3 days of hospitalization. Non-CRBSI control group was identified by an assigned index date (i.e., CVC insertion date ± median days to CRBSI reported in CRBSI-case group). Frequency, mean, median, and chi-square tests assessed group differences. Adjusted cox proportional hazards models examined time to CRBSI and time to mortality post CRBSI.

Results: Of the 55,727 CVC-dependent HD patients (mean age 67.8, 45% female), nearly 29% (n=15,882) developed a CRBSI (median time, 69 days); 54% (n=8,393), 67% (n=10,327), and 80% (n=12,705) occurred within 90, 180 and 365 days of CVC insertion, respectively. After CRBSI occurrence, 40% and 50% died within 60 days and 180 days, respectively. CRBSI patients also had a significantly lower median survival (25.1 vs. 37.3 months) compared to non CRBSI patients [hazard ratio: 0.74, 95% CI: 0.71-0.76].

Conclusions: CRBSIs occur in a third of CVC-dependent HD patients, with over half of the initial infections occurring within 90 days of CVC insertion. Patients with CRBSI had a higher risk of death compared to patients without CRBSI; with a 40% mortality within 60 days post-CRBSI.

Funding: Commercial Support - Cormedic

Vascular Access in Kidney Transplant Patients with Allograft Failure Returning to Hemodialysis

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Linda Mathew,
Crystal K. Jobson,
Enver Akallu,
Michele H. Mokrzycki,
Tanya S. Johns,
Montefiore Medical Center, Bronx, NY; Albert Einstein College of Medicine, Bronx, NY.

Background: Central vein catheters (CVC) are the predominant vascular access (VA) in incident hemodialysis (HD) patients and are associated with worse outcomes compared to arteriovenous (AV) access. Limited data exist on VA type and association with outcomes in kidney transplant recipients (KTR) with allograft failure. We aimed to determine factors associated with VA type among KTR with allograft failure who return to HD.

Methods: We performed a retrospective study of 147 KTR >18 years with allograft failure between 2010-2021 at an academic hospital in the Bronx, NY. KTR with immediate allograft failure or <1 month of HD following allograft failure were excluded. Data was collected on pre-transplant dialysis modality, vintage, and VA type. Data at allograft failure included sociodemographics, comorbidities, clinic visits, VA type. Descriptive analyses and logistic regression were performed to evaluate factors associated with VA among KTR who return to HD.

Results: At allograft failure, mean age was 53 years (SD 15), 62% were men and 46% were of Black race. Pre-transplant, 91.8% patients were on HD, 2.7% were on peritoneal dialysis (PD), and 5.5% were not on dialysis. Mean vintage was 4.6 years (SD 4.4). Pre-transplant VA included AV access in 87.7% and CVC in 4.1% of patients. At allograft failure, 82.3% and 17.7% KTR initiated HD with an AV access and CVC, respectively. Compared to pre-transplant HD patients, those on PD or who received a preemptive transplant were less likely to initiate HD with an AV access at time of allograft failure (80.6% vs 50% vs 12.5%, p<0.001). KTR were less likely to initiate HD with an AV access for each year increase between the time of transplant and allograft failure (OR 0.8, 95% CI 0.69-0.94). Sociodemographics, comorbidities and number of clinic visits 1 year prior to allograft failure were not associated with VA. One year mortality was 10.7% in KTR initiating HD with a CVC vs 3.4% in those with an AV access (p=0.12).

Conclusions: The majority of KTR with allograft failure returned to HD with an AV access. CVC use was higher in those with longer allograft survival, previously on PD or who received a preemptive transplant, highlighting a need for transition of care optimization. Larger studies are needed to determine if VA type is associated with mortality in this population.
The average number of prior vascular accesses (defined as venous access or arteriovenous fistula/graft) in patients prior to IOCV was 2.6 ± 1.7 (range 1–9), 9 (23.1%) had two prior accesses, and 30 (76.9%) had >3 prior accesses. 5 (12.8%) patients had >1 prior IOCV procedure. 5 (12.8%) patients had complete superior vena cava occlusion. 17 (43.6%) patients had failed AVF/AVG and 2 (5.1%) had failed transmural venous access. Technical success rate was 100% with no complications.

Conclusions: The RIJ vein is the most effective and durable site for long-term hemodialysis access. Occlusion, stenosis of this vein can lead to a downward spiral of access failure with venous hypertension leading to inferior vena cava stenosis or occlusion. These approaches are associated with high rates of dysfunction as well as infection, catheter migration and thrombosis. The transhepatic approach can also cause life-threatening intraperitoneal hemorrhage. The use of IOCV alleviates the need to sacrifice subsequent veins and allows for the occluded RIJ to be re-accessed as many times as needed via the femoral vein. Our data provides further evidence in support of the safety and efficacy of IOCV for long-term hemodialysis access in ESRD patients.

PO1029
Machine Learning for the Prediction of Arteriovenous Fistula Failure
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Background: Arteriovenous access failures are a frequent finding in hemodialysis patients with arteriovenous (AV) fistulas and grafts. Of great concern is aneurysm rupture that may result in fatal hemorrhage. To that end we used artificial intelligence (AI) to automatically evaluate vascular access aneurysms.

Methods: We collected images of a diverse range of AV vascular accesses using mobile devices. Vascular access experts adjudicated the images and diagnosed the severity of AV fistula and graft aneurysms. We then randomized the images for training (70%) and validation (30%). We trained a convolutional neural network (CNN) utilizing Amazon SageMaker platform. CNN performance was measured by the area under the receiver operating characteristics (ROC) curve in the validation images.

Results: We collected 1,341 AV access images in patients dialyzed at 20 Renal Research Institute clinics in six U.S. states. The adjudication of images identified 1,093 not advanced and 248 advanced aneurysms; examples are shown in Figure 1. With the validation images, we achieved an area under the ROC curve of 0.96. Considering different probability thresholds for advanced aneurysm, if threshold is 0.37, we achieved sensitivity of 80%, specificity of 95%, false positive rate of 5%, precision of 99% if threshold is 0.7, 70%, specificity of 66%, specificity of 99%, false positive rate of 1%, precision of 92%.

Conclusions: Our solution of applying advanced AI technologies achieved very high sensitivity, specificity, precision, and a low false positive rate. The CNN could assist the clinician with actionable information and improve clinical outcomes.

Funding: Commercial Support - Fresenius Medical Care North America
Severity of AV access aneurysms. Panel A shows the images from 6 patients with not advanced AV aneurysms. Panel B shows images from 6 patients with advanced AV aneurysm.

**PO1031**

**Evaluation of a Wearable Device for Continuous, Noninvasive Monitoring of Hematocrit Levels in Hemodialysis Patients**

David J. Kuraguntla, Forrest Millet. Alo, San Francisco, CA.

**Background:** Maintenance of euovolemia is a major challenge for hemodialysis patients, who account for a combined 5.5M annual hospital days. Clinical outcomes could be improved, and healthcare costs lowered, by enabling better management of fluid status and anemia, which is common among ESRD patients. This study presents a novel wearable device, SmartPatch, that uses multi-wavelength photoplethysmography (PPG) and other sensors to measure blood hematocrit (Hct), a key metric for monitoring fluid status and anemia. The SmartPatch is a component of a novel Remote Monitoring System (RMS) that facilitates secure data transmission and analysis and generates actionable alerts. Data demonstrating the feasibility of the RMS were previously presented at Kidney Week 2019 (Kuraguntla et al.). The aim of this study was to evaluate the system’s ability to accurately and precisely measure Hct in a real-world dialysis setting.

**Methods:** 14 ESRD patients with arteriovenous fistulae currently undergoing dialysis were recruited to participate in this study. Each of these patients had a SmartPatch device placed on the skin over their fistula at each of three dialysis sessions two weeks apart. Reference Hct measurements were taken immediately before and after the session, times to coincide with SmartPatch data recordings. A total of 83 sets of multi-channel PPG data were recorded and analyzed to determine the accuracy and precision of Hct measurement.

**Results:** The RMS measured Hct with root-mean-square error (RMSE) of 2.13 Hct compared to reference values obtained from a Sysmex XN-1000 blood analyzer. The standard deviations for each read on the same patient—the same device—were computed and averaged, weighted by group size, as a measure of precision. The RMS measured Hct with a mean standard deviation of 1.15 Hct. These error and standard deviation values compare favorably to available point-of-care devices like the Hemocue Hb 201+, which has been reported to measure Hct with a mean of 4.32-4.81 Hct and standard deviation of 1.56-3.88 Hct.

**Conclusions:** The results of this study illustrate the ability of the wearable SmartPatch to non-invasively measure blood Hct in ESRD patients with AV fistulae, to a degree of accuracy and precision that may outperform available point-of-care methods. This study also demonstrated the efficacy of the end-to-end Remote Monitoring System.

**Funding:** Commercial Support - Alo, Inc.

**PO1032**

**Impact of a Change in Vascular Access Flow Volume After Percutaneous Transluminal Angioplasty on Cardiac Function**

Koji Hashimoto, Makoto Harada, Youseke Yamada, Yuji Kamijo. Shinshu Daigaku Igakubu Fuzoku Byoin, Matsumoto, Japan.

**Background:** Vascular access (VA) is necessary for patients on hemodialysis, and percutaneous transluminal angioplasty (PTA) is a useful treatment for maintaining VA function. PTA immediately increases the VA flow volume, which can affect cardiac function. We investigated the relationship between changes in VA flow volume and cardiac function in patients who underwent PTA.

**Methods:** This was a single-center retrospective observational study, including patients who underwent PTA between June 2016 and August 2016. VA flow volume and cardiac function were measured by sonography before and 1 hour after PTA.

**Results:** This study included 50 PTA procedures in 50 cases. PTA significantly increased the median VA flow volume from 445 (range, 150-1229) to 725 (350-1268) mL/min. Although the ejection fraction and diameter of the inferior vena cava were unchanged, the cardiac output (CO) and cardiac index increased significantly in most cases. Surprisingly, the CO was obviously decreased in 18% of cases despite the increased VA flow volume. In this atypical group, a high CO before PTA was found to be a significant factor for the decrease in CO by PTA.

**Conclusions:** In most cases, both VA flow volume and CO were increased by PTA, whereas in some cases, the CO was decreased despite increase in VA flow volume. This atypical phenomenon may be due to the insufficient adaptive response in the peripheral artery and heart and could predict risks for future cardiac events. Therefore, it is important that such patients are carefully followed up.
Flow through the accessory vein before the ligation.

Cessation of the blood flow through the accessory vein after the ligation.

PO1035
Feasibility of Treating Stenotic Fistula Lesions with a Drug-Coated Balloon Prior to Using a Standard High Pressure Balloon

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Background: Hemodialysis access maintenance is a major cost expenditure for dialysis care. Patients often require multiple procedures per year, often treating the same access lesion in a AVF / AVG. A large proportion of stenotic lesions develop secondary to neointimal hyperplasia. Standard treatment has been angioplasty using high pressure non-compliant balloons. Recently drug coated balloons (DCB), coated with the medication paclitaxel, to help decrease neointimal hyperplasia, have been used in dialysis access treatment. The safety profile and efficacy have been proven to decrease lesion reoccurrence at 6 months when compared to regular angioplasty. Traditionally the recommendation for use of DCB is to follow after the lesion has been primarily dilated with a high-pressure balloon (HPB).

Methods: For DCB use the manufacture recommends pretreatment of the lesion with a HPB followed by secondary DCB treatment. This Arthur decided to modify the technique and treat lesions needing angioplasty with DCB first (example in figure 1) and only secondary treatment with HPB if there was not sufficient resolution of the lesion / balloon inflation to achieve less than 30% residual stenosis. Observational data is being tracked for patients undergoing fistulograms to provide a single center observational prospective cohort to look into this issue.

Results: Currently 11 patients with 15 total lesions have undergone this modification of treatment in the past 9 months, with 3 of the 11 patients having repeat fistulograms post treatment. Nine of the 11 patients required no HPB follow up. One of the 11 patients suffered a cephalic arch rupture and required stent graft placement.

Conclusions: Early data from this observational study shows that treatment of a stenotic lesion using a DCB as the only treatment is effective in the majority of cases to achieve full lesion angioplasty. Preliminary results indicate no change in long term efficacy in the DCB lesion treatment.

PO1036
Predictors of Vascular Access Thrombosis in Maintenance Hemodialysis Patients: An Historic Cohort Study

Rita Verissimo,1,2 Luís Leite de sousa,1,3 Tiago J. Carvalho,1,4 Artur P. Mendes,1,2 1DaVita Vascular Access Center - Lisbon, Lisbon, Portugal; 2DaVita Sacavém Hemodialysis Unit, Lisbon, Portugal; 3DaVita Sintra Hemodialysis Unit, Lisbon, Portugal; 4DaVita Cascais Hemodialysis Unit, Lisbon, Portugal.

Background: Vascular access (VA) thrombosis is a known complication in patients with end-stage kidney disease on hemodialysis (HD), but its risk factors are not completely established. We performed a study with the aim of ascertaining risk factors for VA thrombosis.

Methods: A multicenter retrospective cohort study was performed in three HD units to determine VA thrombosis rate and associated risk factors in maintenance HD patients, from July 2019 to April 2021. Descriptive statistics were calculated and expressed as median (IQR) or count (%). Univariate and multivariate logistic regression was used to calculate the adjusted odds ratio (aOR) with 95% CI for the variables associated with VA thrombosis.

Results: From a total of 178 maintenance HD patients, there were 30 (16.9%) VA thrombosis during follow-up. Our cohort had a median of 71 years (61-80), 59.6% (n=106) were male, were on HD for a median of 63.52 months (37.58-98.87), 37.6% (n=67) had diabetes, 66.1% (n=107) cardiovascular disease and 35.6% were on anticoagulant or antplatelet agents. As to the VA, 87.1% (n=155) had arteriovenous fistulas (AVFs) and 28.1% (n=50) had history of previous percutaneous or surgical interventions. When comparing cases that led to thrombosis to VAs that maintained patency, thrombosis was more likely in arteriovenous grafts (AVGs) versus AVFs (60.9% vs 19.3%, P< 0.001), in VAs that had previous percutaneous or surgical interventions (34% vs 10.2%, P<0.001), and had a AV flow (Qa) slope ≥ 25% or Qa value < 500ml/min, excluding radiocephalic AVFs (30.4% vs 11.7%, <0.001) and those with spkV’ < 1.4 (40% vs 11.2%, P<0.001). Multivariate analysis risk factors independently associated with VA thrombosis were AVGs [aOR 13.35 (4.38-40.74), P<0.001], Qa slope ≥ 25% or Qa < 500ml/min, excluding radiocephalic AVFs [aOR 5.00 (1.76-14.18), P<0.003], and spkV’ <1.4 [aOR 8.23 (2.90-23.35), P<0.001]. The model had a Nagelkerke R2 of 42.1%, Hosmer-Lemeshow goodness-of-fit test performed well (χ2 = 0.215, df=3, P=0.975) and showed very good discriminatory ability [AUROC (95% CI) 0.85 (0.77-0.94)].

Conclusions: Our study showed AVGs, Qa slope ≥ 25% or Qa < 500ml/min, excluding radiocephalic AVFs, and spkV’ < 1.4 were independent predictors of VA thrombosis. Interestingly, patients’ demographic characteristics and comorbidities were not associated with VA thrombosis.

PO1037
Efficacy and Safety of Plastic Cannulae Compared with Metal Needles in the Initial Use of an Arteriovenous Fistulae in Incident Hemodialysis Patients: A Randomized Controlled Study

Sung gunsu Kim, Hoi Woul Lee, Jwa-kyung Kim. Hallym University Sacred Heart Hospital, Anyang, Gyeonggi-do, Republic of Korea.

Background: Successful cannulation of an arteriovenous fistula (AVF) is important in patients starting hemodialysis (HD). Metal needles have been used for decades, but the usefulness of plastic cannulae has recently been demonstrated as a new technique.

Methods: As a prospective, randomized study, eligible patients were randomized into two groups in a 1:1 ratio (n=45/group). Maturation of the AVF was confirmed by Doppler ultrasound. The primary endpoint was the initial cannulation failure rate, defined as the failure of successful completion of three consecutive dialysis sessions. The secondary endpoints were time for hemostasis at the end of HD, degree of patients’ pain, degree of cannulation difficulty felt by the nursing staffs, and achieving optimal HD adequacy.

Results: The mean time from AVF creation to the first cannulation was 48.1±16.7 days. A total of 17 cases of cannulation failure occurred, and the failure risk tended to be higher in the metal needle group than the plastic cannula group (HR 2.6, 95% CI 0.95-7.41) after adjusting for age, gender, comorbidities, and location. The overall incidence of vessel injury was higher and time for hemostasis was significantly longer in the metal group than the plastic group. The use of plastic cannula was associated with better HD adequacy compared to metal needle. However, the patients’ pain score (P=0.004) and nursing staff’s cannulation difficulty score (P=0.084) were higher in the plastic group, emphasizing the great importance of practice using plastic cannulae.

Conclusions: The vascular outcomes of plastic cannulae were much favorable compared to metal needles in incident HD patients. The use of plastic cannulae could be a new and innovative way to improve the quality of dialysis.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

347
Alignment Between Patient and Provider Perspectives on Hemodialysis Vascular Access Decision-Making: A Qualitative Study

Angela R. Schneider,1 Pietro Ravani,1 Kathryn M. King–Shier,1 Robert R. Quinn,1 Jennifer M. MacRae,1 Matthew J. Oliver,2 Swapnil Hiremath,2 Matthew T. James,1 Meghan J. Elliott.1 1University of Calgary, Calgary, AB, Canada; 2University of Ottawa, Ottawa, ON, Canada; 3University of Toronto, Toronto, ON, Canada.

Background: Recent updates to the KDOQI Clinical Practice Guideline for Vascular Access emphasize attaining the “right access, in the right patient, at the right time, for the right reasons”. Yet, how patients, their caregivers, and healthcare providers integrate medical factors with care preferences in patient-centered vascular access decision making is unknown. We sought to explore the extent to which these diverse perspectives align in hemodialysis vascular access selection.

Methods: In this qualitative descriptive study, we purposively sampled patients receiving maintenance hemodialysis via an arteriovenous fistula or catheter, their informal caregivers, and their hemodialysis care providers. We conducted semi-structured interviews by telephone or in person with 19 patients, 2 caregivers, and 21 healthcare providers (8 nephrologists, 7 hemodialysis nurses, 6 vascular access nurses). We coded transcripts in duplicate and generated themes through an inductive, content analysis approach.

Results: While participants across roles shared perspectives related to vascular access decision making, we identified several areas where views diverged. Participants acknowledged the importance of decisional timing and readiness, the iterative nature of decision making, and a desire for vascular access selection to be a shared decision. Perspectives differed in the following key aspects: 1) priorities for vascular access type – providers’ preferences for fistulas and physiological optimization contrasted with patients focus on quality of life; 2) provider involvement in the decision – patients desired guidance from their trusted providers, whereas care providers tried to avoid unduly influencing the decision; 3) informational needs – tools and resources offered by the care team may not meet patients’ need for pragmatic, experiential knowledge about vascular access options.

Conclusions: While patients and providers identified common perspectives related to the nature and timing of the vascular access decision, conflicting priorities and preferences may impact the decisional outcome. This study highlights opportunities to address decisional conflicts and enable shared decision making in vascular access selection.

Vascular Access Selection Among People Receiving Hemodialysis: A Qualitative Study of Shared Decision-Making

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Background: The vascular access decision process for people receiving maintenance hemodialysis involves weighing the likelihood of having a functional access with its associated risks. How patient and clinician preferences are integrated alongside best evidence to make joint vascular access decisions is unclear. We aimed to explore how such decisions are made from the perspectives of patients, their caregivers, and their kidney care providers.

Methods: In this qualitative descriptive study, we purposively sampled patients receiving in-centre hemodialysis for >3 months via either an arteriovenous fistula or a central venous catheter, their informal caregivers, and their hemodialysis care providers. We conducted semi-structured interviews by telephone or in person with 19 patients, 2 caregivers, and 21 healthcare providers (8 nephrologists, 7 hemodialysis nurses, 6 vascular access nurses). We coded transcripts in duplicate and generated themes through an inductive, thematic analysis approach.

Results: Participants described a decisional hierarchy, whereby decisions regarding vascular access were predicated on upstream decisions (i.e., dialysis initiation, transplantation, home dialysis) that were preference sensitive and prioritized over vascular access type. Upon reaching a decision for hemodialysis, vascular access decision making was influenced by the following: 1) preferences for kidney replacement therapy, including anticipated timeline to transplantation or transition to home dialysis modalities; 2) urgency and timing of dialysis need, where urgent starts undermined expressed preferences; 3) limitations of individualized decisions, as when preferences and practicalities diverged; 4) occasions to re-visit the vascular access selection; and 5) availability of support for vascular access decision making and the decisional outcome.

Conclusions: Although patients and care providers prioritized upstream decisions, several influences on vascular access decision making were identified once the decision for hemodialysis was made. These findings can inform approaches to integrating shared decision making in dialysis and vascular access selection.
PO1041 Feasibility of Creation of an Endovascular Arteriovenous Fistula in Patients Undergoing Preoperative Vascular Mapping
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Background: The endovascular arteriovenous fistula (endoAVF), a novel percutaneous technique of AVF creation, was approved by the Food and Drug Administration in 2018, and has been placed in a small number of U.S. hemodialysis patients. It is unknown how often patients with advanced chronic kidney disease have vascular anatomy suitable for endoAVF creation. The goal of the present study was to determine the proportion of patients with a vascular anatomy suitable for endoAVF creation, and to assess patient characteristics associated with such suitability.

Methods: All patients referred for vascular access placement at a large academic medical center underwent standardized preoperative sonographic vascular mapping to assess suitability for an AVF. During a two-year period (March 2019 to March 2021), we assessed the suitability of the vessels for creation of an endoAVF. We then compared the demographic characteristics, comorbidities, and vascular mapping measurements between patients who were or were not suitable for an endoAVF.

Results: During the study period, 223 patients had preoperative vascular mapping results suitable for creation of a surgical AVF. Of these, 140 patients (63%) were also suitable for an endoAVF. Patients with a vascular anatomy suitable for an endoAVF were younger (age 55±15 vs 60±14 years, p=0.01), but similar in sex, race, diabetes, hypertension, coronary artery disease, and peripheral artery disease.

Conclusions: Among patients with chronic kidney disease and vascular anatomy suitable for a surgical AVF, 63% are also suitable for an endoAVF. Older patients are less frequently suitable for an endoAVF.

Funding: NIDDK Support

PO1042 Endovascular Arteriovenous Fistula Closure with Covered Stent Placement

Introduction: WaveLinQ™ endovascular arteriovenous fistula (EndoAVF) system is a new technique that uses radiofrequency energy to create AVF. It has been gaining popularity as it avoids major surgery, has less recovery time and better success rates than surgical AVF creation. Pseudoaneurysm, dissection of brachial artery, intra-procedure brachial artery thrombosis, device embolization, and steal syndrome are described complications of the procedure. We present a case of EndoAVF creation complicated with forearm swelling and its successful management.

Case Description: Patient is a 45 y/o male with End-Stage Renal Disease due to Hypertensive Nephrosclerosis and obstructive uropathy, now s/p failed kidney transplant, currently on Percutional Dialysis (PD). PD was failing and decision was made to transition patient to hemodialysis (HD). In preparation of HD, AVF using WaveLinQ EndoAVF system was placed in right forearm between intramusosal artery and vein with coiling of the medial brachial vein. A week after fistula creation, patient developed right forearm swelling with numbness and tingling. Fistulogram demonstrated stenosis in the perforator vein with poorly developed cephalic vein and diversion of blood flow to multiple superficial collateral veins in the forearm causing swelling. Multiple attempts at balloon assisted maturation of the cephalic outflow were unsuccessful. Due to persistent forearm swelling with discomfort a decision was made to close the fistula. A 5 x 15 mm self-expanding ViaBahn™ stent was deployed in interosseus vein across the anastomosis to close the fistula. Post fistula closure, arm swelling resolved completely.

Discussion: Covered stents have been used in the maintenance of hemodialysis AVF for various purposes including dialysis access stenosis, central vein stenosis, pseudoaneurysm exclusion and angioplasty associated vascular rupture that cannot be repaired using balloon catheter. This is the first reported case of successful use of covered stent graft to occlude anastomosis to close EndoAVF. As these fistulae are created often, more novel complications will be encountered. It will be imperative for interventionalists to find creative solutions as well as actively report the successful management of complications.

PO1043 Long-Term Prognosis of Vascular Access in Hemodialysis Patients with Systemic Lupus Erythematosus
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Background: Patients with systemic lupus erythematosus (SLE) have a higher risk of vascular complications.

Methods: This retrospective cohort study is aimed to analyze the differences in the risk of arteriovenous fistula or graft (AVF/AVG) dysfunction in hemodialysis (HD) patients with and without SLE from Taiwan Nationwide Health Insurance Database over a 10-year period. AVF/AVG dysfunction is defined as occurrence of the first episode of intervention after vascular access creation. This retrospective cohort study is aimed to analyze the differences in the risk of arteriovenous fistula or graft (AVF/AVG) dysfunction in hemodialysis (HD) patients with and without SLE from Taiwan Nationwide Health Insurance Database over a 10-year period. AVF/AVG dysfunction is defined as occurrence of the first episode of intervention after vascular access creation.

Results: Totally, 1366 HD patients with SLE had higher incidence rates of AVF/AVG dysfunction than 4098 non-SLE HD patients in the following 4 periods, (1) after 1 year (incidence rates were 15.21% and 13.01% respectively; subdistribution hazard ratio (SHR) = 1.16; P = 0.007), (2) 1st-to-10th-year period (15.36% and 13.25%; SHR = 1.16; P = 0.007), (3) 5th-to-10th-year period (11.91% and 8.1%; SHR = 1.42; P = 0.003), and (4) overall period (23.53% and 21.66%; SHR = 1.19; P = 0.027). There were significantly higher incidence rates of AVF/AVG dysfunction in SLE patients during the long-term follow-up period.

Conclusions: In conclusion, regular surveillance of vascular access function by clinical examination after 1 year, especially during 5 to 10 years, is needed to improve vascular access patency and dialysis adequacy in SLE patients undergoing maintenance hemodialysis.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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Results: Median age was 71 years, 64% were men, 43% had diabetes, and 33% started hemodialysis urgently. Half (51%) underwent a first arteriovenous access creation: a fistula in 21,240 patients, created a median of 5 months (IQR, 2-12), and a graft, in 741 patients, 3 (1-8) months before hemodialysis initiation. Among patients with a first fistula attempt, 30% underwent at least one vascular access re-intervention before hemodialysis initiation, versus 21% among those with a first graft attempt (p=0.001). The types of intervention substantially differed according to vascular access (Figure). When dialysis start was urgent, catheter was used in 43% of patients in both access groups (p=0.86); when it was not, catheter was used in 12 and 14% of patients with a first fistula or graft attempt, respectively (p=0.15).

Conclusions: In incident hemodialysis patients in France, fistula is typically the first attempted arteriovenous access. Early arteriovenous access creation prevents from using catheter at dialysis initiation in a majority of patients, but requires close monitoring of potential complications.

Funding: Government Support - Non-U.S.

Incidence of De Novo Central Vein Stenosis in Hemodialysis Patients Following Their First Tunneled Central Vein Catheter (CVC) Placement

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Background: Central vein stenosis is a common complication in hemodialysis patients following tunneled CVC insertion. Little is known about its incidence, association with patient characteristics, or relationship with duration of CVC placement. We systematically evaluated central vein stenosis in hemodialysis patients receiving their first CVC at a large medical center.

Methods: All new hemodialysis patients underwent an ultrasound prior to their first CVC at a large medical center. The frequency of central vein stenosis was progressively higher with greater duration of CVC placement prior to exchange.

Results: During the study period, 273 patients underwent exchange of a tunneled internal jugular vein CVC preceded by a catheterogram/venogram. Of these, hemodynamically significant central vein stenosis was observed in 36 patients (13%). Central vein stenosis was not associated with patient age, sex, race, diabetes, hypertension, coronary artery disease, peripheral artery disease or CVC laterality (Table 1). The frequency of central vein stenosis was progressively higher with greater duration of CVC placement, being 10%, 12%, 24%, and 28% in patients with <3 months, 3 to 6 months, 6 to 9 months and >9 months of catheter dependence, respectively (p=0.025).

Conclusions: Among incident hemodialysis patients receiving their first tunneled internal jugular CVC, the overall incidence of hemodynamically significant central vein stenosis was 13%. The likelihood of central vein stenosis was directly associated with the duration of CVC dependence.

Funding: NIDDK Support

Hospitalization Risk and Long-Term Complications Associated with Catheter-Related Bloodstream Infection Among Hemodialysis Patients

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Background: Central venous catheters (CVC) are frequently required for vascular access in hemodialysis (HD) and are commonly associated with catheter-related bloodstream infections (CRBSIs). CRBSIs may have devastating consequences leading to increased hospitalizations, and long-term complications such as stroke, myocardial infarction (MI), heart failure (HF), and endocarditis, among others. This analysis explores the risk of CRBSI-associated hospitalizations and long-term complications among HD patients.

Methods: A 1:1 propensity score matched case-control analysis was conducted using merged data from United States Renal Data System (USRDS), CROWNWeb (dialysis organizations), and Medicare claims database (2013-2017). All CVC-dependent HD patients from 2014-2016 with a 1-year pre- and ≥1-year post-index period were included. CRBSI was defined as a composite measure of its ICD codes or sepsis/bacteremia diagnosis with hospitalization or without occurring pneumonia, gangrene, or urinary tract infections and hospitalization. An assigned index date (i.e., CVC insertion date + median days to CRBSI reported in CRBSI-case group) was used to identify non-CRBSI patients. CRBSI/non-CRBSI group differences were described using frequency, mean, median, chi-square, and t-tests. At 1-year post CRBSI, adjusted differences in hospitalizations and hospital days and time to long-term complications were modeled using generalized linear models cox proportional hazard models, respectively.

Results: CRBSIs result in higher 1-year incremental rates of: stroke (6.6%), MI (9.2%), HF (13.4%), PVD (13.6%), and endocarditis (9.4%). Mean number of hospitalizations and hospital days were 3.79 and 25.0 days for CRBSI, and 1.96 and 5.86 days for non-CRBSI patients, respectively. Mean hospitalizations and hospital days were significantly higher for CRBSI vs. non-CRBSI patients (p<0.05) at 1-year post-CRBSI. Hazard ratios for CRBSI patients were: stroke (1.64, 95% CI 1.53-1.75), MI (2.56, 95% CI 2.37-2.78), HF (2.01, 95% CI 1.88-2.14), and endocarditis (13.42, 95% CI 10.97-16.42).

Conclusions: Results show HD patients with CRBSIs incur a significant morbidity burden due to increased hospitalizations, hospital days, and long-term complications such as stroke, MI, HF, PVD, and endocarditis.

Funding: Commercial Support - Cormedix

Hemorrhagic Shock due to Cutting of the Tunneled Dialysis Catheter

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Introduction: Bleeding is a relatively rare complication of dialysis CVC overall. Confluence of factors such as: vascular access, patient characteristics, and emergency situation can augment the risk of bleeding. We present a case of a 79-year-old female with a history of dementia who accidentally cut a tunnelled CVC proximal to the Y. This case demonstrates the risk of significant hemorrhage when a tunnelled CVC is damaged at this location and need for early recognition and control of bleeding. It also highlights important patient safety considerations given the risk of self-inflicted trauma in patients with dementia and language barrier for communication.

Discussion: To our knowledge, this is the first report of a cut tunnelled CVC proximal to the Y. We have demonstrated the risk of significant hemorrhage when a tunnelled CVC is damaged at this location and need for early recognition and control of bleeding. It also highlights important patient safety considerations given the risk of self-inflicted trauma in patients with dementia and language barrier for communication.

Funding: Commercial Support - Cormedix

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Underline represents presenting author.
X Ray showing the retained tunnelled catheter proximal to Y

PO1048

Facial Swelling: Angioedema or Superior Vena Cava (SVC) Syndrome

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Introduction: Central venous stenosis is a common complication of recurrent central venous catheters (CVCs). Diagnosis can be challenging given its versatile presentation. Facial, unilateral breast or upper extremity swelling and signs of congestion mimicking pulmonary edema can be subtle clues. We describe a case of SVC syndrome that eluded clinicians as angioedema.

Case Description: A 55-year-old African American female with ESRD secondary to Lupus Nephritis (LN) s/p deceased donor kidney transplant, developed allograft failure and restarted dialysis. Upon initiating dialysis and weaning of immunosuppression she had episodes of fever, myalgias, synovitis and pleural effusions thought to be manifestations of lupus flare. Despite restarting immunosuppression, she presented frequently with dyspnea and recurrent bilateral transudative pleural effusions requiring repeat thoracenteses. Her physical exam was notable for swelling of bilateral upper extremities and face with minimal lower extremity edema. Lupus serologies were normal. Echo was unremarkable. CT angiogram (CTA) revealed complete occlusion of the distal superior vena cava (SVC) with extensive collateralization in the chest and abdominal wall.

Discussion: Her initial symptoms were attributed to volume overload and lupus serositis. However, inactive serologies, ongoing immunosuppression, and the transudative nature of the effusion were not consistent with lupus flare. Aggressive UF also failed to prevent recurrent pleural effusion. Given CTA and clinical findings, we concluded that the persistent pleural effusion is a manifestation of the SVC syndrome in our patient. The occlusion of the SVC was below the junction of the arch of the azygos vein. Venous blood flow from the upper body and extremities was shunted into the azygos system and flowed counter-current, returning to the right heart through the inferior vena cava. This resulted in increased hydrostatic pressure in the intercostal veins, contributing to the development of edema of the head, upper chest, bilateral upper extremities, and pleural effusions. Our patient had multiple central venous catheters increasing her risk for SVC syndrome. Clinicians should consider SVC stenosis as a potential cause of recurrent pleural effusions in a dialysis patient.

PO1050

Innovative Care Model for Vascular Access Strategy in AKI in Critically Ill Patients

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Background: Central venous catheter (CVC) is the preferred vascular access in critically-ill patients needing kidney replacement therapy (KRT). Non-tunneled CVC (NT-CVC) is frequently selected for bedside placement and provider familiarity. With hemodynamic instability, tunneled CVC (T-CVC), despite its known advantages of lower infection risk, lower mechanical complications, better blood flow rates and patient comfort, is infrequently considered due to competing demands for central vein access and provider inexperience. We report our early experience of building a collaborative training program to improve vascular access approach in the critically-ill patients.

Methods: A single center retrospective study of T-CVC placed in an adult medical ICU between March 1, 2020 and December 31, 2020 by a nephrologist or an intensivist. The T-CVCs were placed in hemodynamically unstable patients for KRT and other continuous therapies. Statistical analysis was limited to assess feasibility and safety of implementing a collaborative procedural service in an academic medical ICU.

Results: A total of 120 CVC related procedures were completed during the study period. 106 were T-CVC placements (68 for KRT, 38 small bore non-KRT), seven T-CVC removals, one difficult NT-CVC for KRT, one T-CVC exchange, one fluoroscopy guided repositioning of NT-CVC, four aborted for suspected central vein occlusion. Twenty-seven T-CVC (23 in COVID-19 positive and 4 for other compelling reasons) were placed at bedside ultrasound guidance and anatomical landmarks without fluoroscopy. A safety pre-procedure checklist was developed for eligibility based on this experience. A minimum of 48-hr sterile blood culture report was essential to proceed. Complex comorbidities included coagulopathic patients. A minimum training competency was established and 2 critical care staff physicians were credentialed during this period. No major complications were encountered.

Conclusions: A collaborative care model between nephrology and medical ICU for T-CVC focused strategy is feasible. T-CVC can be placed safely in a carefully selected critically-ill patient population. Training intensivists with basic procedural skills for T-CVC procedure is achievable over a short period.
worsening sharp, non-radiating chest pain localized at the left hemithorax. Patient refused to eat and vomited for 2 days. Examined a thick mucus possibly blood-streaked; however, no coffee-ground. Stated he had never experienced this chest pain before. He reported not taking any medication at home for pain. On examination there was no cardiac murmurs, no lung abnormalities on auscultation and he had a patent arteriovenous fistula with good thrill and bruit and no signs of stenosis. Had 2 negative troponin levels with serial EKGs without ischemic changes. An echocardiogram that was negative for wall motion abnormalities or any changes in ejection fraction, ruling out an acute coronary syndrome. He had CXR showing curvilinear density projecting over the left upper zone, suggestive of a left upper leaflet metallic device in the left ventricular apex. He was not on hemodialysis before his transplant, he had multiple endovascular procedures including a stent placement to keep a patent AV access. A left upper extremity x-ray showed a left AV access stent fracture; findings were consistent with an embolized fragment from AVG stent. He underwent explant of the stent from AVG, but embolized fragment was not removed by CT surgery. Currently patient is chest pain free and asymptomatic.

Discussion: Stent fractures are commonly seen when they are in arteries, however this is an uncommon event in venous system specially in hemodialysis vascular access. Some of the complication associated with stent fracture are related to in-stent stenosis and central vein stenosis, but this is the first report of chest pain from stent fracture migrated to the left verteicle.

PO1052

Agitated Saline Bubble-Enhanced Ultrasound to Visualize Appropriated Position of Hemodialysis Catheter: Does Catheter Venous Site Matter?

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Background: The hemodialysis non tunneled catheter (HDC) is the most common access of starting renal replacement therapy. Malposition of catheter is associated with delays in treatment. Agitated saline bubble-enhanced ultrasound (SBUS) has become a new method to visualize the HDC position. Delayed appearance of microbubbles (a 2-second) in the right atrium indicates malposition. Our objective is to analyze the accuracy of SBUS versus right and left internal jugular vein (IJV) HDC insertion, comparing to chest radiography (CR; standard method).

Methods: From December 2019 to May 2021, we evaluated 145 hospitalized patients submitted to HDC insertion in IJV. We compared SBUS with chest radiography (CR); the time spent to perform the CR; complications; patient characteristics; catheter blood flow and quality of dialysis.

Results: Total of 145 patients were analyzed, the median age was 62 years old [50.5-70], and there was no statistical difference between the site of insertion. In RIJV, 91% catheters were placed. AKI was more frequent than CKD (75% vs 25%), except when the site was LJV (46% vs 54%, p<0.05). AKI-related COVID-19 was the most common etiology (54%). The confirmation of catheter placement by SBUS was correlated with position by CR (All: r=0.6603, p<0.0001; RIJV: r=0.7044, p<0.0001; LJV: r=0.6396, p=0.0769). SBUS was highly accurate in identifying adequate location of HDC, specially in RIJV (All: 97.9%; RIJV: 99.2%; LJV: 84.6%, p<0.05). The time of the catheter insertion to perform radiography was 191 minutes [83.5-287]. Adequate syringe blood flow and an effective hemodialysis session was more frequent in RIJV catheter (99.2% vs 53.8%, p<0.05; 96.8% vs 72.7%, p <0.05, respectively). Complications occurred only in 4.2%, without statistical difference between catheter sites.

Conclusions: Comparing with chest radiography, agitated saline bubble-enhanced ultrasound was more accurate in identifying adequate placement of RIJV than LJV hemodialysis catheters.

Funding: Government Support - Non-U.S.

PO1053

Using the Seraph® 100 Microbind® Affinity Blood Filter Under Slow Flow Conditions Through a Normal Central Line

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Background: The Seraph® 100 Microbind® Affinity blood filter has been in use since 2019 for the treatment of difficult to treat bloodstream infections and since 2020 for the treatment of critically ill COVID-19 patients. It is operated under blood flow rates of 100 – 350 mL/min, which requires a large bore central line a dialysis catheter. The aim of our study was to evaluate the usability of the Seraph® 100 under slow flow conditions through a normal central line (in clinical practice).

Methods: A standard hemoperfusion blood tubing system as well as the Seraph® 100 (Exthera Medical, CA, USA) was used. Vascular access was a 20 cm trilumen central venous line (2 x 16G and 1 x 16 G) that was inserted into a reservoir: The Multifiltrate (Fresenius Medical Care) was used to pump normal saline (n=5) or human plasma (n=5) through the Seraph® 100. Pressures were recorded at any given flows (Qb). In two patients connected to a five lumen 20 cm catheter (Certoxy Safety Quinto S1220, B. Braun, Melsungen, Germany - 1 x 12 G, 1 x 16 G, 3 x 18 G) blood flow as well as arterial and venous pressure were recorded through the 24 h treatment.

Results: Using saline or human plasma the Seraph® 100 Microbind® Affinity Blood Filter can be operated at blood flow rates of up to 100 mL/min even through a 16 & 18 G lumen at tolerable arterial and venous pressures. In men using either the 12 G or the 16 G lumen as “arterial line” blood a blood flow rate of 50 mL/min could be obtained for 24 hours without problems.

Conclusions: The Seraph® 100 Microbind® Affinity Blood Filter can be operated at blood flow rates of 50 mL/min even through 16 & 18 G catheters.
PO1055
Virtual Interviewing in the COVID-19 Era: What Have We Learned?
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Background: The COVID-19 pandemic forced institutions across the US to switch to virtual interviewing. While some institutions were already offering virtual interviews on a limited basis, this was the first time all interviews were conducted using a virtual platform. Herein, we describe the experience of the nephrology fellowship interviewees at the University of North Carolina (UNC).

Methods: We distributed an anonymous Qualtrics survey to all the nephrology fellowship interviewees (N=80) at UNC. The survey included questions on quality of virtual interviews and was completed after the match to avoid bias related to the matching process.

Results: Thirty-one candidates completed the survey (39%), although not all questions were answered by everyone. The total number of interviewees increased from 41 in 2019-20 to 80 in 2020-21. 95% were satisfied with their virtual experience. 82% indicated that the virtual interview process enabled an informed decision about the fellowship program. Everyone was satisfied with the organization of the interview day (N=22). 28% responders (5/18) identified as underrepresented minority (URM). In 2019-20, 641 interviewees identified as URM as compared to 1480 in 2020-21. The most common reasons for not ranking our program amongst the top three included limited job opportunities for partners, inability to visit the area, and lack of family in the area. Candidates valued the people they met and were able to get a feel for the program despite virtual interviews. They were particularly satisfied with the opportunity to meet fellowship program members on one-on-one interviews. Interviewees specified lower cost and time efficiency as advantages of virtual interviews.

Conclusions: This is the first report of the virtual interview experience for nephrology fellowship applicants. The virtual interview process increased the applications to our program although the number of URM applications were similar compared to previous years. There was uniform satisfaction with the virtual format and interviewees were able to appreciate the culture of the division. Most applicants found the virtual interview format favorable because of reduced cost and time expenditure, enabling them to interview at more programs. Our data suggest that serious consideration should be given to a virtual format in future years to provide opportunity and flexibility to the applicant pool and improve geographical diversity.

PO1056
“Breaking Bad News” During the COVID-19 Epidemic: A Virtual Objective Structured Clinical Examination (OSCE) for Nephrology Fellows
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Background: It is critical to ensure the health and well-being of the future nephrology workforce, especially among 1st year and fellowship applicants. The “Breaking Bad News” OSCE assesses fellow counseling/communication skills in 20-minute simulation scenarios: kidney replacement therapy (KRT) in ESKD, urgent KRT in AKI, and kidney biopsy. In-person simulation was impractical during the COVID19 epidemic, so we adapted the OSCE to a virtual platform.

Methods: The AKI scenario was audio only. Fellows called a simulated patient (SP) surrogate for urgent KRT consent. The ESKD and kidney biopsy scenarios were video encounters between fellows and SPs. Faculty observed while muted/video off. After each scenario, fellows received feedback from SPs and faculty (unmuted/video on). Fellows from 3 programs at 2 centers completed the OSCE in May 2021. Post-OSCE, fellows were anonymously surveyed about each scenario, the OSCE overall, and their estimate of the percent of outpatient encounters and inpatient KRT counseling they had done virtually in the past year.

Results: 15 fellows did the OSCE; 14 completed the survey (93% response rate). 93% rated the OSCE overall as a good very good approximation of a telemedicine experience. 100% were satisfied/very satisfied with the AKI scenario, 79% with the ESKD, and 77% with the kidney biopsy scenarios. Several commented that the AKI scenario was most realistic — they often counseled surrogates by telephone for urgent KRT. Fellows estimated that about 25% (median 27.5%; IQR 16-50%) of counseling for acute inpatient KRT was done virtually in the past year. They estimated about 50% (median 52.5%; IQR 36-70%) of outpatient encounters were done virtually in the past year, but several (dissatisfied with the ESKD and kidney biopsy scenarios) indicated they would not have counseled similar outpatients using telemedicine.

Conclusions: Overall, fellows felt the OSCE well-approximated virtual encounters. All were satisfied with the AKI scenario. The majority were satisfied with the ESKD and Kidney Biopsy scenarios, but some did not feel they were consistent with normal practice. The OSCE allows fellows to practice telemedicine communication skills that will remain relevant post-pandemic. The views expressed in this abstract are those of the authors and do not reflect the official policy of the Department of Defense or U.S. Government.

Funding: Other U.S. Government Support

PO1057
Well-Being of Nephrology Fellows: Evolution over the Course of a Pandemic Year
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Background: We sought to assess changes in well-being of nephrology fellows over the first year of the COVID-19 pandemic in the U.S.

Methods: The Resident Well-Being Index (RWBI), a validated tool assessing physician distress, was distributed as part of ASN’s annual nephrology fellow survey to 920 current adult, pediatric, and adult/pediatric fellows. An RWBI ≥ 5 (range 0–7) indicated distress. Demographic and fellowship factors associated with meeting the distress threshold were evaluated in univariable and multivariable logistic regression.

Results: A total of 511 fellows participated (56% response), of whom 463 completed the RWBI instrument. After 1 year of the COVID-19 pandemic, there were a higher proportion of nephrology fellows meeting the RWBI distress threshold—22% in 2021 versus 15% in 2020. Female nephrology fellows had higher RWBI scores (median 3 [IQR 3] versus their male colleagues (median 1 [IQR 3]). Higher proportions of 1st-year fellows (50% vs 42% for 2nd years, OR 1.61 for 2nd years [95% CI 0.93–2.87], p=0.046) and women (27% vs 18% of men, OR 1.71 [95%CI 1.06–2.76], p=0.028) met the distress threshold. There were no significant differences by race, ethnicity, medical school location, or adult vs pediatric fellowship. Despite the higher proportion of distress overall, 88% of respondents would recommend nephrology to medical students and residents.

Conclusions: Our follow-up assessment of nephrology fellows’ well-being after the first year of the COVID-19 pandemic indicate the continued need for supportive measures to ensure the health of the future nephrology workforce, especially among 1st year and women trainees.
Methods: Each of the 6 nephrology fellows filled out a daily survey between November 9, 2020 and January 31, 2021, which was the peak of the COVID-19 pandemic in Wisconsin to address: 1) the total amount of sleep hours 2) quality of sleep (restful or fragmented) and 3) whether on-call fellow reported to hospital from home. Responses were collected the following morning to decrease recall bias.

Results: Over the 3-month study period, 100% of the call night data was recorded. The average amount of sleep per night was 5.3 hours. When necessary to report, the average hours of sleep dropped to 4.3 hours. However, if not called in, sleep increased to 5.8 hours per night. The percentage of nights requiring patient evaluation by coming to the hospital increased by 50% during the study period with a range of 48% of nights in December and 61% in January. Sleep during night call was described as 55% restful vs. 45% fragmented.

Conclusions: This survey has generated discussion amongst fellowship leadership and currently fellows regarding novel ways to improve the night call experience to maximize education and clinical experience during training as well as improve fellow wellness. It was determined that the burden of call did not detract from the fellow education enough to warrant a change to a night float system. However, it did identify changes in management processes such as the timing of labs, implementation of dot phrases, and a sleep expert discussion to improve duration and quality of sleep.

Fellows Home Call Data

<table>
<thead>
<tr>
<th>Month</th>
<th>Average Hours of Sleep Drop to (h)</th>
<th>Average Hours of Sleep (h)</th>
<th>% of Nights Requiring Call (nights)</th>
</tr>
</thead>
<tbody>
<tr>
<td>November</td>
<td>4.3</td>
<td>5.3</td>
<td>48%</td>
</tr>
<tr>
<td>December</td>
<td>5.8</td>
<td>6.1</td>
<td>61%</td>
</tr>
<tr>
<td>January</td>
<td>5.4</td>
<td>5.3</td>
<td>48%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
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</table>

Figure 1: Educational Tools Used by Nephrology Fellows in 2016 and 2021 (left) and Percentage 2021 Nephrology Fellows Ranking Tools as Very Effective (right).

PO1061
Curriculum-Based Online Education Improves Nephrologists’ Ability to Manage Hyperkalemia in Practice
Amy Larkin, Donald Blatherwick, George Boultaslis. Medscape Education, New York, NY.

Background: The goal of continuing medical education (CME) is professional growth and improved patient care. We sought to determine if series of online continuing medical education (CME) activities will improve the clinical knowledge, competence, and confidence of nephrologists related to hyperkalemia management.

Methods: The online CME curriculum consisted of 5 online activities housed on a dedicated collection page. All used repeated pairs pre-/post-assessment study design was used and McNemar’s test (P <.05 is considered significant) to assess educational effect. The last activity was a medical patient simulation that utilized tailored clinical guidance (CG), based on current evidence and expert recommendation, followed by the opportunity for the learner to modify to their decisions. Decisions were collected post-CG and compared with each user’s baseline (pre-CG) decisions using a McNemar’s test to determine P values. The activities launched between March and October, 2020 and data were collected for up to 12 weeks.

Results: The education reached over 15,000 physicians, including over 1,706 nephrologists. Overall, knowledge improved by 24% (P<.001) and competence by 4% (P<NS) for the remaining activities. Specific improvements: 40% relative increase in knowledge related to impact of hyperkalemia (P<.001) 31% relative increase in knowledge related to clinical use of potassium binders (P<.001) 24% relative increase in knowledge related to optimizing RAAS inhibitors in patients with hyperkalemia (P<.05) 7% relative increase in competence related to clinical use of potassium binders (P<NS) Of the nephrologists who were included, 30% (P<.001) had a measurable increase in confidence in hyperkalemia management.

Conclusions: This curriculum demonstrates that a curriculum is effective at moving learners on the continuum for knowledge improvements to competence improvements. Some gaps remain after education. Among these learners, 49% need knowledge improvements related to optimizing RAAS inhibitors in patients with hyperkalemia and 41% related to clinical use of potassium binders. As such, further education needed in these areas.

Funding: Commercial Support - AstraZeneca

PO1062
Level of Confidence, Knowledge, and Literacy in Genetics Among US Nephrologists

Background: Increased availability of genetic tests in nephrology and at reduced costs are promising for improved patient diagnostic and clinical care. Nephrologists’ confidence, knowledge and genetic literacy are likely to impact the utilization of genetic testing (GT). Identifying gaps in nephrologists’ knowledge and confidence and preferred methods of learning are needed to develop tailored approaches to improving it.

PO1059
Shahid N. Muhammad,1,2,3 The University of the West of England (UWE), Bristol, United Kingdom; 2The Renal Patient Support Group (RPSG), England UK, Bristol, United Kingdom.

Background: Technology has allowed patients with Long-Term Conditions (LTCs) to access information through websites, portals, and Patient-centred organisations. 1) To understand, retrospectively, whether there has been an education neglect as part of healthcare delivery and 2) To understand if technology can help join up education. This is the first UK retrospective study found an increase in the adoption of online resources with similar effectiveness ratings as traditional resources.

Methods: Fourteen (14) topic tags were applied over 1-month (March and April 2020) between groups the Renal Patient Support Group (RPSG) (est.2009) and the Kidney Disease and Renal Support (KDARs) (est.2014) for Kids platforms. Group disclaimers encouraged informed consent. GDPR (2018) guidelines were implemented to ensure best practice and data protection is maintained.

Results: 2,560 threads were topic tagged between two groups. For adults, educational gaps surround Renal Replacement Therapy (166 tags, 12.66%); Lab Tests and Biomarkers (137 tags, 10.50%) and Medication and Pharmacy (135 tags, 10.29%). For paediatrics and younger adults, educational gaps include Medication and Pharmacy (148 tags, 11.85%), Renal Replacement Therapy (133 tags, 10.65%); Peer Support (125 tags, 10.01%) and Nursing (115 tags, 9.20%).

Conclusions: Online educational modules should complement CKD pathways, and be developed by wider Allied Health Professionals. This is the first UK retrospective study that examines clinically relevant educational gaps between online paediatric and adult renal cohorts close to two decades. Education is where healthcare requires investment.

PO1060
Nephrology Education Needs Assessment: Five Years and a Pandemic Later
Benjamin S. Ko,1 Rob Rope,2 Kurtis Pivert,2 Anna M. Burgner,3 Joshua S. Waitzman,4 Susan M. Halbach,5 Suzanne Boyle,6 Lili Chan,3 Hitesh H. Shah,2 Stephen M. Sozio,10 University of Chicago, Chicago, IL; 1American Society of Nephrology, Washington, DC; 2Oregon Health & Science University, Portland, OR; 3Beth Israel Deaconess Medical Center, Boston, MA; 4Vanderbilt University Medical Center, Nashville, TN; 5Seattle Children’s Hospital, Seattle, WA; 6Temple University, Philadelphia, PA; 7Icahn School of Medicine at Mount Sinai, New York, NY; 8University of Pennsylvania, Philadelphia, PA; 9Johns Hopkins Medicine, Baltimore, MD.

Background: We sought to identify how educational tools utilized in nephrology training had evolved in the past 5 years and through the COVID-19 pandemic.

Methods: Questions about educational tools were distributed as part of ASN’s annual nephrology fellow survey to 920 current adult pediatric fellows.

Results: 511 fellows participated in 2021 (56% response rate), compared with 377 fellows in 2016 (31% response rate). Fellows indicated that UpToDate was still the most used (82%) and most effective educational tool (66% rated it “Very Effective”); however, ASN Kasas popularity in 2016, 58% rated it was also highly rated (65% Very Effective). Use of online resource and social media increased, including both new opportunities and prior available ones such as NephJC (7% to 32%, with 46% rated Very Effective) (Figure 1). A majority of fellows (84%) rated their education as good or excellent in 2021, a percentage similar to 2016 (81%).

Conclusions: Our follow-up assessment of nephrology fellows’ educational tools found an increase in the adoption of online resources with similar effectiveness ratings as traditional resources.
PO1063
Mind Map, an Educational Tool for Teaching Clinical Reasoning in Nephrology: A Mixed-Method Study

Agnieszka Hamroun,1 Éléonore Lepers,2 Aurélie Dupré,2 Patrick Truffert,3 François Glowacki,4 1Centre Hospitalier Universitaire de Lille, Lille, France; 2Université de Lille Faculté de Médecine, Lille, France.

Background: Nephrology is commonly considered as one of the most complex disciplines for medical students, justifying the implementation of new educational tools. Although its relevance has been well-established, the mind map is still marginally used in medical education. The objective of this study is to assess the contribution of mind map for teaching clinical reasoning in nephrology.

Methods: Between November 2020 and April 2021, three groups of med students (4th to 6th year) were provided with a teaching program of 5 weekly sessions of 30-45 minutes focused on three topics (serum creatinine elevation/AKI, glomerular syndromes, dysnatremia), each developed through a specific mind map.

Results: In total, 12 med students took part in this educational experience (respectively four in 4th, 5th and 6th years). Quiz scores were significantly higher after each teaching session and overall (28.0 [26.0; 31.4], 33.0 [31.2; 36.1], 34.4 [32.4; 37.0]) respectively at baseline, immediately after and after two weeks, p < 0.001 (Fig1). Moreover, focus group interviews highlighted several themes about the specific contribution of mind map (in addition to previous standard lessons): logical and intuitive tool, effective for quick knowledge transmission, promoting long-term memorization and providing a global/integrated vision of clinical reasoning in nephrology.

Conclusions: Mind map appears to be an interesting educational tool in teaching clinical nephrology reasoning to medical students.

PO1064
Improving the Management of Gout in Patients with CKD or Kidney Transplant: Effect of Online Education


Background: Gout is a chronic condition with a considerable effect on patient health and quality of life. Hyperuricemia and gout are associated with declining renal function. Recent studies have shown that renal dysfunction and kidney transplant are risk factors for gout. A study was conducted to determine if online, segmented education could improve knowledge, competence, and confidence of nephrologists regarding the management of gout in patients with chronic kidney disease (CKD) or kidney transplant (KT).

Methods: Educational design included a 45-minute video activity with slides, segmented into a series of 5 mini-lectures by different faculty covering various aspects of gout in patients with or without CKD and KT. Educational effectiveness was assessed with a repeated-pairs pre-/post-assessment study design with 3 knowledge questions and 1 confidence question, in which each individual served as his/her own control. A chi-squared test assessed statistical significance at the P <.05 level. The activity launched 9/25/2020, with data collected through 12/4/2020.

Results: The analysis set consisted of responses from nephrologists (n=89) who answered all assessment questions during the study period. Analysis of pre- vs post-intervention responses demonstrated a significant improvement in overall knowledge; average correct responses increased from 52% pre to 76% post education. Specific areas of improvement include: Treat-to-target strategy with a target of serum UA level < 6 mg/dL in patients taking urate lowering therapy (20% relative improvement, P<.05) Starting low-dose allopurinol in a patient previously diagnosed with gout and stage 3 CKD, presenting with painful subcutaneous tophi (25% relative improvement, P<.01) Recommending pegloticase without dose adjustment for the management of refractory gout in patients with stage 4 or 5 CKD (22% relative improvement, P<.001) Post-education, 48% of nephrologists had a measurable increase in confidence in their ability to manage patients with CKD who may develop gout.

Conclusions: This study demonstrated the success of online, segmented, mini-lectures on improving the evidence-based knowledge, competence, and confidence of nephrologists in appropriately managing gout in patients with CKD or kidney transplant.

Funding: Commercial Support - Horizon Pharma
IS (3.3 (0.8) compared to 2.3 (0.7) for attending physicians). In May 2021, 5 nephrology fellows received the IS toolkit and completed surveys. Self-efficacy improved post-intervention from mean (SD) 3.0 (1.2) to 2.2 (1.6). All 5 fellows (100%) strongly agreed that the toolkit added value to training, provided a guide they would use and recommended the toolkit for future fellows.

Conclusions: Nephrology faculty and fellows strongly agreed that there is a need for guides and protocols for prescribing and monitoring IS medications. Our pilot IS toolkit incorporated into nephrology fellow training was well received and improved fellow self-efficacy.

Funding: Veterans Affairs Support

<table>
<thead>
<tr>
<th>PO1068</th>
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<tbody>
<tr>
<td>Quality Improvement Study on Dialysis Education for Residents in an Outpatient Nephrology Clinic</td>
</tr>
<tr>
<td>Young C. Hsu, Jonas Kwok, Annika K. Khine, Thanh Cao. University of Southern California, Los Angeles, CA.</td>
</tr>
</tbody>
</table>

**Background:** In a large safety net hospital outpatient nephrology clinic in Southern California, resident physicians provide a significant portion of care to patients who have chronic kidney disease (CKD) stages III to V. Many of these patients eventually require initiation of long-term renal replacement therapy (RRT). However, there are many barriers to a timely and safe initiation of RRT in this patient population. One such barrier is a deficiency in education regarding dialysis between residents and patients in nephrology clinic. We attempted to identify barriers of resident education with patients regarding the topic of RRT and assess the effects of our educational intervention. Objectives: 1. Increase resident’s knowledge regarding RRT based on pre and post intervention questionnaire 2. Increase resident’s subjective preparedness/confidence level regarding discussions of RRT 3. Increase the frequency with which residents discuss RRT with patients.

**Methods:** We created and distributed a pre-assessment survey to all Internal Medicine and Internal Medicine-Pediatrics residents at a large teaching hospital and received an approximately 50% response rate. Residents overwhelmingly responded that they do not feel prepared to initiate dialysis by the time they are deemed to require renal replacement therapy, nor did residents feel that they were adequately prepared or knowledgeable about the nuances of dialysis in order to counsel patients with CKD. We created a short teaching presentation with video reviewing dialysis topics and strategies to approach discussions with patients for residents who rotate through nephrology clinic, after which a post-survey was administered. Results are currently being collected.

**Results:** Results are currently being collected. We expect resident physicians will demonstrate increased knowledge regarding RRT based on pre- and post-intervention questionnaire, feel more comfortable discussing RRT with patients, and will discuss RRT more often with patients in clinic.

**Conclusions:** We expect to be able to conclude that resident education is a vital aspect in increasing patient's understanding and comfort regarding their disease process and dialysis at similar teaching centers where residents represent the majority of patient-physician interface in renal subspecialty care.

**PO1069**

**The Impact of Electronic Sign-Out Dot-Phrase and Simulation Exercises on Inpatient Nephrology Transitions of Care**

James D. Alstott,1 Anand K. Ramadorai,1 Sayee Sundar Alagusundaramoorthy,2 Samantha J. Strennen,1 Laura J. Maursette,1 Gauri Bhutani.1 University of Wisconsin-Madison, Madison, WI; 2University of Kentucky, Lexington, KY.

**Background:** A fellow-led QI project was initiated in 2018 after division surveys indicated a need for change in the ongoing division transitions of care (TOC) practice. **Methods:** We developed a standardized “sign-out score” to objectively assess TOC on the EMR sign-out. We next developed and implemented a standardized electronic medical record (EMR) dot-phrase as our first QI intervention. Case-based simulation sessions highlighting TOC pearls were conducted as the second QI intervention. Pre- and Post-intervention data for sign-out score was evaluated.

**Results:** A total of 647 patient EMR sign out scores were assessed between 2018-2021. Overall sign-out accuracy score (0-2) significantly improved with QI interventions (pre-intervention mean 0.9 [95% CI: 0.9-1.1; N=298] to 1.6 post-dot-phrase [1.5-1.6; N=220] to 1.7 post-simulation [1.6-1.8; N=129]; p<0.001). Table 1 provides details on the results of sign-out score. After adjustment for level of training, improvement in overall accuracy was independently associated with both dot-phrase (adjusted odds ratio (aOR) 7.6 [95% CI: 4.9-11.9]; p<0.001) and simulation (aOR 1.88 [1.1-3.16]; p=0.001). Although 2 sign-out score measures which were high performing pre-intervention worsened with dot-phrase implementation: anticipated changes and non-RRT management (aOR 0.15 [0.1-0.23]; p=0.001 and 0.07 [0.02-0.23]; p<0.001, respectively), improvement was seen with standardized care (aOR 1.36 [0.84-2.2]; p=0.21 and 4.6 [1.74-14.5]; p=0.002).

**Conclusions:** A fellow-led QI intervention including standardized sign-out dot-phrase and simulation exercises both improved the overall accuracy of TOC practiced in inpatient Nephrology consult service. The impact of dot-phrase alone on previously high performing TOC measures suggests the need for further optimization of dot-phrase and continuing simulation to enhance provider self-realization of important components of TOC.

**Table 1:** Frequency of best possible “sign-out score” before and after QI interventions

<table>
<thead>
<tr>
<th>Sign-out categories</th>
<th>Pre-intervention (N=298)</th>
<th>Post-dot-phrase (N=220)</th>
<th>Post-simulation (N=129)</th>
<th>Overall P-value</th>
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<tbody>
<tr>
<td>Incorrect Discharge</td>
<td>14 (48)</td>
<td>7 (32)</td>
<td>5 (45)</td>
<td>0.001</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td>54 (32)</td>
<td>41 (19)</td>
<td>54 (26)</td>
<td>0.001</td>
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<tr>
<td>Missed Encounter</td>
<td>65 (22)</td>
<td>44 (20)</td>
<td>29 (26)</td>
<td>0.001</td>
</tr>
<tr>
<td>Dot-Phrase Accuracy</td>
<td>38 (13)</td>
<td>67 (31)</td>
<td>77 (67)</td>
<td>0.001</td>
</tr>
<tr>
<td>Non-RRT documentation</td>
<td>97 (33)</td>
<td>67 (31)</td>
<td>89 (76)</td>
<td>0.001</td>
</tr>
<tr>
<td>Overall accuracy (%)</td>
<td>59 (20%)</td>
<td>71 (33%)</td>
<td>77 (67%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Anticipated Changes (%)</td>
<td>67 (23%)</td>
<td>71 (33%)</td>
<td>77 (67%)</td>
<td>0.001</td>
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</table>

**PO1070**

**Point-of-Care Ultrasound Training for Nephrologists: A National Survey of Nephrology Fellows**

Catherine A. Moore,1 Daniel W. Ross,2 W. Charles O’Neill3.1 University of Rochester Medical Center, Rochester, NY; 2Northwell Health, New Hyde Park, NY; 3Emory University, Atlanta, GA.

**Background:** Despite many potential applications of PoCUS in nephrology, nephrologists have been slow to adopt this technology. The past five years have seen an increase in ultrasound training within nephrology fellowship programs, although the scope of training is unknown. We conducted a national survey of nephrology fellows in United States-based training programs. The main objective of this survey was to identify the current landscape and clinical use of PoCUS in US nephrology training programs.

**Methods:** We surveyed post-graduate year (PGY) 4-8 trainees in US nephrology fellowship programs. Survey items were included in a broader trainee survey disseminated to all programs by the American Society of Nephrology in April, 2021. The six-item survey instrument probed attitudes toward PoCUS, current use, preferred instruction format, and perceived competence.

**Results:** Out of 822 US nephrology fellows surveyed, 631 (76.8 %) responded. A majority of respondents were 30-34 years of age with the majority of participants graduating from international medical schools. The majority of fellows (64.6%) indicated interest in PoCUS education, with highest interest in procedural ultrasound and diagnostic kidney imaging. Only 240 (38%) of fellows reported receiving PoCUS education during training. Of the fellows who received PoCUS training, 112 of 227 (49%) reported incorporation of PoCUS at a frequency of less than monthly, with only 62 of 227 (27%) incorporating PoCUS once per week or more. 83 of 226 (36%) fellows reported receiving adequate instruction to independently perform PoCUS, and 74 of 224 (33%) reported that they expect to be competent to independently perform PoCUS by the end of training. Handson-training, particularly with an instructor, was highly valued as a teaching technique.

**Conclusions:** Despite high trainee interest in PoCUS, the majority of current nephrology fellows are not receiving training in this domain and do not feel competent to independently perform PoCUS procedures. Handson-training guided by a skilled instructor is a highly valued PoCUS teaching technique. This survey identifies a need for the development of PoCUS programs within nephrology fellowships that incorporate hands-on teaching techniques.

**PO1089**

**Point-of-Care Ultrasound Education in Nephrology During the COVID-19 Pandemic**

Andrew A. Moses,1 Hilda E. Fernandez, Columbia University Irving Medical Center, New York, NY.

**Background:** The COVID-19 pandemic led to changes in the way people taught and learned, with higher reliance on online learning. Unfortunately, point of care ultrasound is a difficult topic to teach without hands-on practice. Here we discuss the implementation of a novel ultrasound curriculum during the COVID-19 pandemic.

**Methods:** The curriculum was based on published curriculum on point of care ultrasound for the nephrologist, with focus on four fundamental exams: kidney, lung, cardiac, and volume status. We employed a flip the classroom approach with pre-reading and videos, a pre-session quiz, followed by hands on application of skills. Standardized patients or volunteers would have been used for the hands-on session, but this was eschewed for safety concerns. The fellows and instructors themselves modeled, with proper sanitation and PPE. The hands-on sessions were well received and attended by all fellows. The skills were then applied on the wards.

**Results:** As the restrictions for front line providers were available, standardized patients were available in small groups. The learners were scheduled for two hour-long sessions with standardized patients, for practice of the skills acquired as well as the Objective structured clinical examination (OSCE). After the first session with all learners, we added a third session focused on OSCEs, as well as line placement as requested by the learners. By the end of the third session, all learners felt more confident in their skills and had passed their OSCEs.

**Conclusions:** Given the positive reception, this course is planned to continue as current, structured as well as expanded upon by rising fellows. The use of flipped classroom helped maximize the time of supervised scanning by learners. The use of ultrasound by fellows has risen and will continue to climb with further development of this important curriculum.
PO1071
Patient Navigators and Study Coordinators: A Team Approach Towards Patient Support in Decentralized Clinical Trials
Cynthia J. D’Alessandri-Silva,1 Kimberly D. Cranston,2 Anna Klochak,3 1Connecticut Children’s Medical Center, Hartford, CT; 2Advancen Inc., Ardmore, PA; 3Children’s Hospital Colorado, Aurora, CO.

Background: COVID-19 related restrictions have accelerated adoption of decentralized clinical trials(DCT). DCTs offer increased patient flexibility via online study platforms, telemedicine and home-based nursing. DCTs reduce travel, hospitalization and in-person interactions, all problematic under COVID. Potential drawbacks exist for both patients and study coordinators, however. In DCTs, removal of study-site visits may leave patients feeling confused, unsafe, disempowered and disengaged, potentially increasing drop-out risk. While DCTs may mean increased enrollment for sites, management of novel patient pathways may prove more time-consuming for study coordinators. Crucial protocol driven events or patient concerns/questions may be missed due to complex patient tracking.

Methods: The role of the patient navigator(PN) was developed to support both patients and study coordinators in DCTs. PNs will provide culturally-appropriate psychosocial education to ensure patients feel safe, informed, and supported. PNs serve as conduits between the patient and the study site, ensuring bi-directional communication of patient progress. This unique approach is being trialed in ARENA2, a pediatric Phase III study in primary distal renal tubular acidosis, a rare renal disease.

Results: A multi-lingual team with unique educational and counseling experience was recruited and trained on the protocol and disease. The team will provide weekly check-ins with patients to facilitate engagement as well as identify any concerns the patient may be having in home healthcare. This role will offer around the clock patient support which will increase accessibility and decrease burden experienced by study coordinators with heavy caseloads. PNs have also developed educational videos in target languages using lay-friendly terminology to ensure patient understanding. Topics include clinical trials, ARENA2 and research in rare diseases. The study website contains additional resources including written articles that help set expectations and provide subjects with strategies for success as they go through ARENA2.

Conclusions: The concept of sponsor-driven PN team services in DCTs will offer both patients and study sites the added benefits of support.

Funding: Commercial Support – Advancen Inc.

PO1072
Do Undergraduates Know “Nephrology”? – A Single-Site Survey of College Students
Julia M. Hopkins,1 Juan Carlos Q. Velez,2 John M. Arthur,3 Michael G. Janetch.1 1College of Charleston, Charleston, SC; 2Ochsner Medical Center - New Orleans, New Orleans, LA; 3University of Arkansas for Medical Sciences, Little Rock, AR.

Background: Over the past decade, Nephrology has experienced a 43% decline in fellowship applicants. A factor to choosing Nephrology could be a lack of early exposure. While studies have been conducted to explain why residents choose a specific fellowship program, none have surveyed the undergraduate student population to inquire whether the name “Nephrology” was even a recognizable medical specialty compared to other medical specialties. To this end, we conducted a survey of undergraduate students at the College of Charleston (CoC) to test the hypothesis that Nephrology will rank amongst the least recognizable specialties.

Methods: 274 undergraduates at CoC responded to a survey where they were asked to select every medical specialty they recognized by name (15 real specialties 3 fictious). Demographic questions regarding sex, race, collegiate level, high school location, pre-med track, and household income were included. Differences were considered by comparing 95% confidence intervals or Chi-Square test. Spearman-Rank test was used to examine whether the number of applicants per specialty fellowship position was correlated with the proportion of responses.

Results: Out of 15 medical specialties, Nephrology ranked lowest (29%); whereas, Pediatrics (97%) and Surgery (97%) ranked highest. The fictitious specialty, “diaysymptomology” was recognized least (4%). Sex, race, collegiate level, and household income were not different between those students that recognized the word Nephrology versus those that did not. Pre-med students were about twice as likely (p=0.001) to have recognized Nephrology versus non pre-med students (49% vs. 22%, respectively). There was no correlation between the proportion of undergraduate students who recognized a specific medical specialty and the number of applicants per fellowship position in 2019 (r=0.2, p=0.7).

Conclusions: Nephrology was the least recognized, non-fictional, specialty amongst undergraduates. Lack of correlation between student responses and fellowship applications, suggest that name recognition alone will not predict fellowship applicant number. The discrepancy between Nephrology and other specialties highlights a gap in name recognition at an early career stage, even amongst premedical students.

Funding: NIDDK Support

PO1070
Teaching Application of Ultrasound in Nephrology Practice in Medical Schools Using Student Peer Teaching: A Prospective, Randomized Pediatric Trial
Rainer Büscher, Philip Geiling, Fiona Schmitt. Universitätsklinikum Essen, Essen, Germany.

Background: Ultrasound has become the leading diagnostic technology in pediatrics due to its high sensitivity, easy applicability and lack of invasiveness and plays critical roles in many aspects of nephrology practice. However, it is associated with a higher examiner dependent variance. Teaching ultrasound in medical schools has grown in importance over the past years, while pediatric aspects are mainly reserved for postgraduate education. Student peer teachers take on the task of lecturers at many faculties with promising results in ultrasound education.

Methods: We designed a prospective, randomized trial in a pre-post-test design for 257 4th year medical students in our pediatric classes to investigate the effectiveness of peer teaching in pediatric ultrasound. Besides a mandatory theoretical training by the student peer teacher in our skills lab using similar ultrasound machines. The success of pre-med students were split in smaller groups and received a standardized practical training by right kidney volume of their partners in advance to test pre-existing practical skills and the course and clinical trial was well received. Over 95% of students presented the learning contents.

Results: Method: The concept of student peer teaching seems to work very well also for the right kidney volume of their partners in advance to test pre-existing practical skills and the course and clinical trial was well received. Over 95% of students presented the learning contents. However, we also observed a high interindividual variance in the volumetric renal topography sonographically well with no significant differences between both groups. However, we also observed a high interindividual variance in the volumetric results. The use of a supporting pediatric ultrasound manual did not show any significant benefit.

Conclusions: The concept of student peer teaching seems to work very well also in specific disciplines such as pediatric ultrasound and pediatric nephrology education. Therefore peer teaching seems to be of value in medical schools also in teaching complex learning contents.

Funding: Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: Two separate, identical surveys were administered: one directed to Urine Task Force members (28 respondents at the time of reporting) and one directed to the ISEV community (42 respondents).

Results: The mean time studying eUVs was 7.8 years for task force members and 5.4 years for community respondents. For task force members: 48.3% of respondents primarily focus on kidneys, 13.8% on other NOD tissues, and 6.9% by other. For the community, the focus was 29.4% kidney, 21.5% prostate, 19.6% bladder and 29.4% “other”. Both communities largely collect spot urine samples compared with timed collection (Task Force: 78.6% spot vs 21.4% timed, Community: 75.8% spot vs 24.2% timed). Urine storage was a significant focus of the survey. For the Task Force: 92.9% of respondents studied samples stored >3 months, 57.1% samples stored <3 months, and 50% studied fresh samples. The community studied less often fresh samples. Both groups predominantly stored samples as “cell-free urine”: 85.7% for task force and 65.6% for community. All task force respondents study samples frozen at -80 °C with 10.7% of respondents also studying samples stored at 4 °C. By contrast, 93.8% of community respondents stored samples at 80 °C, 9.4% at -20 °C and 6.3% at 4 °C. The task force ranked the following isolation methods in order of priority 1) centrifugation, 2) size exclusion chromatography, and 3) filtration. For the community survey this was similar. Both surveys prioritized the same downstream applications: 1) protein analysis, 2) RNA analysis, 3) functional analysis.

Conclusions: In summary, the present survey identified key similarities and differences between current practices for the Urine Task Force and the urinary eUV research community. Such information will be used to help guide future efforts to address key knowledge gaps.

Poster
PO1076
A Potential Novel Variant of Slc4a4 Can Regulate the Functional Activity of the Electrogenic Na/HCO3 Cotransporter NBCe1-B
Seong-Ki Lee,1 Marie Michenkova,1 Michael F. Romero,2 Rosanna Occhipinti,1 Andrey Desai2
1The University of the West of England (UWE), Bristol, United Kingdom; 2Mayo Clinic, Rochester, MN.

Background: The electrogenic Na/HCO3 cotransporter (NBCe1) regulates intracellular pH in many tissues and elicits vectorial HCO3⁻ flow across many epithelia. Five variants of NBCe1 have been identified: α, mainly in kidneys; β, ubiquitous; -c, in brain; -d/E, in mouse reproductive organs. Because the A/D and B/C/E variants are transcribed from two distinct promoters, they have different NH2-termini (Nt). The Romero Lab developed an isoform-specific knockout (KO) mouse of NBCe1-A/D by causing a frameshift mutation in the A/D variants’ unique Nt region (Chen et al., JASN 25:71A, 2014). Fang et al found that NBCe1-B (e1B) is expressed in kidneys of both WT and KO mice, and that e1B expression increases with metabolic acidosis in KOs (JAP Renal, 2018). They reached this conclusion by RT-PCR-amplification of B-variant–specific bands from KO kidneys. However, these amplifications generated several unidentified bands. Intrigued by these additional bands, we repeated the RT-PCR in an attempt to identify them.

Methods: Using TA cloning, we determined the sequences of two of the unidentified bands: (1) partial Slc4a4 product missing exon 4, which would lead to a frameshift, and (2) partial Slc4a4 product missing exons 4 & 5, but remaining in-frame. Because Fang et al confirmed lack of C/D/E variants, we introduced mutations (1) and (2) in e1B and e1C tagged with Flag and Myc and expressed intracellularly by two-electrode voltage-clamping in Xenopus oocytes. We also determined protein abundance/interaction by surface protein immunoblotting. Inasmuch as e1B has low activity, we co-expressed WT e1B and/or mutant e1B with super-IRBIT (which lacks binding sites for IRBIT).

Results: We found that neither mutant, alone, has activity even though Δexon 4/5-e1B interacts with super-IRBIT. However, Δexon 4/5-e1B has a dominant-negative (DN) effect on WT e1B. To test if these mutants are specific for KO mice, we inspected other WT tissues.

Conclusions: Contrary to our hypothesis, we found that e1B mutants (1) and (2) exist at least in kidneys, brain, and pancreas, leading us to conclude that cells could in principle regulate NBCe1-B activity by adjusting the amount of the novel DN variant Δexon 4/5-e1B.

Funding: NIDDK Support, Other U.S. Government Support

Poster
PO1077
A Novel I551F Variant of Na/HCO3 Cotransporter NBCe1 Shows Reduced Cell Surface Expression and May Exert a Dominant Negative Activity
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Background: Homozygous mutations in SLCA44, encoding the electrogenic Na/HCO3 cotransporter NBCe1, cause proximal renal tubular acidosis (pRTA) associated with extrarenal symptoms. Although 17 mutated sites in SLCA44 have thus far been identified among pRTA patients, physiological significance of other non synonymous single nucleotide variants (SNVs) in this gene remains largely underestimated.

Methods: To identify functional impact on NBCe1 (SLCA44) sequence variants, we used an integrated pipeline of bioinformatics and functional assays. We prioritized sites for functional analysis based on allele frequency, conservation, and physical location. We generated stable cell lines expressing wild type and mutant NBCe1 variants and measured cell surface expression by immunofluorescence analysis.

Results: Using an integrated approach to prioritize variant alleles for functional studies, we generated stable cell lines expressing wild type and mutant NBCe1 variants. We measured cell surface expression of wild type and mutant NBCe1 variants using immunofluorescence analysis. We found that the I551F variant showed reduced cell surface expression compared to wild type NBCe1. Additionally, we observed changes in other cellular characteristics associated with the I551F variant, suggesting a potential role in dominant negative activity.

Conclusions: Our study highlights the importance of functional studies to elucidate the physiological significance of non-synonymous single nucleotide variants in SLCA44, particularly in the context of proximal renal tubular acidosis. Further research is needed to determine the full spectrum of clinical implications of the I551F variant and to explore its potential role in other non-synonymous variants in SLCA44.

Funding: NIH grant K08DK115243.
Methods: We investigated the functional properties of SNVs in NBCe1 using immunocytochemical, molecular, and electrophysiological assays. From NCBi database, we identified 13 SNVs that have not previously been characterized in highly conserved, transmembrane domains of NBCe1-A.

Results: Immunocytochemical analysis revealed that I51F variant was present predominantly in the cytoplasm in HEK293 cells, whereas all other SNVs did not show obvious changes in subcellular distribution. Western blot analysis in HEK293 cells demonstrated that the I51F variant showed impaired glycosylation and a 69% reduction in cell surface levels. To determine the role of I51 in more detail, we examined the significance of various artificial mutants both in non-polarized HEK293 cells and polarized MDCK cells, which indicated that only I51F substitution resulted in cytoplasmic retention. Moreover, functional analysis using Xenopus oocytes demonstrated that the I51F variant had a significantly reduced activity corresponding to 39% of that of wild-type, whereas any other SNVs and artificial I51 mutants did not show significant changes in activity. Finally, immunofluorescence study in HEK293 cells indicated that the I51F variant retains wild-type NBCe1-A in the cytoplasm.

Conclusions: These data demonstrate that I51F-NBCe1-A shows impaired transport activity predominantly through cytoplasmic retention, and suggest that the variant can have a dominant-negative effect by forming complexes with wild-type NBCe1-A.

Funding: Government Support - Non-U.S.

PO1078

Diacidic Motif Is Required for Efficient Transport of NKCC2 to the Plasma Membrane

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Background: Mutations in the apical Na-K-2Cl cotransporter, NKCC2, cause type I Bartter syndrome (BS1), a life-threatening kidney disease. We have previously demonstrated that BS1 nonsense mutation Y998X, which interferes with the highly conserved dileucine like motifs of NKCC2 C-terminus, compromises NKCC2 surface delivery through ER retention mechanisms. However, whether these dileucine like motifs are sufficient for anterograde trafficking of NKCC2 remained to be determined. Consequently, the aim of the present study was to investigate whether additional motifs are required for NKCC2 efficient transport to the plasma membrane.

Methods: NKCC2 protein expression was monitored in transiently transfected OKP and HEK cells, using immunoblot and confocal imaging. NKCC2 surface expression was measured by cell surface biotinylation assay. NKCC2 stability and maturation was monitored by cycloheximide chase assay.

Results: Among the motifs identified as ER export signals in ion channels are the diacidic D/E-X-D/E motifs, which have been shown to promote interaction of cargo with the coat complex II (COPII) budding machinery. Interestingly, sequence analysis of NKCC2 C-terminus revealed the presence of two di-acidic motifs, WEEE996 and HDAE1012, located upstream and downstream of BS1 mutation Y998X, respectively. Importantly, mutation of HDAE1012 to A1012AA disrupted glycosylation and cell surface expression of NKCC2, whereas mutation of WEEE996 had no effect. Cycloheximide chase analysis demonstrated that the absence of the terminally glycosylated form of HDAE1012 was not due to increased rates of degradation of mutant co-transporters, but was instead caused by defect in maturation. Accordingly, co-immunolocalization experiments showed that HDAE1012 was trapped in the ER. Finally, overexpression of dominant negative mutants of Sar1 GTPase completely abolished NKCC2 maturation, clearly indicating that NKCC2 exit from the ER is COP II dependent.

Conclusions: Our data indicate that in addition to highly conserved dileucine like motifs of NKCC2 C-terminus, the cotransporter uses also a di-acidic exit code for export from the ER and targeting to the cell surface. Elucidating the molecular mechanisms of the motif-facilitated export may help to develop therapeutic strategies targeting NKCC2 transport from the ER to the cell surface.

Funding: Government Support - Non-U.S.

PO1079

Furosemide Alleviates Hypercalciuria and Hypomagnesemia in Claudin 16-Deficient Mice

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Background: Loss-of-function mutations in the CLDN16 gene encoding for Claudin 16 (Cldn16) cause type I Bartter syndrome (BS1), a life-threatening kidney disease. We have previously demonstrated that BS1 nonsense mutation Y998X, which interferes with the highly conserved dileucine like motifs of NKCC2 C-terminus, compromises NKCC2 surface delivery through ER retention mechanisms. Therefore, we hypothesize renal tubular ABCA1 ablation will lead to Na dependent changes in BP.

Methods: Transgenic mice (Tg^BS1^-/-;ABC1^-/-), which express CRE recombinase in tubular epithelia when fed doxycycline (dox), were bred with mice expressing floxed ABCA1 to generate a model deficient in tubular ABCA1 (FF). Tail cuff systolic BP (SBP; Visitech) and urine volume after diuretic administration was measured in mice. Immunoblotting was performed on kidney protein lysate.

Results: Immunoblotting of renal PA showed reduced ABCA1 (50±11%; n=6, p<0.05) in FF compared to littermate wildtypes (WTs, 100±7%; n=5) mice. The SBP of FF (n=11) mice was greater immediately post-dox and during chol or high Na feeding (Fig. 1; *, p<0.05 vs WT) compared to WTs (n=15). Low Na diet abolished SBP differences between mice, while 6 weeks (W) of 1% chol diet raised the SBP in ABCA1 (FF). Tail cuff systolic BP (SBP; Visitech) and urine volume after diuretic administration was measured in mice. Immunoblotting was performed on kidney protein lysate.

Conclusions: Tubular ABCA1 deficiency stimulates Na dependent SBP which we speculate is related to enhanced Na dependent ENaC and NKCC2 activity.

Funding: Veterans Affairs Support, Private Foundation Support

SBP of FF and WT mice in days (D) and weeks (W) of diet

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
WNK4 Is a Transducor of V2 Receptor Signaling in the Thick Ascending Limbs and Distal Convoluted Tubules

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Background: Vasopressin (AVP) is essential for water and Na+ homeostasis. In the kidney, its actions are mediated by the V2 receptor (V2R), which signals through protein kinase A (PKA). The phosphorylation of the Na+-Cl cotransporter (NCC) and the Na+-K+-Cl cotransporter (2NCC) by the WNK-SPAK/OSR1 pathway facilitates the activation of NCC and NCC2 in response to AVP. WNK4 can be regulated by PKA through the phosphorylation of its 388 motifs in vitro models. Thus, we hypothesized that WNK4 mediates the activation of NCC and NCC2 in response to AVP.

Methods: We transfected HEK293 cells with NCC2 or the V2R with SPAK and either WNK1, WNK3, WT WNK4 or WNK4 with Ala instead of Ser in its 5 RRS5 motifs. Cells were stimulated with 30 nM forskolin or 1 nM desmopressin (DDAVP). We crossbred our WNK4 strain (in a C57BL/6 background) with 129sv mice while selecting for the full-length allele of NCC2 to evaluate the phosphorylation status of NCC2.

Results: AVP-stimulated NCC2 phosphorylation was increased in WNK4+/+ and WNK4-L319F compared with WT mice. WNK4-L319F mice fed with normal or low K+ diets for 12 hrs. Generation of WNK4-L319F mice with CRISPR/Cas9, which inactivates the full-length allele of NCC2, did not affect total or phosphorylated NCC2 protein levels.

Conclusions: Our data suggest that WNK4 is a transducer of AVP signaling in the TAL and DCT, modulating NCC2 and NCC. This might contribute to the anti-natriuretic effects of this hormone and the increase in medullary osmolality that occurs with antidiuresis.

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Upregulation of NCC by Hypokalemia Involves Additional Mechanisms to Direct Cl- Sensing by WNK4

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Background: Cl-sensitive WNK4 kinase plays an important role in the modulation Na+ homeostasis in the distal convoluted tubules (DCT). WNK4 activates the Na+-Cl- cotransporter (NCC) in response to hypokalemia, promoting its phosphorylation. Low plasma [K+] decreases intracellular [Cl-] and Cl binding to WNK4's active site, leading to its activation. We have previously shown that hypokalemia and low [Cl-] increase WNK4 phosphorylation at S1196 and S1196. Hypokalemia also promotes phosphorylation of KHL3, a residue located on the C-terminal subunit of the Cl- sensing domain. We hypothesized that this Cl- sensing domain facilitates the localization and activation of the WNK-SPAK/OSR1 pathway. Mice deficient in WNK4-L319F have decreased AQP2 expression, but increased pNCC and KS-WNK1 protein levels were observed by immunoblot, and 18S was carried out by Taqman probes. 12 hrs urine collections were conducted and water intake between the groups was equalized using gelled diets.

Results: In HEK293 cells, we found that an increase in phosphorylation of SPAK and NCC2 (in response to hypokalemia, and stimulated with forskolin), WNK4 with mutants, WNK4-L319F and WNK4-R286F with forskolin requires WT NCC. In contrast, phosphorylation of S130 of NCC2 was WNK4-dependent. Cells with WT NCC and the V2R showed an increase in SPAK phosphorylation when stimulated by DDAVP. DDAVP also increased WNK4's phosphorylation at S1196. DDAVP-induced phosphorylation of both total and phosphorylated WNK4, NCC, and NCC2, as well as phosphorylated SPAK and Slc12a3 mRNA levels. These effects were absent in WNK4-/- animals. In contrast, WNK4-L319F mice did respond to DDAVP by increasing AQP2 protein levels. In addition, WNK4-/- mice fed with low K+ diets for 7 days had increased water consumption at baseline and increased urine output when water-restricted, with a tendency towards lower total body water.

Conclusions: Our data suggest that WNK4 is a transducer of AVP signaling in the TAL and DCT, modulating NCC2 and NCC. This might contribute to the anti-natriuretic effects of this hormone and the increase in medullary osmolality that occurs with antidiuresis.

Funding: Government Support - Non-U.S.

PO1084 Calcium-Sensing Receptor-Mediated Activation of the WNK4-SPAK-NCC Pathway by Glucose/Fructose In Vivo and Ex Vivo

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Background: NCC is activated via the CaSR-WNK4-NCC pathway. Glucose and other sugars act as positive allosteric modulators of the CaSR. In vitro from our lab (ASN 2019-2020) showed that extracellular glucose or fructose increases activation of the WNK4-Spark-NCC pathway via the CaSR. Since glucose reabsorption occurs proximally in the nephron, the distal cell has little opportunity to function (DCT) is negligible. Fructose delivery depends largely on intake. Thus, sugars delivery to DCT could result in NCC activation via CaSR-WNK4-NCC pathway.

Methods: We used wild-type mice treated with vehicle, oral fructose +/− calcitropic NPS2143, or a single dose of dapagliflozin 1mg/kg i.p to induce transient glycosuria +/− NPS2143. Kidneys were extracted after 3 hours to assess activation of the WNK4-Spark-NCC pathway by immunoblotting. To rule out a effect of dapagliflozin in the WNK4-Spark-NCC pathway by angiotensin II, we pre-treated mice with losartan. The response to a thiazide challenge in vehicle, fructose or dapagliflozin treated mice was assessed. Finally, we used an ex vivo Langerhans rat kidney preparation to evaluate the effect of different concentrations of glucose infusion in the renal artery.

Results: In WT mice, we observed increased activity of the WNK4-Spark-NCC pathway following dDAVP infusion in the kidney after exposure to 20% fructose. Glucose or osmotic stimulation of dapagliflozin (p<0.01). These effects were abrogated by NPS2143 (p<0.01) and was not observed in WNK4-KO mice (p<0.001). Additionally, the effect of dapagliflozin was present in mice pre-treated with losartan (p<0.01). Natriuresis induced by a thiazide challenge was significantly lower in vehicle or fructose, or dapagliflozin, than in vehicle/dapagliflozin, suggesting activation of NCC. Finally, we observed increased NCC and SPARK phosphorylation by infusing glucose above proximal tubule reabsorption threshold levels to ex vivo rat kidney preparations (p<0.001); notably, this effect was prevented by NPS2143.

Conclusions: Glycosuria by fructose increases NCC, SPARK and WNK4 phosphorylation in a CaSR-dependent fashion. Our data thus suggest a calcimetric-like behavior for sugars in the DCT. This effect may have implications for salt-retention mechanisms induced by disorders of glucose metabolism and increased dietary fructose intake.

Funding: NIDDK Support, Government Support - Non-U.S.

PO1085 Kidney-Specific WNK1 Amplifies NCC Responsiveness to Potassium Imbalance

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Background: The distal convoluted tubule (DCT) NaCl cotransporter (NCC) is activated by phosphorylation, a process that is potassium (K+) regulated and dependent on the Na+-Cl- cotransporter (NCC). WNK4, a kidney-specific WNK1 isoform lacking the kinase domain, controls WNK signaling pathway localization in the DCT. Its role in NCC regulation, however, is unresolved: while early studies proposed that WNK1 functions as an NCC inhibitor, recent work suggests that it activates NCC. Here, we show that the role of WNK1 in NCC regulation, we studied KS-WNK1 mice across a wide range of plasma K+ (2.0-9.0 mmol/L), induced by dietary maneuvers and diuretic challenges.

Results: KS-WNK1 KO mice exhibited blunted NCC phosphorylation compared to littersmates, indicating that KS-WNK1 activates NCC during K+ deficiency. In contrast, NCC phosphorylation was augmented in K+-loaded KS-WNK1 mice relative to controls, consistent with KS-WNK1-mediating NCC inhibition during hyperkalemia. Focusing on K+-restricted mice: 1) KS-WNK1 +/- mice had mislocalized WNK-Spark-AKT, 2) KS-WNK1 +/- mice had blunted activation of the WNK4-Spark-OSR1 kinase cascade, 3) KS-WNK1 +/- mice had sex-specific alterations to K+ and Ca2+ plasma levels, 4) KS-WNK1 +/- mice had no change to blood pressure, but were less sensitive to thiazide diuretics compared to littermates.

Conclusions: KS-WNK1 has a bimodal effect on NCC activity, activating NCC during K+ restriction and inhibiting NCC during high K+, thus expanding the inverse relationship between NCC phosphorylation and plasma [K+]. During K+ deprivation, KS-WNK1 facilitates the localization and activation of the WNK4-Spark-OSR1 pathway. Mice (and rats) with WNK1 have sex-specific differences in electrolytes, as well as aldosterone resistance. These observations clarify the role of KS-WNK1 on NCC, and identify a novel mechanism that contributes to sexual dimorphism in the mammalian nephron.

Funding: NIDDK Support, Other NIH Support - NIDDK R01DK998145, NIDDK K08DK118211, NHLBI R01HL152680

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360
**PO1086**

High Dietary Potassium Increases Blood Pressure in a Rat Model of CKD

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**Background:** Potassium dysregulation is recognized as a major factor in the development and progression of CKD. The aim of this study was to investigate the role of dietary potassium in the early development of CKD in a rat model.

**Methods:** Male Sprague-Dawley rats were fed a low-potassium (0.05%) or high-potassium (2.5%) diet for 8 weeks. Blood pressure, kidney function, and histological changes were assessed.

**Results:** Rats on the high-potassium diet showed a significant increase in blood pressure compared to the low-potassium group. Kidney function tests, including serum creatinine and blood urea nitrogen, were also elevated in the high-potassium group. Histological analysis revealed early signs of tubulointerstitial damage.

**Conclusions:** Dietary potassium plays a significant role in the early development of CKD, highlighting the importance of potassium regulation in the prevention and management of CKD.

**PO1087**

Rescuing Low Blood Pressure in Amiloride-Treated Mice by Low-Potassium Diet Relies on NCC Activation

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**Background:** Amiloride is a diuretic that inhibits the sodium-potassium-2-chloride cotransporter (NCC). This inhibition is associated with hypotension, but the molecular mechanisms underlying this response are not fully understood.

**Methods:** Mice were treated with amiloride and fed diets containing varying levels of potassium. Blood pressure and kidney function were measured.

**Results:** Mice on low-potassium diets showed a significant increase in blood pressure compared to those on high-potassium diets. This effect was reversed by the administration of a potassium-sparing diuretic.

**Conclusions:** The hypotensive response to amiloride is mediated by a decrease in NCC activity, which is further suppressed by low-potassium diets.

**PO1088**

SALL3 Is a Salt-Responsive Distal Convoluted Tubule-Specific Transcription Factor Induced in Distal Neprhon Remodeling

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**Background:** Distal tubular damage is a common feature of chronic kidney disease. The mechanisms underlying these changes are not well understood.

**Methods:** Mice were induced with unilateral ureteral obstruction and fed diets containing varying levels of potassium. Gene expression analysis was performed.

**Results:** Sall3, a transcription factor, was found to be upregulated in distal tubules of mice with unilateral ureteral obstruction and low-potassium diets. Knockdown of Sall3 resulted in blunted tubular remodeling.

**Conclusions:** Sall3 is a key transcription factor in distal tubular remodeling, providing a potential target for therapeutic intervention.

**PO1089**

Chemogenetic Activation of the Distal Convoluted Tubule Enhances Sodium Excretion Through Rapid Dephosphorylation of the Sodium-Chloride Cotransporter

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**Background:** The distal convoluted tubule (DCT) is a critical site for the regulation of sodium and potassium balance. The mechanisms underlying sodium excretion in this region are not fully understood.

**Methods:** Mice were genetically engineered to express a potassium channel (Gq) in the DCT. The response to a high-sodium diet was assessed.

**Results:** Mice expressing Gq in the DCT showed an increased sodium excretion rate compared to control mice. This effect was reversed by the administration of a potassium channel blocker.

**Conclusions:** Chemogenetic activation of the DCT provides a novel approach to modulating sodium excretion, potentially offering new therapeutic avenues for kidney disease.

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*P < 0.01 compared to normal KCl diet (ANOVA with post-hoc testing).

A.U., arbitrary units; BP, blood pressure; N.M., not measured.
PO1090
Mechanistic Importance of Reduced KLHL3 and CUL3 Expression in Cul3-A9-Mediated Familial Hyperkalemic Hypertension
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Background: Mutations in the ubiquitin ligase scaffold protein Cullin 3 (CUL3) cause the disease familial hyperkalemic hypertension (FHH). In the kidney, the mutant Cul3Δ–/– mice co-expressed with C99p signalosomes subunits JAB1 that negatively regulates CUL3 activity. This leads to Cul3-A9 autodegradation, and increased abundance of With-No-Lysine [K] Kinase 4 (WNK4), which inappropriately activates the downstream kinase SPAK, which then phosphorylates and hyperactivates the Na+/Cl– cotransporter (NCC). We showed lower that Cul3 alone does not increase WNK4, so the precursor mechanism by which Cul3-A9 causes FHH is unclear. We hypothesized Cul3-A9 degrades Kelch-like 3 (KLHL3), the CUL3 substrate adaptor for WNK4; thus reduced abundance of KLHL3 combined with reduced CUL3 are mechanistically important in Cul3-A9-mediated FHH.
Methods: We studied Cul3 KO (Cul3Δ–/–), mice, Cul3 KO mice expressing CUL3-A9 (Cul3Δ–/–; Cul3-A9), Cul3 heterozygotes expressing CUL3-A9 (Cul3Δ+/–; Cul3-A9), compound Cul3Δ–/– and Cul3Δ+/– heterozygotes (Cul3Δ+/–; Cul3-A9), and Jabi KO (JabiΔ–/–) mice. All mouse lines were inbred and all experiments were performed at 14 weeks of age.
Results: Cul3Δ–/– did not promote degradation of Cul3 targets that accumulate in Cul3Δ–/– kidney: WNK4, cyclin E, or NQO1 (a surrogate for the CUL3 substrate Ntr2). In Cul3Δ–/– mice, Cul3-A9 prevented KLHL3 accumulation seen in Cul3Δ–/– kidney and promoted KLHL3 degradation in Cul3Δ–/– mice. Higher NQO1 and lower cyclin E abundances were observed in Cul3Δ–/– mice compared to control mice. Cul3Δ–/– mice displayed increased WNK4-SPAK activation and phospho-NCC abundance, and FHH-like phenotype with increased plasma [K+] and salt-sensitive blood pressure. Similarly, reduced Cul3 and KLHL3 abundances and increased abundances of WNK4 and phospho-NCC were observed in JabiΔ–/– mice.
Conclusions: Together, these data provide evidence for a mechanism of reduced KLHL3 and reduced Cul3 in Cul3-A9-mediated FHH. Cul3-A9 potently degrades KLHL3, but also exerts modest effects on other Cul3 targets, raising the possibility of unidentified reduced phenotypes in the human disease.
Funding: NIDDK Support, Private Foundation Support

PO1091
Non-Reabsorbable Anions Enhance Potassium Excretion by Multiple Mechanisms
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Background: Potassium (K+) secretion in the distal nephron (DN) is governed, in part, by the lumen-negative transepithelial potential (Vte), created by ENaC-mediated sodium reabsorption, and partially attenuated by paracellular chloride (Cl+) reabsorption. K+ secretion increases when nonreabsorbable ions (NRA), such as HC03 or beta-hydroxybutyrate, replace luminal Cl+. Although this allows an appropriate response to alkaline-ash rich diets, it can drive exaggerated K+ secretion in alkalosis. According to textbook views, NRA facilitates K+ secretion solely by increasing the lumen-negative Vte. However, the effects of NRA on the potassium secretory machinery have not been determined.
Methods: Wild-type C57BL/6J mice were randomized to control (1%K+), potassium chloride (KC15.5%) or potassium bicarbonate (KHCO3:5.5%) diets for 10 days. Physiological, molecular and imaging analysis were performed. Pendrin-KO mice were examined to assess the specific role of pendrin in NRA-mediated potassium excretion.
Results: Consumption of the high KHCO3 diet increased urinary potassium K+ excretion and the trans-tubular K+ gradient (TTK) significantly more than with the high KC1 diet, consistent with an NRA response. Both diets increased aldosterone to the same extent, correlating with similar increases in ENaC expression and proteolytic activation. Surprisingly, the high KHCO3 diet significantly enhanced ROMK protein expression and apical localization in the late distal convoluted tubule and CNT more than the high KC1 diet. The diets also induced opposite changes in Pendrin protein and apical membrane localization.
Conclusions: The high KC1 diet increased urinary K+ excretion in the high KC1 diet increased in the high KHCO3 diet. The high KHCO3 diet also uniquely induced a remodeling of the intercalated cells in the late DCT and CNT, whereby the number of pendrin-positive cells increased without change in principal cells. Pendrin-KO mice excrete the high dietary KHCO3 lead to the same extent as WT mice but develop metabolic alkalosis.
Funding: NIDDK Support

PO1092
The Effect of Epidermal Growth Factor Inhibition on Distal Nephron Sodium Reabsorption in Mice
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Background: Studies have shown that the epithelial growth factor (EGF) decreases the activity of ENaC while the influence of EGF on renal Na+ transport via NCC is unknown. Previous investigations in mDCT-15 cells showed that EGF increases endocytosis of NCC. Using radio-telemetry, we found that EGF inhibition increases systolic blood pressure in response to increasing the dietary Na+ intake. Our results in consolidation with other researchers, suggest that EGF affects BP by influencing the activity of ENaC and NCC. Our goal is to determine whether EGF inhibition increases BP via alterations in Na+ reabsorption.
Methods: Using metabolic cages, we collected urine samples at three time points over 24 hours in 7 week old male mice. Normal salt (LS) diet (0.4% Na+ was given for baseline collections and high salt (HS) diet (4% Na+ was given for experimental collections. Only the experimental (E) group, n=4 received gefitinib (an EGF receptor tyrosine kinase inhibitor) orally at 100 mg/kg and the control (C) group received placebo. Hydrochlorothiazide (HCTZ) 2.4 mg per 10 kg BW orally and amiloride 1.45 g/kg via IP injection were administered. Following a washout period, HCTZ and amiloride were given simultaneously to assess the total effect on NCC and ENaC.
Results: There was no difference in the average urinary Na+ excretion over 24 hours for baseline measurements between the groups when receiving the LS diet (experimental (E) group: 105 ± 13 mmol vs. control (C) group: 82 ± 23 mmol, N.S.). However, when giving the HS diet and HCTZ, the E group had a higher average urinary Na+ excretion in response to a higher dietary Na+ intake (E group: 24 ± 15 mmol vs. C group: 13 ± 5 mmol, p<0.05). For amiloride with HS diet there was no difference in average urinary Na+ excretion between the groups (E group: 110 ± 127 vs. C group: 92 ± 48 mmol, N.S.). When giving both HCTZ and amiloride to the mice while receiving the HS diet, the E group had a significantly higher urinary Na+ excretion compared to the C group (E group: 997 ± 66 vs. C group: 777 ± 48 mmol, p<0.05).
Conclusions: Therefore, our data suggests that inhibition of EGF increases Na+ reabsorption via NCC. As previously suggested, this may indicate that EGF ligands act as tonic inhibitors of NCC tubular sodium reabsorption. Future experiments will explore the in vivo effects of EGF inhibition on sodium excretion along other components of the nephron.
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PO1093
Role of mTORC2/SKGl Signaling in Rapid Response to Acute K Load to Maintain K+ Homeostasis
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Background: The kinase mTORC2 phosphorylates SGK1 and is required for normal K+ secretion in the aldosterone-sensitive distal nephron. Aldosterone is known to play a role in mediating a sustained response to changes in SGK1 gene transcription, however, it is unknown how rapid responses are mediated. Here we have explored the role of mTORC2 and ENaC activity in the early response to an acute K+ load to regulate K+ secretion.
Methods: Inducible tubule-specific Rictor (a core component of mTORC2) knockout mice (TRKO) were generated (Pax8-rtTA/LC-1/Rictorflx/flox). Both WT and TRKO mice received control or 2% KCl via gavage following intraperitoneal vehicle or EGF (20 µg, EGF inhibitor) injection. After 30 min (E group) or 48 h (C group) reversal of placebo. Hydrochlorothiazide (HCTZ) 2.4 mg per 10 kg BW orally and amiloride 1.45 g/kg via IP injection were administered. Following a washout period, HCTZ and amiloride were given simultaneously to assess the total effect on NCC and ENaC.
Results: Adult TRKO mice on normal diet displayed no abnormality except significantly elevated aldosterone. K+ administration by gavage triggered markedly greater Na+ excretion and lower K+ excretion in TRKO than WT mice, with differences detectable within 1 h of gavage. Benzamil induced a greater natriuresis in TRKO than WT mice, with more pronounced potassium conservation, consistent with greater ENaC activation in WT than in TRKO. The response of WT occurred rapidly, before significant change in aldosterone. In benzamil-treated mice, the natriuresis and kaliuresis of WT and TRKO mice were comparable, strongly supporting the idea that KC1 inhibited via alterations in Na+ reabsorption and thus the aldosterone system.
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ENaC-dependent K⁺ secretion in WT, and that this response is defective in TRKO. Patch clamp studies showed similar increased ENaC activity in WT but not in TRKO mice, and no change in ROMK activity in WT or TRKO by KC1 gavage. Membrane expression of cleaved α- and γENaC were significantly increased in WT but not in TRKO mice receiving KC1 gavage. No significant increase in membrane expression of ROMK was observed in WT or TRKO A gavage. Finally, both SGK1 and Nedd2-2 phosphoprotein levels were increased in WT but not TRKO mice receiving KC1 gavage.

Conclusions: Overall, the data strongly suggest that an acute K⁺ load acts through mTORC2/SGK1 to rapidly stimulate ENaC but not ROMK to promote K⁺ secretion. These effects are primarily due to local renal tubular K⁺ sensing.

Funding: NIDDK Support, Private Foundation Support

POI1094

Structural Determinants of mTORC2 Substrate Specificity and SGK1 Phosphorylation Revealed by Cryogenic Electron Microscopy
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Background: mTORC2 is a multi-subunit kinase complex central to multiple essential signaling pathways. Notably, it responds to hormonal signals and local electrolyte concentrations to phosphorylate SGK1 and regulate K⁺ secretion in the renal tubules. Two core subunits, Rictor and mSin1 distinguish mTORC2 from its much better characterized relative, mTORC1. Two other subunits, mTOR itself and a small scaffold, mLST8, complete the core complex. Previous mTORC2 reconstructions have lacked key regions of the > 1 MDA complex, particularly determinants of specificity.

Methods: Core mTORC2 subunits were expressed in Expi293F cells and purified using new methods for no grid purification. cryo-EM was performed using Krios at SLAC for high energy electrons for density maps of human mTORC2. Structures were solved for apo-complex at overall 3.23 Å resolution, and for co-complexes with substrates, SGK1 and AKT, at 3.38 and 3.44 Å, respectively.

Results: The apo-complex reveals architectural features of functionally important domains, including specific side chain positions and interactions, which are visualized for the first time. In particular, Rictor/Ser-1624 and Ser-1625 were observed to engage in hydrogen bond interactions with mTOR Thr-2998, in a manner that provides steric hindrance to binding of Rapamycin, and explains mTORC2 resistance to the effects of this clinically important mTORC1 inhibitor. In addition, mSin1, the other defining subunit of mTORC2, is seen to form extensive contacts with Rictor, including an extended strand, which makes multiple weak contacts with a Rictor helical cluster. Most notably for the apo-complex, Rictor plays a key role in forming the co-complex structure with mLST8—but not the mLST8 complex, we see a marked change in the conformation of the mSin1 N-terminal extended strand in a manner consistent with previous functional data identifying this region as required for phosphorylation of SGK1, but not Akt, thus providing a structural basis for differential regulation.

Conclusions: These findings provide new structural insight into mTORC2 specificity and context-dependent activities, and foundation for further mechanistic studies. Further, these findings provide a potential avenue toward highly selective mTOR modulators with potential clinical utility.

Funding: NIDDK Support, Other NIH Support - National Institute of General Medical Sciences, Private Foundation Support

POI1095

In Vivo Influence of a Protease-Resistant Epithelial Sodium Channel Gamma Subunit on Fluid Homeostasis

Background: Extracellular fluid depletion promotes proteolytic processing of ENaC's γ subunit. Removal of the subunit's inhibitory tract enhances channel open probability. Although several cleavage sites exist distal to the γ subunit's inhibitory tract, only one known site resides proximal to the inhibitory tract: a furin cleavage site (RKRK 143 to QQQQ 143, or "Q4") to reduce ENaC activity in WT but not TRKO post-gavage. Finally, both SGK1 and Nedd2-2 phosphoprotein levels were increased in WT but not TRKO mice receiving KC1 gavage.

Conclusions: Overall, the data strongly suggest that an acute K⁺ load acts through mTORC2/SGK1 to rapidly stimulate ENaC but not ROMK to promote K⁺ secretion. These effects are primarily due to local renal tubular K⁺ sensing.

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POI1096

A Rare Case of Acquired 11-Beta-Hydroxysteroid Dehydrogenase Deficiency
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Introduction: 11-Beta Hydroxysteroid Dehydrogenase (HSD11B1) is an enzyme that is involved in steroid hormone physiology. HSD11B1 enzyme exists in two isoforms, HSD11B1-type 1 and type 2. Type 2 isozyme is responsible for converting cortisol to inactive cortisone. Plasma concentration of cortisol is approximately 100-fold higher than aldosterone and activation of mineralocorticoid receptors by cortisol is normally limited due to its conversion to inactive cortisone at the sites of aldosterone action by the enzyme HSD11B1-type 2. We are presenting a rare case of HSD11B1 deficiency in a patient taking herbal supplementation.

Case Description: A 73-year-old female with PMH of hypertension, hyperlipidemia and chronic pain was admitted to the hospital with fatigue and shortness of breath. She denied any history of diarrhea or recent use of diuretics or laxatives. She has a history of using some herbal supplements in large quantities for pain control. Initial blood pressure was 140/80 mmHg. EKG showed sinus bradycardia with PVCs and bigeminy. The lab results are summarized in table A. She received aggressive potassium supplementation and spironolactone with subsequent improvement of her condition.

Discussion: HSD11B1 deficiency is either congenital or acquired by ingestion of licorice or its derivatives (glycyrrhizic and glycyrrhetinic acids). The deficiency results in a decreased conversion of cortisol to accumulation of cortisol. The effect of cortisol on the mineralocorticoid receptor results in hypokalemia, metabolic alkalosis, and low aldosterone and renin activity. The diagnosis requires careful history and identification of specific clinical features and biochemical abnormalities.

POI1097

New Method to Discriminate Function of A and B Type of Intercalated Cells in Split-Opened Collecting Ducts
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Background: The collecting duct (CD) is a highly adaptive terminal part of the nephron in which its essential functions are maintenance of electrolyte homeostasis. Electrically uncoupled principal and intercalated cells (PCs and ICs) perform different physiologic tasks and exhibit rather distinctive morphology. However, acid-secreting A- and base secreting B-type of ICs cannot be easily separated in functional studies despite visually mirrored localization of their transport acid-base systems. Thus, there is no consensus of whether chloride transport is localized to specific CD segment. A BICUC chloride-stimulated cAMP and spironolactone with subsequent improvement of her condition.

Methods: We used BCECF-sensitive intracellular pH (pH) measurements in split-opened CDs followed by immunofluorescent (IF) detection of AQP2 and pendrin from A/B cell type ratio in the CD. The technique of split-opening isolated CD allows unambiguous monitoring of alterations in function in many individual cells within the split-opened area. However, it is not possible to specifically change the driving force for Cl⁻ at luminal or basolateral sides, which is used for established tubule studies to identify IC types of certain cells on periphery.

Results: Expression of the prostatein in oocytes, along with ENaC (N = 15), increased amidolactone-sensitive currents, compared to oocytes with ENaC but no prostatin (N = 15; p < 0.0001). In oocytes expressing a Q4 gamma subunit (N = 15), prostatin no longer increased currents (N = 15). Western blot of PNGase-digested tissue lysates revealed a full-length (60 kDa) γ subunit and two shorter proteins, consistent with subunits either cleaved at the furin site (~53 kDa) or at a more distal site. Tissues from Q4 mice lacking the 53 kDa band, suggesting impaired Furin site cleavage. Blood K⁺ was normal in Q4 mice (N ≥ 7 for each sex and genotypes). On a LSD, Q4 male mice exhibited greater loss of body water than control males (p = 0.04; N = 6-7), but females exhibited no difference in body weight (N = 7-8).

Conclusions: These findings support a role for proteolytic activation of ENaC in male mice maintaining total body fluid in response to dietary Na depletion. Females did not show a impaired body fluid retention, suggesting additional compensatory mechanisms.

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Disorder.

Presented with respiratory exhaustion. Hemodialysis was started to correct the acid-base and sodium bicarbonate was started, the patient showed no clinical improvement and of severe malnutrition, and no worsening of kidney function. The patient was screened (pH 7.35; pCO2 16 mmHg; pO2 102 mmHg; HCO3 8 mmol/L; anion gap 22 mmol/L; dose paracetamol (4 g daily), and Flucloxacillin (12 g daily). After 10 days she presented severe pain complaints. In that context, she was started on opioids, NSAIs and high-

We found that metabolic acidosis leads to augmented transport rate and increased total population of A-type in the CD.

PO1098 Piezol in Intercellular Cells (ICs) Mediates Flow-Induced [Ca2+]i Transients in Mouse Cortical Collecting Duct (CCD)
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Background: Within the CCD, an acute increase in tubular fluid flow rate (TFFR) exposes principal cells (PCs) and ICs therein to hydrodynamic forces. In response, a biphasic increase in [Ca2+]i is observed, with an immediate high amplitude increase due to release of IP3-sensitive internal Ca2+ stores coupled to extracellular Ca2+ entry at the basolateral membrane. This is followed by a decay to a plateau that is higher than baseline and sustained by luminal Ca2+ entry. This increase in [Ca2+]i is necessary for BK channel-mediated flow induced K+ secretion (FIKS) in the microperfused mammalian CCD. We have recently reported that PIEZO1, a mechanosensitive, Ca2+-permeable channel, is expressed on the basolateral membranes of PCs and ICs in the mouse CCD (Dalghi et al., 2019).

Methods: To examine whether IC PIEZOL expression contributes to the increase in [Ca2+]i triggered by TFFR, we generated a mouse with targeted deletion of PIEZOL in ICs (IC-Piezol-KO).

Results: Immunofluorescence analyses of kidneys harvested from mice (C57BL/6) expressing PIEZOL-tdTomato revealed a significant increase of PIEZO1 expression in ICs from mice fed a high K (HK, 5% K+, n=4) vs. normal K (SK, 1% K+, n=4) diet for 10 days. Fluorescence intensity ratios (FIRs; ratio of the Ca2+ indicator Fura-2 emission signals measured at excitation wavelengths of 340 nm and 380 nm), corresponding to [Ca2+]i, were measured in individually identified PCs and ICs in CCDs isolated from (i) HK-fed IC-Piezo1-KO (n=3), (ii) SK-fed littermate control (n=3), and (iii) HK-fed control (n=3). FIRs in response to the PIEZO1 activator Yoda1 (1 mM). PCs and ICs from HK-fed control mice exhibited a greater increase in [Ca2+]i in response to Yoda1 than SK-fed control mice (p=0.001). However, ICs from HK-fed IC-Piezo1-KO mice exhibited a reduced or absent increase in [Ca2+]i in response to Yoda1 vs. SK-fed control mice (p=0.001). In microperfused CCDs isolated from IC-Piezo1-KO mice, an increase in TFFR did not elicit a typical increase in [Ca2+]i in ICs (p=0.001, n=3 controls and n=4 KOs).

Conclusions: We conclude that Piezo1 is upregulated in the CCD by a HK diet and contributes to the TFFR-induced increase in [Ca2+]i, ICs necessary for FIKS.

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PO1099 An Extremely Rare Interaction Between Two Commonly Used Drugs
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Introduction: The use of Paracetamol and Flucloxacillin can result in an elevated anion gap metabolic acidosis. Interaction between these drugs is a rare disorder that results from accumulation of pyroglutamic acid. Affected patients are usually women with chronic illness, sepsis, and malnutrition.

We found that inhibition of CIC-K2-dependant H+ conductance was observed in cell lines (pH 7.35; pCO2 16 mmHg; pO2 102 mmHg; HCO3 8 mmol/L; anion gap 22 mmol/L; lactate 0.4 mmol/L). Laboratory tests showed hyponatremia of 141g/dl in the context of severe malnutrition, and no worsening of kidney function. The patient was screened for lactic acidosis, ketoacidosis, toxic alcohol ingestion and salicylate poisoning with no positive findings. Finally, we concluded accumulation of pyroglutamic acid secondary to the constant use of flucloxacillin and paracetamol in high doses as the leading cause of elevated anion gap metabolic acidosis. Despite these drugs were immediately stopped and sodium bicarbonate was started, the patient showed no clinical improvement and presented with respiratory exhaustion. Hemodialysis was started to correct the acid-base disorder.

Discussion: Despite being extremely rare, metabolic acidosis induced by drug interaction between Paracetamol and Flucloxacillin is a severe and potentially life-threatening disorder. We recognize the relevance of this case since these drugs are commonly prescribed together.

PO1100 Dietary Ammonium Exacerbates Pyelonephritis in Mice Prone to Vesicoureteral Reflux
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Background: In a mouse model of urinary tract infection with Uropathogenic E. coli (UPEC-UTI) dietary NH4Cl (AC) induces metabolic acidosis and increases UPEC burden in reflux prone C3H-HeN, but not Ctrl deficient, C3H-HeJ mice. We have confirmed and extended these studies by comparing the inflammatory response in C3H-HeN mice fed AC-diet vs. standard chow (SC), and by examining the effect of HCl-acidosis.

Methods: Female C3H-HeN mice were fed: standard chow (SC), NH4Cl (2% w/w; AC), or 1g/mol 0.4 N HCl supplemented chow (HCl-A). Acid-base state was assessed and other epithelial tissues, and the dysregulation of this channel has been implicated in cancers. TRPV6 and its close homologue TRPV5 are activated by phosphatidylinositol 4,5-bisphosphate (PIP2, a soluble form of PIP2, was determined by cryo-electron microscopy. Based on this molecular model of human TRPV6 with PIP2, a structural model of human TRPV6 was set up. This model was then exposed to hydrodynamic forces. In response, TRPV6 undergoes structural and position changes, suggesting the opening of the lower gate. Recently, a structure of rabbit TRPV5 in complex with dioctanoyl (diC8) phosphatidylinositol 4,5-bisphosphate (PIP2) was determined by electron microscopy. Based on this structure, a structural model of human TRPV5 with PIP2 was set up. This model was then embedded in a 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) lipid bilayer with water molecules added on both sides of the bilayer using CHARMM-GUI. Using the protein disease research group, department of physiology, faculty of medicine and dentistry, university of alberta, edmonton, ab, canada.

Background: Transient receptor potential vanilloid subfamily member 6 (TRPV6) is a Ca2+-selective channel that mediates Ca2+ entry into epithelial cells as the first step of the transepithelial Ca2+ transport pathway. TRPV6 is expressed in the kidney, intestine, and other epithelial tissues, and the dysregulation of this channel has been implicated in cancers. TRPV6 and its close homologue TRPV5 are activated by phosphatidylinositol 4,5-bisphosphate (PIP2); however, it is less clear how PIP2 activates TRPV6 at the molecular level.

Results: Recently, a structure of rabbit TRPV5 in complex with diocetyl (diC8) PIP2, a soluble form of PIP2, was determined by cryo-electron microscopy. Based on this structure, a structural model of human TRPV5 with PIP2 was set up. This model was then embedded in a 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) lipid bilayer with water molecules added on both sides of the bilayer using CHARMM-GUI. Using the AMBER18 software, three 500-ns molecular dynamics simulations were performed for the two systems of TRPV6 with and without PIP2.

Results: Interaction energy analyses show that the distance between the diagonally opposed residues R302, R305, K484, and R584 of TRPV6 play a significant role in the binding of diC8 PIP2. The binding of PIP2 to TRPV6 increases the distance between the diagonally opposed residues D542 in the selectivity filter as well as the distance between the diagonally opposed residues M578 in the lower gate. Secondary structure and density analyses show that residue M578 in TRPV6 in the presence of PIP2 undergoes structural and position changes, suggesting the opening of the lower gate. Principal component analysis also indicates that the binding of PIP2 increases the dynamic motion of both the selectivity filter and the lower gate of TRPV6.
PO1102
Lithium Treatment Induces Changes in E-Cadherin, β-Catenin, and Na+/K+-ATPase β1 in Rat Inner Medullary Collecting Duct in a Time-Dependent Manner
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Background: Lithium (Li) induced Nephrogenic Diabetes Insipidus (NDI) develops in around 40% of psychiatric patients receiving Li treatment. NDI is characterized by the inability of the kidney to concentrate urine due to insufficient water reabsorption in the kidney collecting duct (CD). Studies in rats have shown that Li induces a cellular compositional change of the CD with a fractional decrease in the ratio of principal-to-intercalated cells after 4 weeks of Li. This cellular remodeling is reversible in rats undergoing recovery for 19 days following 4 weeks of Li treatment. We aimed to investigate if regulation of the cell-contacts E-cadherin and β-catenin have a role in the cellular remodeling. The Na/K-ATPase was also investigated due to previously shown influences on cell polarity and cell-contact formation in kidney cells (Rajasekaran et al. Mol Biol Cell).

Methods: Immunohistochemistry (IHC) was performed on rat kidney sections used in previously published studies (Christensen et al., AJP; 2006; Treviccone et al., AJP, 20: 107, 2020) from sections from rats treated with Li for 4, 10 and 15 days and 4 weeks were stained using antibodies against the cytoplasmic domain of E-cadherin, β-catenin and Na/K-ATPase β1-subunit. Sections from rats that had undergone recovery for 6 and 12 days following 4 weeks of Li treatment were stained for β-catenin.

Results: E-cadherin and β-catenin labeled basal and lateral plasma membrane domains in the inner medullary CD (IMCD). In the proximal part of IMCD, the labeling was absent from the basal plasma membrane domains of multiple cells after 4 and 10 days of Li treatment and was present again after 4 weeks of Li. In addition, the basal labeling of E-cadherin was absent from some cells after 12 days of recovery. IHC of the Na/K-ATPase β1-subunit revealed a similar subcellular localization, and the protein was not present in the basal plasma membrane domains of multiple cells in the proximal part of the IMCD already after 4 days of Li.

Conclusions: The subcellular localization of the adherens junction proteins E-cadherin, β-catenin and Na+, K -ATPase β1 is affected by Li treatment in the proximal part of the IMCD. In addition, the absence of labeling from the basal plasma membrane domains appears to occur prior to the cellular remodeling.

Funding: Private Foundation Support

PO1103
Deletion of the EP3 Receptor in the Kidney Tubule of Adult Mice Has No Impact on the Major Channels and Transporters Involved in Kidney Water Handling
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Background: Prostaglandin E2 (PGE2) is an important lipid mediator modulating various aspects of kidney function. PGE2 exerts its effects via four PGE2 receptors, EP1, EP4, but it is unclear which PGE2 effects are mediated through which receptor. The EP3 receptor is expressed in the thick ascending limb (TAL) and the collecting duct, where it is proposed to inhibit CAMP generation and NaCl and water reabsorption. However, EP3 is also expressed in endothelial cells of arteries and arterioles, that also play a role in kidney function.

Methods: To assess the tubular role of EP3 in adult mice we generated a mouse model based on the Pax3Cre system with doxycycline-dependent deletion of EP3 along the renal tubule and assessed their renal phenotype in respect to water handling. qPCR and RNAseq confirmed that EP3 was highly expressed in cortical and medullary TAL and collecting ducts, but it was not detected in proximal tubule and thin limbs.

Results: Two weeks after treatment with doxycycline, EP3 mRNA expression was reduced by >80% in whole kidney (RT-qPCR) and non-detetable (RNAseq) in tubules of knockout mice compared to control mice. The other EP receptors expression remained unchanged in the kidney except for a slightly increase in EP4 expression. Under basal conditions, there were no significant differences in food and water intake, bodyweight, urinary output or plasma and urine biochemistry in both male and female control and knockout mice. There were no differences between genotypes in their kidney handling of water during an acute water load, or in their response to the vasopressin V2 receptor agonist Arterenol. Moreover, relative expression levels of the main channels and transporters involved in kidney water handling, including AQP2, AQP3, AQP4, NKKCC2, eNaC and UT-A1, ROMK and Na-K-ATPase remained similar to the control mice.

Conclusions: This new model provides a novel tool for examination of the role of EP3 in other aspects of kidney function or kidney disease independently of potential developmental abnormalities or systemic effects.

Funding: NIDDK Support

PO1104
Bayesian Identification of Transcription Factors That Regulate Aqp2 Transcription
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Background: Renal collecting duct and connecting tubule cells selectively express the water channel aquaporin-2 (AQP2) and Aqp2 gene transcription is strongly regulated by vasopressin. However, the transcription factors (TFs) responsible for regulation of expression of AQP2 remain largely unknown. Here, we used Bayesian data integration techniques to identify these TFs.

Methods: The general strategy is to use Bayes’ Rule to integrate several -omic datasets, most notably a curated list of 1344 TFs present in the mouse genome with regard to probability of regulating Aqp2 gene transcription. To prioritize TFs, existing proteomic and transcriptomic data, ATAC-Seq, histone H3K27-acetylation ChIP-Seq, and RNA-polymerase II ChIP-Seq data are used. Beyond this, we use additional -omic datasets to prioritize TFs that are regulated by vasopressin. Finally, we carried out new RNA-Seq experiments mapping the time course of vasopressin induced changes in the transcription of mouse mpkCCD cells to further prioritize TFs that change in tandem with AQP2.

Results: The analysis identified 17 TFs out of 1344 in the mouse genome that are most likely to be involved in regulation of Aqp2 gene transcription. These TFs included eight that have been proposed in prior studies to play a role in Aqp2 regulation, viz. Cebp, Elf1, Elf3, Ets1, Jun, Jnk, Nrk1, and Sp1. The remaining nine represent new candidates for future studies (Aif1, Irf3, Klf5, Klf6, Nfly, Nrk2b, Stat3, Nrk4a).

Conclusions: The Bayesian analysis has identified the TFs most likely to bind to Aqp2 cis-regulatory elements and likely to be regulated by vasopressin stimulation, providing a roadmap for future studies to understand regulation of Aqp2 gene expression.

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PO1105
The Enhanced Expression of AQP4 in Cerebral Ischemia Is Attenuated in AQP11 Heterologous Knockout Mice
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Background: The role of aquaporins (AQPs) in the brain edema needs to be clarified to advance its treatment. Since the importance of AQP4 for the formation of brain edema has been shown in AQP11, expressed in the brain capillary, may also be important for the regulation of brain edema. In fact, we recently reported the associated expression of AQP4 and AQP11 in osmotically challenged AQP11 heterologous knockout mice (HKM) (Koike S et al. Biochimie. 2021).

Methods: Both common cervical arteries were ligated for 15 min or 60 min to produce an ischemic-reperfusion model of brain infarction. On one or two days after the reperfusion, total RNA in the brain between Bregma and Lambda was isolated from wild mice and HKM. A real-time RT-qPCR was employed to examine the expression levels of several genes including AQP1, AQP4, AQP11, Iba1 (microglial marker), GFAP (astrocyte marker), Lamp2 (pro-apolipotic factor), Bax (pro-apototic factor).

Results: Gene expression profiles were similar between wild mice and HKM in 60a1 (increase), Lamp2 (increase) with more severity in 60 min ligation and in the second day. A similar profile was also observed with slightly decreased AQP1 by 5-22%. In contrast, the expression profiles of AQP4 and GFAP were outstanding in that both were more highly induced in wild mice than HKM, by 56% vs. 21% and by 75% vs. 335%, respectively, with further increases in 60 min ligation and in the second day. The results suggested the activation of astrocytes expressing AQP4 by the reperfusion, which might be attenuated in HKM. In agreement with this, the expression of Bax was increased in wild mice by 18% with 60-min ligation while it was decreased by 12% in HKM, suggesting a smaller brain damage in HKM. Interestingly, AQP11 expression was decreased after reperfusion by 13-25% in wild mice while it was decreased more in HKM in 25-30%. The results suggest that this further AQP11 decrease in HKM may have attenuated the increasing detrimental AQP4 in brain infarction.

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PO1106
Acute Hemoglobin Level Drop Based on Body Volume Gained
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Background: Hemoglobin (Hb) changes with blood transfusions have been widely studied, but to our knowledge, Hb drop associated with volume gain have not been studied. High fluid infusion volume in critically ill patients always result in Hb drop, but the general extent of Hb drop may vary among individuals. We undertook a pilot study to assess Hb changes based on daily volume gained among anuric hemodialysis patients.
Methods: Chronic anuric hemodialysis (HD) patients without active bleed admitted to our institution for reasons other than dialysis were included. Strict input/output measurements and Hb levels peri-HD were obtained. Post-HD levels were obtained at least 12h post treatment to allow for equilibrated fluid compartmentalization. Changes in Hb per L of body volume gained were calculated.

Eighty-five individuals were included. Average age 60±7.2 years, 6 males, 4 females, estimated fat free mass (FFM) 49±3.5 Kg, pre-HD Hb 9.7±1.28, post-HD Hb 9.36±1.28 g/dL, positive fluid balance per patient 1182±775 mL, Average Hb drop was -0.19±0.38 g/dL per L of fluid gained, or 0.004±0.12 g/dL/L of fluid gained/ Kg of fluid lost.

Conclusions: Hemoglobin drop with large fluid infusion may be studied in the anuric HD population. Our pilot study indicates thus far that Hb drop may be ~0.2 g/dL/L on average or a maximum of ~0.8 g/dL per liter of positive fluid balance. Additional data are being collected. Our study may help clinicians gauge for possible blood loss during large fluid infusion required for hemodynamically unstable patients.

PO1107
A Salty Goodbye to Diuretic Resistance: Hypertonic Saline
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Introduction: Understanding the interplay of cardiorenal physiology and pathophysiology in diuretic resistance requires a deep understanding of RAAS, ADH, and virtually all segments of the nephron. To treat, requires not only understanding but also the ability to investigate and differentiate. However, a treatment that can inhibit RAAS (directly and indirectly), stimulate Cardiac Output, improve GFR, and increase natriuresis could be the universal answer. 3% Saline has the ability to improve Cardiac Output and decrease SVR, improve renal blood flow, stimulate ANP, decrease SVR, improve renal blood flow, inhibit RAAS, inhibit ADH, and stimulate ANP. Therefore, the answer to Diuretic Resistance is 3% Saline.

Case Description: A 55 y.o. AAF presented to the hospital for severe edema and shortness of breath. PMHx of HFpEF, DM, ITN, CKD3a3 (non-nephrotic). She presented with AKI II, severe hyponatremia, and anasarca. Echo revealed EF 40%, biatrial enlargement, RV overload and reduced RV function. She was initially treated with high dose furosemide but did not improve. She was given Metolazone which caused worsening hyponatremia which was treated with 100mL of 3% Saline. This caused an immediate increase in urine output and sodium. She was then changed to a bumex drip and high dose spironolactone (200mg) with some improvement (via objective urine electrolyte assessment) she was still inadequately diuresed. She was then treated with 3% + Loop pulse dosing and sustained a robust diuresis of >3L of urine and maintained urinary sodium >50.

Discussion: The potential causes of diuretic resistance arise from the RAAS system and the individual nephron segments. The RAAS system however is the most universal target (when inhibited). While DCT, ASDN, CD and CCT. are involved, regardless of which segment is primary, targeting the RAAS system would likely have significant benefits in all diuretic resistance. 3% Saline works as a potent IVF to improve Cardiac Output, decrease SVR, improve renal blood flow, inhibit RAAS, inhibit ADH, and stimulate ANP. Using 100mL of 3% saline to augment diuresis (or alone) causes improvement in virtually all cardiorenal parameters. The NaCl load directly inhibiting RAAS through distal NaCl delivery (salt load also increases salt wasting), this causes decreased arterial arteriolar constriction and thus further improving GFR. It also stimulates ANP in the RA to inhibit RAAS and ADH indirectly.

PO1108
Enhanced Diuresis with Sequential Nephron Blockade
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Introduction: Achieving volume control in patients with severe edema can be challenging, as diuretic resistance may occur. In such cases, sequential nephron blockade (SNB), a treatment not considered in the use strategy should be considered.

Case Description: A 60-year-old woman with HIV and Dilated Cardiomyopathy s/p CRT-D presented with dyspnea and anasarca due to torsionde and lossartan. In the ED she weighed 370 Lbs., had stable hemodynamic parameters, hypoxemia, diffuse lung infiltrates and left CDA causes. Oxygen, IV loop diuretics and Bactrim were initiated for concerns of PCP and HF. Despite an average UO of 3 L/day she had no meaningful weight loss after CTA. Fluid restriction and SNB with IV thiazide and loop agents were instituted.

Methods: We conducted an exploratory pilot study for 10 healthy controls following water load then 5 cardiodrenal patients with kidney disease. 1) Fasting healthy controls provided urine samples to measure osmolality and baseline 2Na/Mg scans were performed. They were instructed to ingest water (15 mL/kg) within 15 minutes. Four subsequent sodium images and urine samples were acquired at 15 min intervals starting one hour after water ingestion. 2) Cardiodrenal patients underwent an MRI scan, provided a blood and urine sample, but no water loading.

Results: Mean age of the 10 healthy controls was 41.8 ± 15.3 years. In the morning fasting, medulla/cortex ratio was 1.55 ± 0.11 with concurrent urinary osmolality measured at 814 ± 121 mOsm/L. Mean a SD fasting urinary osmolality dropped significantly to 73 ± 14 mOsm/L, p=0.001. Mean medulla/cortex ratio dropped significantly to 1.31 ± 0.09 mOsm/L for maximal dilution, p=0.002. Figure 1 displays changes of Na/Mg pictures before (A) and after (B). 1H15 (C), 1h30 (D) and 1h45 (E) after a water load. Urinary osmolality and medulla/cortex ratio are significantly correlated, r=0.54, p=0.0001. Mean age of the 5 cardiodrenal patients was 76.6 ± 12.2 years, eGFR was 54 ± 37 mL/min/1.73m2.

Conclusions: We explored CMG dynamically every 15 min in healthy controls and demonstrated significant changes after a water load. We were also able to acquire 2Na/Mg pictures in cardiodrenal patients with kidney disease with plans for future analyses.
PO1111

Attenuated Urinary Sodium and Volume in Response to Saline Load in Heart Failure with Preserved Ejection Fraction


Background: Heart failure (HF) is characterized by fluid overload due to impaired sodium (Na) excretion. Impaired urinary Na excretion in response to intravenous Na load has been demonstrated in HF with reduced ejection fraction (HFrEF). We hypothesized that patients with HF with preserved ejection fraction (HFpEF) also have impaired sodium excretion.

Methods: All participants were instructed to follow a low (2-3 g/d) sodium diet for a week prior to the study. Urinary results were normalized using urine creatinine. Cases and controls were compared using Wilcoxon rank-sum tests.

Results: Mean age and body mass index for the HFpEF participants were 62+/-12 years and 36.3+/-8.5 Kg/m², and for control participants were 47+/-18 years and 24.6+/-3.7 Kg/m² respectively. Plasma BNP tended to be higher (median 54.0 (29.0, 118.0) versus 5.0 (5.0, 34.0) pg/ml; p = 0.15), while ucGMP/plasma BNP ratio was lower (median 0.7 (0.4, 0.8) versus 7.3 (1.7, 8.5) (pmol/mg)/(pg/ml); p = 0.014) in cases as compared to controls.

Conclusions: In this rigorous, controlled human pilot study, patients with HFpEF had lower urinary volume and attenuated urinary sodium excretion compared to controls after intravenous sodium and volume load. Data and biospecimens collected in this study should inform the pathogenesis of sodium retention in HFpEF.

PO1112

Attenuated Renal Response to Endogenous Natriuretic Peptides in Heart Failure with Preserved Ejection Fraction


Background: The pathophysiology of sodium retention in heart failure with preserved ejection fraction (HFpEF) remains largely unknown. A potential mechanism is attenuated renal response to natriuretic peptides (NPs). Urinary cyclic guanosine monophosphate (ucGMP) is an intracellular messenger of NPs, and an attenuated ucGMP/B-type NP (BNP) ratio suggests decreased renal response to BNP. We hypothesized that patients with HFpEF have attenuated response to NPs.

Methods: We studied ucGMP/plasma BNP ratios in 9 HFpEF patients and 5 controls (no history of renal or heart disease). All participants were placed on a low (2-3 g/d) sodium diet for a week prior to the study. Urinary results were normalized using urine creatinine. Cases and controls were compared using Wilcoxon rank-sum tests.

Results: Mean age and body mass index for the HFpEF participants were 62+/-12 years and 36.3+/-8.5 Kg/m², and for control participants were 47+/-18 years and 24.6+/-3.7 Kg/m² respectively. Plasma BNP tended to be higher (median 54.0 (29.0, 118.0) versus 5.0 (5.0, 34.0) pg/ml; p = 0.15), while ucGMP/plasma BNP ratio was lower (median 0.7 (0.4, 0.8) versus 7.3 (1.7, 8.5) (pmol/mg)/(pg/ml); p = 0.014) in cases as compared to controls.

Conclusions: Our pilot study shows that ucGMP/plasma BNP ratio, which reflects renal response to BNP, was attenuated in patients with HFpEF. These data suggest that impaired renal response to NPs may be implicated in the pathogenesis of fluid retention in HFpEF.

PO1113

Association of Urinary Potassium Excretion with Progression of CKD

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Background: Out of range serum potassium levels are associated with worsening renal function and increased occurrence of cardiovascular disease (CVD) events in
Licorice-Induced Syndrome of Mineralocorticoid Excess
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Introduction: Edema and volume overload are common complaints. Here, we present a case of edema resolution with reduced licorice consumption.

Case Description: A 34 y/o Caucasian woman with history significant for hypothyroidism and recurrent episodes of bronchitis presented for evaluation of recurrent facial, arm, and lower extremity swelling over the past year. She has been evaluated extensively with no etiology found in the past. She takesBuena 0.5 mg at least once weekly when she has swelling. She does not have any evidence of kidney dysfunction, heart failure, liver failure, or evidence of proteinuria on laboratory findings. She has been evaluated by rheumatology and was only found to have a weakly positive ANA with no other associated findings (hematuria, arthralgias, or muscle pain). She denies any shortness of breath or orthopnea. Her vitals were within normal limits (BP: 115/70, Pulse: 55). She is very active and exercises daily. Despite limiting her sodium intake, she continues to have recurrent swelling. On further questioning, she mentioned drinking a tea high in licorice. Her basic metabolic panel shows Na+ at 140, K+ at 4.3, Cl- at 100, and CO2 at 26. Her urinalysis was bland with her urine Na+ < 20. Measured plasma renin and aldosterone activity, shown in the table, were found to be low at baseline. Afternoon free cortisol level was measured to be 0.199. After discontinuation of licorice, she increased back to normal limits with complete resolution of symptoms.

Discussion: Chronic ingestion of licorice is a rare but a known cause of syndrome of mineralocorticoid excess (AME). Licorice contains a steroid, glycyrrhetinic acid, which inhibits the function of the enzyme 11-beta-HSD2. This same enzyme is deficient in AME. This case occurred even when small amounts of licorice (50g per day). Typically, these cases present with hypertension, hypokalemia, metabolic alkalosis, low plasma renin activity, and low plasma aldosterone levels. The only treatment necessary is cessation of licorice and symptoms typically resolve in about 1 week. This case illustrates the importance of obtaining a complete medication history including supplement use.

POI115
Not Just Licorice: Abiraterone and Apparent Mineralocorticoid Excess
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Introduction: Abiraterone is a CYP17A1 inhibitor which blocks androgen synthesis and is used to treat castration-resistant prostate cancer. This drug also decreases cortisol synthesis, causing a compensatory increase in adrenocorticotropic hormone (ACTH) and accumulation of mineralocorticoids. The result is the syndrome of apparent mineralocorticoid excess (AME) which manifests clinically as hypokalemia, metabolic alkalosis and hypertension. Abiraterone is approved for use only with concurrent glucocorticoid replacement to mitigate these effects. We present a case of refractory hypokalemia resulting from abiraterone use.

Case Description: A 74-year-old man with metastatic prostate cancer and head and neck cancer presented with urinary retention and acute kidney injury (AKI) as well as hyponatremia and metabolic alkalosis which were present a week prior. Home medications included abiraterone, ciprofloxin (given two weeks prior), prednisone 5 mg daily (recently decreased from 5 mg twice daily) and spironolactone. A urinary catheter was placed, the AKI improved rapidly and the patient remained with refractory hypokalemia. A urine potassium-to-creatinine ratio was high. Post-obstructive polyuria was considered as a reason for kaliuresis; however, hypokalemia and metabolic acidosis preceding this event made it unlikely to be the sole cause. Given abiraterone use, serum cortisol was checked and was low with no increase after giving cosyntropin. Serum aldosterone, renin and their ratios were normal. The patient was diagnosed with abiraterone-induced AME. Prednisone was increased to 5 mg twice daily and eplerenone was started in place of spironolactone. Two months later, the serum potassium was normal without supplementation.

Discussion: Abiraterone-induced AME is characterized by low serum cortisol but unlike adrenal insufficiency, presents with hypokalemia, metabolic alkalosis and hypertension. In this case, AME resulted from the inhibition of a 17alpha-hydroxylase activity of the CYP17A1 enzyme, leading to decreased cortisol, increased ACTH, and accumulation of the potent mineralocorticoid deoxycorticosterone. Glucocorticoid supplementation (prednisone 5 mg twice daily recommended) is needed to suppress ACTH and prevent these effects. Eplerenone is an aldosterone receptor blocker and is preferred over spironolactone in patients with castrate-resistant prostate cancer as spironolactone interacts with the androgen receptor.
Pseudo-hyperaldosteronism. Renin, aldosterone levels were checked which are low. CT scan of hyperplasia was not done and reported that hyperplasia. Renal function showed minimal potassium was high significant of renal loss. High 24 hour urine cortisol/cortisol ratio suggestive of mineralocorticoid excess. Posaconazole was changed to Voriconazole on 10/28/20. Due to persistent hypertension, spironolactone was increased and due to hyperkalemia, oral potassium was added. Twelve days after stopping Posaconazole all electrolyte and acid base abnormalities are resolved.

Discussion: Combination of hypokalemia, hypertension and metabolic alkalosis need to suspect mineralocorticoid excess. Posaconazole inhibits 11 beta-hydroxysteroid dehydrogenase-2 which prevents conversion of cortisol to cortisone. Fracal sodium and aldosterone leads to amplification of mineralocorticoid receptor action causing increase in activity, number of epithelial sodium channels (ENaC), Na-K-ATPase channels. Excess uptake of sodium leads to hypertension and creates increased negativity causing K+ and HCO3- to leave the cell. Hypokalemia with hypertension lead us to suspect a hyper mineralocorticoid state. Workup revealed spot urine K of 4.3 mEq/L, bicarbonate (HCO3) 29 mEq/L and newly elevated liver enzymes. He was diagnosed with immune checkpoint inhibitor hepatitis and treated with prednisolone 70 mg via nasogastric tube (NGT). Two days later, blood pressure increased to 170/80 mmHg with severe hypokalemia and alkalosis. Patients with mineralocorticoid excess can be treated with aldosterone receptor antagonist or ENaC blockers or by stopping or decreasing the dose of Posaconazole. Patients on posaconazole need to be monitored for hypokalemia, hypertension and alkalosis. However, not every patient will develop these which may be likely due to genetic predisposition.

POI118
Prednisolone-Related Mineralocorticoid Excess: Case of Hypokalemia and Metabolic Alkalosis
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Introduction: We report a case of the mineralocorticoid effect of prednisolone resulting in hypokalemia and metabolic alkalosis in a patient treated with checkpoint inhibitor in the setting of oropharyngeal cancer.

Case Description: A 78-year-old male with past medical history of oropharyngeal squamous cell carcinoma presented with fatigue. One week prior, he was treated with pembrolizumab. Admission vital signs were significant for fever to 39.1°C and normotensive blood pressure 130/88. Laboratory results revealed serum potassium (K+) 4.1 mmol/L, bicarbonate (HCO3) 26 mEq/L and newly elevated liver enzymes. He was diagnosed with immune checkpoint inhibitor hepatitis and treated with prednisolone 70 mg via nasogastric tube (NGT). Two days later, blood pressure increased to 170/80 mmHg and laboratory studies revealed hypokalemia and metabolic alkalosis with serum K+ 3.0 mmol/L and HCO3 33 mmol/L. Potassium was repleted with a total of potassium chloride (KCl) 80 mEq via NGT. The next morning, blood pressure 164/78, serum K+ 2.7 mEq/L and HCO3 33 mmol/L. Nephrology was consulted for persistent hypokalemia and metabolic alkalosis. The triad of hypokalemia, metabolic alkalosis and hypertension lead us to suspect a hyper mineralocorticoid state. Workup revealed spot urine K+ of 100 mmol/L, serum aldosterone <3.0 ng/dL and serum renin <0.1 ng/dL. Findings were consistent with an exogenous source of mineralocorticoid activation. Prednisolone was thought to be the cause. He required a total of KCl 150 mEq (40 mEq intravenous, 140 mEq NGT) to raise serum K+ to 3.4 mmol/L in 24 hours. As such, we recommended discontinuing prednisolone in favor of dexamethasone which has no mineralocorticoid effect. Two days after discontinuation of prednisolone, serum K+ was 5.1 mmol/L and KCl 40 mEq via NGT twice a day and serum HCO3 was 28 mmol/L. Supplemental KCl was discontinued. One week later, serum K+ remained in normal range at 4.1 mmol/L.

Discussion: We documented clinically significant mineralocorticoid effect of prednisolone resulting in hypokalemia and metabolic alkalosis. Physicians should be aware of electrolyte disorders associated with steroid use. With increased use of checkpoint inhibitors, this scenario may be encountered more often. Treatment may require stopping prednisolone and using alternative steroids with no mineralocorticoid checkpoint inhibitors, this scenario may be encountered more often. Treatment may be required.

POI119
From Hypokalemia to Sjögren Syndrome: What a Twist!
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Introduction: Potassium disorders are one of the many serious conditions that could attempt against a patient’s life. Understanding the clinical presentation, diagnosis, management and treatment of hypokalemia is paramount for the development of successful clinical physician. In addition, being aware of the associations between electrolyte disturbances and rheumatologic conditions increases the benefits of correctly treating and preventing underlying disease.

Case Description: This is the case of a 24-year-old female patient, GIP2-AO, with a past medical history of hypoglycemia and hypokalemia since pregnancy with twins. Patient presented to emergency department with shortness of breath, general malaise, muscle weakness, and unable to ambulate. Physical examination was remarkable for proximal muscle weakness, diminished deep tendon reflexes with intact sensation. Laboratory bloodwork reported positive mycoplasma pneumonia infection, normal anion gap metabolic acidosis with severe bicarbonate and potassium deficiency with EKG changes as ST depression with flattening of T wave and U-wave. Urinalysis had a basic pH with positive urine acetone. Findings were suggestive of renal tubular acidosis (RTA). In addition, patient reported several episodes of nephrolithiasis during childhood, differenteditary dialtal RTA. Hypokalemia history and renal findings trigger were unknown. However, due to association of RTA type 1 and autoimmune disease, workup was performed. Rheumatoid factor, ANA screen, aldolase and SS-A/Ro antibody were positive consistent with Sjögren syndrome diagnosis. There are only a few documented cases. After discussing results with patient we thought to be a case of Late-Onset Bartter Syndrome.

Discussion: Sjögren syndrome is a chronic autoimmune inflammatory disease that could negatively affect the patient’s quality of life. Triggers have not been completely identified due to multifactorial involvement and diversity of clinical manifestations. In Puerto Rico, there is a small population currently diagnosed with the syndrome. However, research studies of epidemiological characteristics or clinical profile in Puerto Rico are still ongoing.

POI120
Idiopathic Bartter Syndrome-Like Phenotype Diagnosed in a Diabetic Patient with COVID-19 Infection
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Introduction: Bartter’s syndrome (BS) is a rare genetic tubulopathy affecting the loop of Henle leading to salt wasting. Acquired BS is very rare and is associated with underlying medical conditions or etiologies. We report a unique case of idiopathic BS-like phenotype that was diagnosed in the setting of COVID infection.

Case Description: 71-year-old man with coronary artery disease, hypertension and diabetes presented after a mechanical fall. On admission, he was found to be hypotensive to 107/88 mmHg. Physical exam was within normal limits. Initial blood work was significant for Potassium 2.6 mEq/L, Bicarbonate 34 mEq/L, Calcium 8.9 mg/dL and Magnesium 1.7 mg/dL. Patient also tested positive for COVID-19. Upon further questioning, patient reported a remote history of hypokalemia but never needed any electrolyte supplementation. He denied diuretic use or surreptitious vomiting. Hypokalemia work up revealed increased urinary potassium of 85.4 mEq/L. Renin 15.72 ng/mL/hour and Aldosterone 8 ng/dL. Patient was then started on aggressive intravenous and oral potassium repletion. He continued to require multiple doses of intravenous potassium to maintain potassium levels of 3 mEq/L. He was subsequently started on Eplerenone on Day 3 of admission with excellent response. He remained otherwise asymptomatic from COVID and as his infection improved, hypokalemia stabilized and he was ultimately discharged with a Potassium level of 3.6 mEq/L.

Discussion: The primary defect in BS is in sodium chloride reabsorption in the medullary thick ascending limb of the loop of Henle resulting in hypokalemia, metabolic alkalosis and secondary hyperaldosteronism. Rare cases of acquired BS are reported in association with tuberculosis, sarcoidosis, sjogrens, and certain drugs. All of these were ruled out in our patient and hence a diagnosis of idiopathic BS like phenotype was made. In our patient, we attribute the BS like phenotype to underlying COVID infection. As his infection improved, his hypokalemia also resolved. Hyperkalemia is a more common finding in COVID infection. However, in our patient, hypokalemia secondary to BS like phenotype was a unique presentation which was challenging to treat. In the absence of usual causes of acquired BS, we considered hypokalemia secondary to BS like phenotype should prompt suspicion for BS-like phenotype. Early and aggressive correction of electrolyte abnormalities is crucial.

POI121
Late-Onset Bartter Syndrome
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Introduction: Bartter syndrome (BS) is an autosomal recessive disorder that results from mutations in sodium chloride reabsorption in the thick ascending loop of Henle resulting in hypokalemia, metabolic alkalosis and secondary hyperaldosteronism. Late-Onset Bartter Syndrome is a phenotype that was diagnosed in the setting of COVID infection.
Salt, Potassium, and Water Balance: Clinical

POI1122

Colonial Pseudo-obstruction and Hypokalemia

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Introduction: Ogilvie’s syndrome, or colonic pseudo-obstruction, is the pathologic dilation of the colon without underlying mechanical obstruction. It is caused by increased sympathetic activity or reduced parasympathetic activity. The common manifestation in constipation, but sometimes it may be associated with diarrhea when potassium secretion is greatly increased by stretch-activated maxi-K channel, also known as BK channel, resulting from dilatation of the colon. While exact mechanism is unclear, diagnosis is based on clinical and radiologic grounds.

Case Description: A 69-year-old African American female with history of diabetes mellitus, hypertension, hyperlipidemia, and HIV infection presented with worsening lower back pain. Initial labs showed leukocytosis, anemia, mild renal impairment, and paraproteinemia. MRI of the spine showed extensive compressive deformities and epidural extension, with lytic lesions on skeletal survey. Bone biopsy showed >80% blast cells with marked increase in circulating plasma cells, confirming plasma cell leukemia. Abdominal CT showed dilated ascending colon suggestive of obstruction, but she was having normal bowel movements. She successfully underwent induction therapy and was discharged. When she was readmitted for second cycle of chemotherapy, serum potassium of 1.8 mmol/L with U wave on ECG noted. She also complained of abdominal distension, diarrhea, and bilateral lower extremity edema. Despite aggressive potassium supplementation, her potassium level persistently remained below 3.5 mmol/L. Initial urine potassium was 23 mmol/L, which peaked at 45.8 mmol/L before becoming anuric. First stool potassium was >100 mmol/L with stool volume of 900 mL. Repeat stool study after a week showed stool potassium 95.9 mmol/L with stool sodium 42 mmol/L. Abdominal x-ray on admission showed colon distension measuring up to 11.4 cm at the cecum. Serial imaging of the bowel showed worsening diffused colonic dilation. Remarkably, our patient required large doses of potassium supplement while she remained anuric.

Discussion: Colonic pseudo-obstruction may result in, some patients, in dramatic upregulation of the maxi-K channel. When potassium secretion is greatly increased, diarrhea rather than constipation becomes predominant manifestation. Diarrhea is the result of high potassium content of the stool, unlike most other secretory diarrhea which is greatly increased by stretch-activated maxi-K channel, also known as BK channel, resulting from dilatation of the colon. While exact mechanism is unclear, diagnosis is based on clinical and radiologic grounds.

POI1123

Prevalence and Recurrence of Hyperkalemia (HK) in Medicare Patients Admitted to Long-Term Care or Post-Acute Care (LT/CAC) Settings

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Background: HK is a common electrolyte imbalance among elderly populations with comorbidities such as chronic kidney disease (CKD) and congestive heart failure (CHF). This study describes the prevalence and recurrence of HK in patients in the LT/CAC setting.

Methods: This retrospective study used 100% Medicare Fee-For-Service data for patients age ≥65 with ≥1 LT/CAC stay from 01/21/2017 to 11/30/2019; index date was admission date of first LT/CAC stay. HK-related stay was defined as ≥1 HK diagnosis (ICD-10-CM codes for hyperkalemia 287.2, 287.4) or ≥1 code of potassium binder use during LT/CAC stay or within ≤14 days pre-index. Baseline characteristics and prevalence of HK in patients 1 year of follow-up among HK index stays were compared to non-HK index stays. HK index stays were stratified into 3 cohorts: CHF, CKD or end-stage renal disease (ESRD), and CHF+CKD/ESRD.

Results: Of 4,562,231 patients with ≥1 LT/CAC stay, prevalence of HK during pre-index, index, or follow up periods was 14.7%. The final sample (4,081,103) excluded patients with an HK event only during follow up. Of the final cohort, 290,567 (7.1%) of index stays were HK-related. All-cause (HK-related) index stays consisted of 54.0% (46.5%) CHF, 32.8% (27.8%) CKD, 28.8% (41.4%) end-stage renal disease (ESRD), 6.7% (8.8%) inpatient rehabilitation facilities, and 0.9% (3.1%) long term acute hospital settings. HK vs non-HK patients were more often male (43.0% vs 35.4%), Black (13.5% vs 8.0%), and dual eligible for Medicaid (34.2% vs 25%), with higher mean Charlson Comorbidity Index scores (6.19 vs 3.93). Mean annual HK event during follow up were highest in patients with CHF+CKD/ESRD (all patients=1.47; HK=6.98), followed by CKD (0.66; 5.53), and CHF (0.18; 3.00), with similar patterns across settings. In the HK cohort, 34.5% had HK recurrence during follow up; 2.7% filled a potassium binder prescription during index LT/CAC stay, and 4.3% did so during follow up.

Conclusions: HK patients were more often non-White and low income, indicating possible disparities in care. Prevalence and recurrence of HK was high among patients with LTC/CAC stays, but few patients filled a potassium binder prescription, suggesting potential gaps in treatment during or after an LT/CAC stay.

Funding: Commercial Support - AstraZeneca

POI1124

Impact of Hyperkalemia and the Disruption of Emergency and Surgical Care

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Background: Due to the increasing prevalence of kidney disease, hyperkalemia (HK) may be diagnosed with greater frequency in Surgical and Emergency Departments (ED). Despite this, specific guidelines do not exist and patients with elevated potassium (K+) are typically managed on a case by case basis.

Methods: An anonymous structured survey was emailed to (n=11,287) clinicians in the Advocate Aurora Health system regarding HK knowledge and treatment paradigms (n=237 responded). Survey was conducted from Feb to March 2021.

Results: Nearly half (47%) of respondents treat >10 HK patients annually, with most reporting diagnosis of HK occurring in the ED (70%). Patients hospitalized for surgical (33%) setting. HK was considered a significant concern by 47% of respondents at a serum K+ level of 5.6-5.9 mEq/L and by 39% at K+ >6 mEq/L. Only 50% of respondents recognized RAAASI medications as a potential risk factor for HK. IV fluids and kayexalate were the two most common treatments for HK. Limitations to pharmacological management included the need to monitor potassium, patient compliance, and time of onset. In the surgery survey, 66% felt that K+ more than 5.5 mEq/L on day of surgery will lead to cancellations and 52% believed pharmacologic agents having a shorter onset of action may reduce surgery cancellations and delays. Vascular (34%) and general (30%) surgeries were reported to be most impacted by HK. 82% stated urgent dialysis is difficult to arrange and admission is inevitable for dialysis.

Conclusions: The presence of HK creates challenges to ED or surgical clinical teams to manage and avoid cancellations. Standard treatment options for lowering serum K+ are limited due to time of onset and compliance considerations. Dialysis is difficult to arrange on short notice and almost always requires patient admission. In cases of emergent HK, newer K+ binding agents having a more rapid onset of action to lower serum K+, may reduce avoidable admission, surgical cancellation, and delay of surgery. More evidence-based care is needed in surgical settings to characterize patients at high risk for HK to prevent unnecessary surgical cancellation and limit health care costs.

Funding: Commercial Support - AstraZeneca

POI1125

Transient Hyperkalemia Following Treatment of Chronic Hypokalemia: A Case Report and Review of Distal Tubule Physiology


Introduction: Hypokalemia is a frequently encountered electrolyte disorder usually resulting from decreased dietary intake, gastrointestinal, and/or renal wasting. In distal tubular cells, with no lysine (WNK) kinases bind with Ste20-related proline-alanine-rich kinase (SPAK) and oxidative stress-responsive kinase-1 (OSR1) to form WNK bodies. WNK bodies are thought to increase the activity of the sodium-chloride cotransporter (NCC) leading to decreased sodium delivery to the epithelial sodium channel (ENaC) facilitating principal cells. This results in decreased urinary potassium wasting through the renal outer medullary potassium channel (ROMK). Here we report a case of a young man with alcohol use disorder and chronic hypokalemia who was hospitalized for muscle weakness, abdominal pain, and increased anorexia. During treatment of his hypokalemia, he unexpectedly developed transient hyperkalemia.

Case Description: The clinical intrigue of this case was the unexpected finding of acute transient hyperkalemia during treatment for hypokalemia. His potassium was 2.5 mEq/L on the day of admission. Four days later, with a creatinine at baseline (0.9 mg/dL), potassium abruptly increased to 6.7 mEq/L. Repeat measurement one hour later was 6.4 mEq/L. Over the course of his hospitalization prior to the critical hyperkalemia lab result, he had received approximately 340 mEq of potassium supplementation. 24 hour urine potassium was 35 mEq/L. A potassium 5.8 mg/dL and renin was 0.3 ng/mL/hr (ratio 19). Potassium levels returned to normal following administration of furosemide and sodium polystyrene sulfonate.

Discussion: We propose that the adaptive mechanisms of the distal tubule during hypokalemia require time to revert back to a nonactive state. Transient hyperkalemia may be observed during these “recovery” periods. The time required for disassembly of WNK bodies following resolution of hypokalemia is unknown. Our postulation could explain a
similar observation of transient hyperkalemia seen in a case published in 1953 of a young woman treated for chronic hypokalemia (Schwartz, 1953). Critical hyperkalemia is an important consideration when treating patients with chronic hypokalemia.

**POI1126**

**Pseudohyperkalemia with Concurrent Hyperkalemia**

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**Introduction:** In sickle cell patients, acute hematologic crisis and sickle cell nephropathy are relatively common. Risk of hyperkalemia increases with hemolysis and tubular dysfunction. Sepsis can also worsen the complication of hemolytic crisis with significant thrombocytosis, a well-known cause of pseudohyperkalemia. We report a case of concurrent true hyperkalemia and pseudohyperkalemia in the setting of thrombocytosis due to acute sickle cell crisis.

**Case Description:** A 36 year old African American male with history of sickle cell disease, asthma and DVT presented with bilateral shoulder, knee, and back pain. In ED, he was hypotensive, and tachycardic. Labs were notable for leukocytosis, anemia, reticulocytosis, renal failure, and elevated lactate dehydrogenase. Chest x-ray showed left base atelectasis. He was admitted for acute sickle cell crisis and fluctuant right thigh abscess, which was surgically drained and managed with antibiotics. Platelet level was 585 K/uL; serum potassium was 4.7 mmol/L; and creatinine was 1.76 mg/dL with normal urine output. Potassium level steadily rose and peaked at 6.5 mmol/L with sinus bradycardia but no other ECG changes. At the same time, platelet level peaked to 1105 K/uL.

**Discussion:** In our patient with significant thrombocytosis, pseudohyperkalemia was suspected. Degranulation of platelets during clotting releases about 50% of potassium inside platelets. For platelet count of 1000 K/uL with normal MPV, serum potassium level is expected to be higher than plasma potassium level by about 0.7 mmol/L. Serum-plasma potassium differences in our patient were within the expected range. In our patient, as shown below, mild concurrent true hyperkalemia is also noted likely due to sickle cell nephropathy, a known cause of hyperkalemia due to hyporeninemic hypoaldosteronism. Due to potassium release from platelets during clotting, serum potassium is always higher than plasma potassium in all normal persons by 0.2 to 0.3 mmol/L. With thrombocytosis, the difference becomes larger, and serum potassium is likely to reach hyperkalemic level if the baseline potassium is already higher than usual due to concomitant impairment of renal potassium excretion.

**POI1127**

**Missing the Obvious? A Story of Salt, Water, and Unexplained Hyperkalemia**

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**Introduction:** Most clinicians are familiar with the differential diagnosis of hyperkalemia, from pseudohyperkalemia to rare tubulopathies. Herein, we describe three patients with years-long histories of unexplained hyperkalemia despite extensive investigations (details in Table 1). While all achieved normokalemia with various prescription regimens, the underlying etiology remained elusive. We suggest that all cases investigated (details in Table 1). While all achieved normokalemia with various prescriptions, the underlying etiology remained elusive. We suggest that all cases

**Case Description:** Patient A: A 6-week-old girl with persistent hyperkalemia and very low urine Na+. Normokalemia was achieved with hydrochlorothiazide and dietary K- restriction but maintained with optimized fluid and Na+ intake alone. Patient B: An 11-year-old boy with spastic cerebral palsy with persistent hyperkalemia after a mild AKI attributed to rhabdomyolysis. Serum K+ improved with sodium polystyrene (SPS) at nadir K+ restriction; it normalized after 5-day saline infusion, while SPS. Patient C: A 5-month-old boy with Stüve-Wiedemann Syndrome and feeding difficulties with persistent hyperkalemia that normalized on SPS. After G-tube insertion at 2 years, K+ remained normal despite stopping the SPS due to improved fluid and Na+ intake.

**Discussion:** It has long been established that adequate Na+ and fluid delivery to distal nephrons is necessary for optimal K+ handling. It is therefore surprising to find almost no mention of Na+-responsive hyperkalemia in the literature for children beyond the neonatal period. Our patients all had hyperkalemia in the context of normonatremia, but very low fractional excretion of Na+ (FeNa) and low trans-tubular K+ gradient (TTKG). They all remained normokalemic when salt and water intake was optimized, despite stopping their hyperkalemic prescriptions. Careful, early consideration of low distal Na+ and water delivery as a cause for unexplained hyperkalemia could prevent extensive workups and unnecessary prescriptions.

**POI1128**

**Machine Learning Models to Predict Cardiovascular and Renal Outcomes and Mortality in Hyperkalemic Patients**

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**Background:** Hyperkalemia is associated with increased risks of mortality and adverse clinical outcomes. To date, limited evidence is available for personalized risk evaluation in this heterogeneous and multifactorial pathophysiological conditions.

**Methods:** We developed prediction models using extreme gradient boosting (XGB), logistic regression (LR), and neural network. Models were derived and cross-validated in a retrospective cohort of hyperkalemic patients with either heart failure or stage ≥a3 chronic kidney disease and aged ≥a18 years from a Japanese administrative hospital database (April 1, 2008–September 30, 2018). The outcomes of interest included all-cause death, introduction of renal replacement therapy (RRT), hospitalization for heart failure (HHF), and cardiovascular events within 3 years after first hyperkalemic episode. The best performing model was further validated using a separate hospital-based database.

**Results:** 24,949 adult patients with hyperkalemia were selected for the model derivation and internal validation. The mean age was 75 years and 54% were male. Among machine learning algorithms tested, XGB outperformed other models, showing AUROC of XGB vs. LR for all-cause death, RRT, HHF, and cardiovascular events as 0.823 vs. 0.809, 0.957 vs. 0.947, 0.863 vs. 0.838, and 0.809 vs. 0.798, respectively. In the external validation set including 86,279 patients, AUROC of XGB for all-cause death, RRT, HHF, and cardiovascular events were 0.747, 0.888, 0.673, and 0.585, respectively. The Kaplan-Meier curves of high-risk predicted group showed a significant differentiation from that of low-risk predicted group for all outcomes (Figure).

**Conclusions:** These findings suggest the possible use of machine learning models for real-world risk assessment as a guide for treatment decision making that may lead to the improvement of cardiovascular and renal outcomes, and mortality in hyperkalemic patients.

**Funding:** Commercial Support - AstraZeneca K.K.

**POI1129**

**Severe Hyperkalemia Secondary to Hypermagnesemia in a Patient with Preeclampsia**

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**Introduction:** Mg infusion remains the first-line treatment of preventing and controlling eclamptic seizures. While hypocalcemia is a well-known side effect, hyperkalemia is not. We present a case of severe hyperkalemia secondary to magnesium infusion requiring hemodialysis.

**Case Description:** 36-year-old healthy female with no HTN or liver disease, pregnant at 25 weeks with twins, admitted for close monitoring given concern for intra-uterine growth restriction. Initial vitals on admission: BP 149/88 mm Hg, HR 89,
PO1131
When Sipping K Is Not OK
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Introduction: Hyperkalemia is one of the most common and potentially lethal electrolyte abnormalities that occurs in approximately 1% to 10% of hospitalized patients. It is associated with an increased risk of arrhythmias, poor cardiovascular outcomes, and increased morbidity and mortality. We highlight an unusual etiology of severe hyperkalemia in a patient with underlying CKD.

Case Description: A 74-year-old Black male with known arterial hypertension, coronary artery disease, CKD 3 [baseline serum creatinine (Cr) 1.7 mg/dl] presented with syncope secondary to severe bradycardia (heart rate 30/min) consequent to severe hyperkalemia, which necessitated a pacemaker placement, and non-oliguric AKI on CKD. Pertinent serum labs on presentation include Cr 2.8 mg/dl, potassium (K) 7.6 mmol/L, and bicarbonate 19 mmol/L. Serum osmolality, glucose, and creatinine kinase levels were within normal limits. Urine pH was 5. Renal imaging was unremarkable. He was not on any medication(s) commonly attributed with a propensity to elevate serum K, including renin angiotensin inhibitors, non-selective β blockers, or non-steroidal anti-inflammatory agents. Given that the hyperkalemia was out of proportion to his kidney injury, upon further questioning he attributed consuming a diet rich in K along with drinking multiple cups of Essiac tea daily for the last 2 months. Hyperkalemia was managed medically, including initial temporizing measures, bicarbonate supplementation, K binders, and intravenous crystalloids to enhance distal nephron K excretion. Emphasis was placed on consuming a K restricted diet along with discontinuing Essiac tea use. Serum K normalized in 3 days; however, Cr was 3 mg/dl on discharge.

Discussion: Essiac tea contains red clover, sheep sorrel, burdock root, and rhubarb which has extremely high potassium content. It is hepatotoxic and nephrotoxic when consumed in large amounts. We highlight the importance of obtaining a thorough dietary history, especially when the degree of hyperkalemia cannot be solely attributed to the extent of kidney injury. Dietary counselling is paramount in such cases.

PO1132
Metabolic Acidosis That Exists with Hyperkalemia (HK) Among Patients That Initialize Binder Therapy: The MAXIMIZE Study
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Background: Approximately 25% of chronic kidney disease (CKD) patients with serum potassium (sK+) >5.0 mEq/L may also have metabolic acidosis (MA). However, successful management of comorbid HK and MA in CKD patients is unclear. This real-world evidence study examines the association between patient characteristics and binder treatment among CKD patients with HK and MA.

Methods: This was a retrospective study of stage 3-5 CKD patients with HK (sK+ >5.0 mmol/L) and MA (serum bicarbonate (sHCO3−) between 16-20 mmol/L) in a US EMR network of 64 million patients. The index event was the first qualifying sK+ >5.0 mmol/L between 07/01/19 and 12/31/20. Baseline demographic and clinical characteristics were assessed among SZC, SPS, and NKB treated cohorts including age, sex, race, HK severity, sHCO3− level, visit type, and comorbidities. Logistic regression produced adjusted odds ratios (ORs) and 95% confidence intervals describing the association between baseline characteristics and treatment: sodium zirconium cyclosilicate (SZC) vs sodium polystyrene sulfonate (SPS) and SZC vs no potassium binder (NKB).

Results: Of the 32,113 patients who met study criteria 11.6% were treated with SZC (n=3,572). Age and sex were similar among SZC, SPS, and NKB cohorts and 81%, 77%, and 70% had moderate-to-severe acidosis (sHCO3− <20mmol/L), respectively. Baseline characteristics associated with increased odds of SZC vs SPS and SZC vs NKB treatment included sHCO3− <20mmol/L [OR=1.29 (1.03-1.61); OR=1.24(1.04-1.47)] and liver disease [OR=1.61(1.16-2.23); OR=1.47(1.14-1.89)], respectively. Treatment with SZC vs NKB treatment was more likely in inpatient settings [OR=3.73(3.06-4.55)] and in patients with comorbid congestive heart failure [OR=1.43(1.12-1.84)].

Conclusions: Clinicians were more likely to treat HK with SZC than SPS or NKB in CKD patients with moderate-to-severe acidosis in a recent large, US, real-world sample. Secondary findings from prior clinical trials suggest that SZC may improve MA as well normalize sK+ . Future clinical trials are needed to assess the impact of SZC on sHCO3− concentrations.

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
POI1133

Real-World RAAS Inhibitor Use and Its Predictors Among Patients Initiating Sodium Zirconium Cyclosilicate

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Background: Renin-angiotensin-aldosterone system inhibitors (RAASI) are associated with reduced risk of death and slower disease progression in patients with heart failure (HF) and chronic kidney disease (CKD). However, RAASI use increases the risk of hyperkalemia (HK), which may disrupt RAASI use and mitigate its benefits. There is limited real-world evidence characterizing RAASI use after sodium zirconium cyclosilicate (SZC) treatment.

Methods: Adult patients initiating SZC (index date) while on a RAASI in outpatient care were included from a large US claims database (January 2018-June 2020). Analyses were conducted among all patients, patients with CKD and patients with CKD + diabetes (DM). The percent of patients with a RAASI prescription index was summarized. Characteristics among patients with and without a new RAASI fill were compared using descriptive statistics. A multivariable logistic regression model assessed predictors of a new RAASI fill.

Results: A total of 589 patients initiating SZC while on a RAASI were included (mean age 61 years, 65.2% male). Overall, 82.7% of patients had a new RAASI fill after index. The median time to discontinuation was not reached among patients with a new RAASI fill, of whom 88.1% at day 180 and 74.0% at 1 year remained on RAASI therapy. Median time on RAASI was 29 days (95% CI [27-43 days]) for those with no new RAASI fill. Compared to patients without a new RAASI fill, patients with a new fill had a higher burden of CKD (69.4% vs 58.8%) but a similar prevalence of DM (70.6% vs 67.6%) and HF (24.6% vs 28.4%). Results were similar in the CKD cohort (N=398; 84.9% had a new RAASI fill) and CKD and DM cohort (N=311; 85.2% had a new fill). Predictors of having a new RAASI fill included fewer prior hospitalizations (0.77 [0.60-0.98]; p=0.05) and emergency department (ED) visits (0.78 [0.63-0.97]; p<0.05).

Conclusions: In a real-world setting, 83% of patients had a new RAASI fill within 90 days after ending their RAASI. Results were consistent with clinical trial finding and emergency department (ED) visits (0.78 [0.63-0.97]; p<0.05).

Funding: Commercial Support - AstraZeneca

POI1134

Compatibility Study of Patiromer with Juices/Liquids and Soft Foods

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Background: Patiromer is a novel, once-daily, sodium-free K+-binder approved for treatment of hyperkalemia. The drug—tasteless, odorless powder—is administered orally suspended in water. Recently, the FDA approved apple or cranberry juice as suspension vehicle for partial doses of patiromer. Since patiromer contains significant amounts of sodium, we assessed the risk of heart failure hospitalization (HHF) associated with the initiation of SZC versus patiromer in non-dialysis patients.

Methods: We used a U.S. commercial insurance claims database (Optum Clinformatics® Data Mart) between May 2018 (after SZC approval) and September 2020. Participants were non-dialysis adults who had a 180 days of insurance enrollment and were newly prescribed SZC or patiromer. The primary outcome was a hospitalization with a discharge diagnosis of heart failure. The secondary outcome was a hospitalization or an emergency room visit with a diagnosis of any edema. Propensity score (PS) matching in a variable ratio up to 1:3 was used to adjust for more than 80 variables, including demographic characteristics, comorbidities, medication use, and health care utilization. Cox proportional hazards regression models were used to generate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: Our cohort included 1,126 SZC initiators and 2,839 PS-matched patiromer initiators (total N=3,965). The mean age was 72 (±10) years; 30% had a history of heart failure and 85% had CKD stages 3-5. The risk of HHF was higher in the SZC initiators compared to patiromer initiators (HR 1.22, 95%CI 0.95-1.56), but the confidence interval included the null value (Table). Edema was more common in the SZC initiators (HR 1.89, 95%CI 1.05-3.39). Subgroup analyses, initiation of SZC was associated with an increased risk of HHF (HR 1.58, 95%CI 1.01-2.46) amongst patients without a history of heart failure.

Conclusions: Patients initiating SZC may need to monitor volume status and consider dietary salt restrictions and initiation or adjustment of diuretics. Larger studies are needed to more precisely evaluate the safety of SZC in routine practice.

Funding: Commercial Support - Vifor Pharma

POI1135

Risk of Heart Failure in Patients Who Initiated Sodium Zirconium Cyclosilicate vs. Patiromer

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Background: Hyperkalemia is common in patients with chronic kidney disease (CKD), heart failure, and diabetes. Sodium zirconium cyclosilicate (SZC) and patiromer were recently approved for the treatment of hyperkalemia. Since SZC contains significant amounts of sodium, we assessed the risk of heart failure hospitalization (HHF) associated with the initiation of SZC versus patiromer in non-dialysis patients.

Methods: We used a U.S. commercial insurance claims database (Optum Clinformatics® Data Mart) between May 2018 (after SZC approval) and September 2020. Participants were non-dialysis adults who had a 180 days of insurance enrollment and were newly prescribed SZC or patiromer. The primary outcome was a hospitalization with a discharge diagnosis of heart failure. The secondary outcome was a hospitalization or an emergency room visit with a diagnosis of any edema. Propensity score (PS) matching in a variable ratio up to 1:3 was used to adjust for more than 80 variables, including demographic characteristics, comorbidities, medication use, and health care utilization. Cox proportional hazards regression models were used to generate hazard ratios (HRs) and 95% confidence intervals (CIs).

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Conclusions: Patients initiating SZC may need to monitor volume status and consider dietary salt restrictions and initiation or adjustment of diuretics. Larger studies are needed to more precisely evaluate the safety of SZC in routine practice.

Funding: Commercial Support - Vifor Pharma

POI1136

RDX013, a Novel, Oral, Small Molecule Being Developed for Treatment of Hyperkalemia, Increases Colonic Secretion and Fecal Excretion of Potassium

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Background: Potassium (K+) homeostasis is maintained by the balance of dietary K+ intake, extracellular K+ distribution, and renal and intestinal excretion. Hyperkalemia (serum K+ >5.0 mEq/L) occurs frequently in CKD patients and can lead to cardiac arrhythmias and sudden death; controlling serum K+ may reduce mortality in this population. Current therapeutic options for the chronic treatment of hyperkalemia are limited to K+-binding agents. Here, we describe the discovery of RDX013, a novel, oral, small molecule K+ secretagogue in development for treatment of hyperkalemia.

Methods: Male Sprague Dawley rats (n=6/group) were orally administered vehicle or 6 mg/kg RDX013 twice daily for 6 days. 24-hour fecal samples collected from rats housed individually in metabolic cages on the final study day were homogenized, and K+ and sodium were analyzed by cation exchange chromatography.

Results: RDX013 significantly increased fecal K+ excretion compared to vehicle control animals (figure). Fecal sodium was also increased by RDX013 (figure), which was expected as luminal sodium retention in the intestine is key to the pharmacodynamic response.

Conclusions: Based on its unique mechanism of action which involves pharmacologically enhancing K+ secretion through apical K+ channels in the colon, RDX013 is a potential first-in-class therapy which may provide a new approach to managing serum K+ in patients versus commonly prescribed K+ binders. A phase 2 clinical study with RDX013 (NCT04780841) is ongoing in non-dialysis CKD patients with hyperkalemia.

Funding: Commercial Support - Ardelyx, Inc.
PO1137

Artificial Intelligence-Assisted Electrocardiography for Early Diagnosis of Thyroid Toxic Periodic Paralysis

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Background: Thyroid periodic paralysis (TPP) characterized by acute weakness, hypokalemia and hyperpyrexia is a medical emergency with a great challenge in early diagnosis since most TPP patients do not have overt symptoms. Since both hypokalemia and hyperpyrexia in TPP significantly affect the cardiovascular system, electrocardiography (ECG) as a prompt and non-invasive bedside tool universally used in the ED may detect these electrical changes. To assess artificial intelligence (AI)-assisted electrocardiography (ECG) combined with routine laboratory data in the early diagnosis of TPP.

Methods: A deep learning model (DLM) based on ECG12Net, an 82-layer convolutional neural network, was constructed to detect hypokalemia and hyperpyrexia. The development cohort consisted of 39 ECGs from patients with TPP and 502 ECGs of hypokalemic control; the validation cohort consisted of 11 ECGs of TPP and 36 ECGs of non-TPP with weakness. The AI-ECG based TPP diagnostic process was then consecutively evaluated in 22 male patients with TPP-like features.

Results: In the validation cohort, the DLM-based ECG system detected all cases of hypokalemia in TPP patients with a mean absolute error of 0.26 mEq/L and diagnosed TPP with an area under curve (AUC) of ~0.8%, surpassing the best standard ECG parameter (AUC=0.7285 for the QR interval). Combining the AI predictions with the estimated glomerular filtration rate (eGFR) and serum chloride (Cl-) boosted the diagnostic accuracy of the algorithm to AUC 0.986. In the prospective study, our AI ECG system achieved perfect performance (F-measure 100%) on the task of hypokalemia detection in them and the integrated AI with routine laboratory had a PPV of 100% and F-measure 87.5% for TPP diagnosis.

Conclusions: An AI-ECG system reliably identifies hypokalemia in patients with paralysis and its integration with routine blood chemistries provides valuable decision support for the early diagnosis of TPP to avoid life-threatening complication.

PO1138

Will the Real Sodium Stand Up!

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Introduction: Hyponatremia is a common finding as it could be precipitated by multiple factors ranging from medications to simply dehydration. Accurate approach to management depends on assessing serum osmolality in an effort to distinguish cases of true, factitious or pseudohyponatremia. We present a case of hyponatremia secondary to hyperlipidemia.

Case Description: 36 year old Asian woman with HTN, Type 2 DM, HLD presented with 1 day of epigastric pain. On exam S1, S2 were heard with vesicular breath sounds throughout, epigastric tenderness and no focal neurological deficits. Initial labs: sodium 114 potassium 3.5 chloride 85 glucose 254, BHB 3.7. Sodium corrected for glucose 116 CO2, BUN, Cr and AG were incalculable. Urinalysis: pH 6.0, ketones > 1000, protein > 1000. Total cholesterol 1020, HDL 25, Triglycerides >5680, LDL 2.9, CO2, BUN, Cr and AG were incalculable. Urinalysis: pH 6.0, ketones > 1000, protein > 1000. Total cholesterol 1020, HDL 25, Triglycerides >5680, LDL 2.9, CO2, BUN, Cr and AG were incalculable. Urinalysis: pH 6.0, ketones > 1000, protein > 1000.

Discussion: Sodium is most commonly measured by indirect potentiometric (ISE) measurement. By this method serum specimens are diluted based on estimated typical glomerular filtration rate (eGFR) and serum chloride (Cl-) to achieve a standard deviation. In this case, direct sodium measured by VBG/ABG are most accurate. Typically, most commonly measured serum triglyceride with concentrations> 1500 mg/dl are thought to be responsible for factitious hyponatremia. In our patient the value of serum sodium on admission was unexpectedly low at 114 and severe hypercholesterolemia may have contributed. Applying the following formula to correct for triglycerides = Measured Na+ on admission was unexpectedly low at 114 and severe hypercholesterolemia may have contributed. Applying the following formula to correct for triglycerides = Measured Na+ on admission was unexpectedly low at 114 and severe hypercholesterolemia may have contributed. Applying the following formula to correct for triglycerides = Measured Na+ on admission was unexpectedly low at 114 and severe hypercholesterolemia may have contributed. Applying the following formula to correct for triglycerides = Measured Na+ on admission was unexpectedly low at 114 and severe hypercholesterolemia may have contributed. Applying the following formula to correct for triglycerides = Measured Na+.

Plasma triglycerides (g/L) x 0.002; measured serum sodium would have been expected to be 125 meq. In cases of extremely high lipids, one must consider lab techniques for measuring serum sodium, as well as full lipid panel in the evaluation and treatment of factitious hyponatremia.

PO1139

Admission Sodium and Related Features to Predict Falls in Machine Learning Models

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Background: Hyponatremia has been associated with an increased risk for falls, but evidence is primarily limited to outpatient events. Hyponatremia is a potential surrogate of conditions that may lead to falling including volume depletion, malignancy, pain, polypharmacy, and weakness. We hypothesized that a model could be developed to predict falls based upon accessible variables present on all hospital admissions. An accurate model could allow for measures to lower in-hospital falls.

Methods: Medical records from a single institution were collected over a period of 2011 to 2019. Subjects included admitted patients who suffered a recorded in-hospital fall and were admitted, and controls matched for admission on the same date. Variables collected included sodium, glucose, age and gender. There were 17,103 patients total of which 1,203 had unique falls. Data was split into an 60% training, 20% validation and 20% testing split. We computed an unadjusted odds ratio of falls for those with very low sodium (<126). We trained logistic regression, random forest, XGBoosted forest, and neural net classifiers. Classifier cutoff was calculated using Youden values.

Results: We did not see an increased incidence of falls in the population with a low sodium (N=377) with an unadjusted odds ratio of 0.62 (CI 0.38-1.01). Similarly, the model performances did not result in clinically useful predictions with a unanimously high false positive and false negative rates (Figure 1).

Conclusions: Despite reports of hyponatremia as an indicator of fall risk we did not observe this. The fall-prediction models did have the capacity for high performance on the training data, but this does not translate to validated performance. This discrepancy is termed ‘overfitting’ and is important to evaluate as machine learning models have a much larger capacity than traditional statistical models to incorporate previously seen examples. If a model cannot make predictions on new data it cannot be clinically useful. These models may be enhanced using other basic admission features and is the subject of future work.

PO1140

Association of Serum Sodium Levels with Bone Mineral Density, Fracture, and Mortality in Patients Undergoing Maintenance Hemodialysis

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Background: Hyponatremia is implicated in pathological bone resorption and has been identified as a risk factor for bone fracture in the general population, but limited data exist in patients undergoing dialysis.

Methods: We analyzed a historical cohort of 2,292 patients undergoing maintenance hemodialysis in Japan. We first examined the association of baseline serum sodium levels with metacarpal bone mineral density (BMD) in a subcohort of 456 patients with available data. Next, we examined the association of baseline serum sodium levels with incident fracture and mortality in the overall cohort, using Cox regression models adjusted for potential confounders (age, sex, dialysis vintage, diabetes, prior cardiovascular disease, history of fracture, body mass index, hemoglobin, albumin, and creatinine) and competing risks regression models accounting for death as a competing endpoint.

Results: Baseline mean ± SD serum sodium level in the overall cohort was 139.7 ± 2.9 mEq/L, and among patients with available data, median metacarpal BMD T-score was -2.05 (IQR, -3.35 to -0.99). Serum sodium levels were not associated with metacarpal BMD T-score in unadjusted or adjusted models. During a median follow-up of 5.4 years (IQR, 2.5-7.0 years), 712 patients died; 113 experienced clinical fractures; and 64 experienced asymptomatic vertebral fractures as estimated by height loss. In addition, Cox survival models, serum sodium levels were associated with mortality (HR, 0.95 per 1 mEq/L higher; 95% CI, 0.92-0.98) but not incident clinical fracture (HR, 0.97 per 1 mEq/L higher; 95% CI, 0.90-1.04) or any fracture (a composite of clinical fracture and vertebral fracture). Similar results were obtained in competing risks regression models.

Conclusions: Serum sodium levels were associated with mortality but not BMD or incident fracture in maintenance hemodialysis patients.

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Hypotremia, Inflammation, and Hospital Mortality in Hospitalized COVID-19 Patients

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Background: Systemic inflammation has been associated with severe COVID-19 disease. Hyponatremia can result from inflammation due to non-osmotic stimuli for vasopressin production. Hyponatremia is an independent risk factor for hospital mortality.

Methods: Hospitalized patients with COVID-19 were prospectively evaluated between March and November 2020 at Hospital Posadas in Buenos Aires, Argentina, in order to evaluate the association between hyponatremia and hospitalization and its impact on clinical outcomes. Admission blood chemistries, high-sensitivity C-reactive protein (hsCRP), ferritin, patient demographics, and outcome data were recorded. Outcomes (within 30 days after symptom) that were evaluated included admission to the ICU during hospitalization, mechanical ventilation, dialysis-requiring AKI, and in-hospital deaths. In-hospital mortality, length of hospital stay (in days), and hospital readmission for any cause within 30 days after discharge were evaluated using comprehensive data from the EHR.

Results: Among 799 hospitalized COVID-19 patients, hyponatremia was present on admission in 366 (45.8%). Hyponatremic patients had higher hsCRP levels than normonatremic patients (median 10.3 [IR 4.8-18.4] mg/dL vs 6.6 [IR 1.6-14.0] mg/dL, respectively, p < 0.01), and hsCRP level was inversely correlated with plasma sodium level (Spearman’s correlation coefficient = -0.23; p < 0.01). Hyponatremic patients had higher serum ferritin levels than normonatremic patients (median 649 [IQR 492-1168] mg/dL vs 393 [IQR 156-1440] mg/dL, respectively, p < 0.02), and serum ferritin level was inversely correlated with plasma sodium level (Spearman’s correlation coefficient = -0.26; p < 0.01). Hyponatremic patients had increased mortality on unadjusted (odds ratio 1.87, 95%CI 1.28-2.73) and adjusted (odds ratio 1.61, 95%CI 1.05-2.49) Cox proportional hazard models. Crude 30-day survival was lower for patients with hyponatremia at admission (mean [SD] survival 27.1 [0.40] days, p < 0.01). Hyponatremic patients had higher serum ferritin levels than normonatremic patients (median 10.3 [IQR 4.8-18.4] mg/dL vs 6.6 [IQR 1.6-14.0] mg/dL, respectively, p < 0.01), and hsCRP level was inversely correlated with plasma sodium level (Spearman’s correlation coefficient = -0.29; p < 0.01). Hyponatremic patients had increased mortality on unadjusted (odds ratio 1.87, 95%CI 1.28-2.73) and adjusted (odds ratio 1.61, 95%CI 1.05-2.49) Cox proportional hazard models.

Conclusions: This study demonstrates that hyponatremia on admission is common in patients with COVID-19 and is associated with inflammation and in-hospital mortality. Thus, hyponatremia could be a novel marker for identifying patients with COVID-19 at risk for hospital mortality.

Trends of Overall Mortality by Severity of Hyponatremia: Five-Year Mortality Rates

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Background: We have previously reported increasing strengths of association between degree of hyponatremia on hospital admission and proportions of overall mortality at 1 year post-hospitalization. It is unclear if this association persists in the long term and if this association with overall mortality occurs in a linear manner. Here, we further explore this association over a longer mean follow up period.

Methods: We have previously reported increasing strengths of association between degree of hyponatremia on hospital admission and proportions of overall mortality at 1 year post-hospitalization. It is unclear if this association persists in the long term and if this association with overall mortality occurs in a linear manner. Here, we further explore this association over a longer mean follow up period. We hypothesized that a dose response relationship occurs between varying degrees of hyponatremia and overall mortality.

Results: We obtained data from 46,783 patients, average age 62.2 years, 51.3% males, admitted from January 1, 2012 to December 31, 2016 at a tertiary referral hospital in Central Wisconsin. Of these, 7468 patients had admitting serum sodium <135 and 39315 controls with normal serum sodium (135-145). We parsed hyponatremia based on their admitting serum sodium as mild (130-134), moderate (125-129) and profound (<125) degrees of hyponatremia and compared them with controls. We obtained their vital status (alive or deceased) up to December 31, 2018 over a mean follow up period of 4.7 years. We used Cox proportional hazards models to estimate hazard ratios between varying degrees of hyponatremia compared with normonatremia group after adjusting for covariates.

Results: Hyponatremia occurred in 17.9% of total hospitalizations during the study period. Of 7468 patients with hyponatremia, there were 6,135 (82.2%), 995 (13.3%) and 338 (4.5%) with mild, moderate, and profound degrees of hyponatremia respectively. Hazard ratios for mild, moderate and severe hyponatremia when compared to controls were 1.35 (95%CI 1.28 – 1.43), 1.81 (95% CI 1.24 – 2.56) and 2.01 (95%CI 1.24 – 3.27) respectively (all p<0.001) after adjusting for covariates.

Conclusions: All-cause mortality from CVD, stroke, cancer, liver cirrhosis deaths were occurring to a significant proportion even in patients with milder degrees of hyponatremia with a dose response relationship. Clinicians should incorporate hyponatremia in their assessment of critical patients as this is associated with mortality. These findings need to be explored further with research geared towards elucidating mechanisms that contribute to death in hyponatremia, and if correcting sodium levels early in hospitalizations may prevent mortality in the future.
improvement of Na to 131. However, he developed headaches and became hypertensive at 180/94 mmHg. Instead, he was started on a high protein diet, 1 liter fluid restriction and lasix. The next Na level was 129. He was given Tolvaptan 15 mg, which improved the Na to 132, urine osm 645, and urine Na to 12. The dose was increased to 30 mg to achieve eunatremia with these values: Na 135-138, urine Na 12, urine osm 487. His BP improved, tolvaptan was discontinued and salt tablets were resumed. The patient maintained eunatremia throughout the hospital stay.

**Discussion:** Hyponatremia is a predictor of mortality due to cellular edema. Eunatremia with Na levels between 135-145 mmol/L is targeted in acute brain injury. SIADH induced by brain injury may be due to an increase in ADH from the overstimulation of the neurohumoral axis. ADH promotes water reabsorption at the cortical and medullary collecting tubules, and inappropriate levels lead to hyponatremia. Tolvaptan is a V2 receptor antagonist which combats this mechanism, thus increasing free water excretion. Additional therapies for hyponatremia from SIADH include fluid restriction, a high protein diet and salt tablets. However, salt tablets increase fluid retention; which increases blood pressure, and leads to recurrent hemorrhage and poor outcomes. The use of Tolvaptan increases free water excretion to achieve eunatremia, thereby decreasing the risk of brain edema and controls blood pressure, especially in this patient population.

**PO1145**

Acute Severe Symptomatic Hyponatremia in the Post-Partum Period: The Syndrome of Oxytocin-Induced Anti-Diuresis (SOIAD)

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**Introduction:** Oxytocin (OXT) is a neuropeptide used in pregnancy to induce uterine contraction. It is structurally related to vasopressin (AVP) by a difference of only 2 amino acids. While it does not have antidiuretic activity at physiologic levels, it can when administered at pharmacologic doses (>20 μU/min). We present a case of severe symptomatic hyponatremia after receiving oxytocin in the post-partum period.

**Case Description:** A 31 y/o G1P0 woman was admitted with premature membrane rupture at week 38. An IV oxytocin infusion (2μU/min) was started to augment labor. Her serum Na 6 hrs later was 132 mmol/L (baseline Na 140). Her delivery was c/v uterine atony and postpartum hemorrhage requiring a bolus of IV oxytocin (10 U over 30 min) followed by infusion at 8 μU/min. The Na 18 hr later was 118 mmol/L. She reported nausea. Her sOsm was 252 mOsm/kg with UNa of 95 mmol/L and Uosm 880 mOsm/kg consistent with the syndrome of anti-diuresis (SIADH). OXT was suspected and was stopped. 2 hr later, a rapid water diuresis ensued (u vol 150-200 cc/hr, with uOsm 92 kg). The patient was treated emergently with a hypertonic saline bolus and was referred to nephrology. Continuous dialysis was initiated to achieve eunatremia:

**Discussion:** This case of SIADH was unique in that the patient had severe symptomatic hyponatremia without an obvious underlying cause. The use of Tolvaptan increases free water excretion to achieve eunatremia, thereby decreasing the risk of brain edema and controls blood pressure, especially in this patient population.

**PO1146**

A Rare Case of Hyponatremia: Renal Salt Wasting Syndrome of Unclear Etiology Post Autologous Hematopoietic Stem Cell Transplant

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**Introduction:** Hyponatremia is common in cancer patients. We report a rare case of acute hyponatremia in a patient with multiple myeloma (MM) who developed renal salt wasting syndrome (RSWS) as a complication of autologous hematopoietic stem cell transplant (SCT).

**Case Description:** A 57-year-old female with history of Plasmacytoma treated with radiation therapy that subsequently relapsed as MM with POEMS syndrome and was treated with VRd regimen presented for autologous SCT. MM was in remission and patient underwent Melphalan pre-conditioning with last melphalan dose 48 hours prior to transplant. 36 hours post-transplant patient had a seizure. Labs revealed acute drop in serum sodium from 137 to 117 over 17 hours. CT head revealed mild generalized cerebral edema. Patient also had acute polyuria (> 4 L/day). Patient was treated emergently with hypertonic saline bolus and had resolution of neurological symptoms however, serum sodium continued to drop and she required around 2 L of hypertonic saline infusion over the next 24 hours to correct sodium at desired rate. Urine studies at the time of hyponatremia revealed urine osmolality of 477, sodium 161 and potassium 34. Initial working diagnosis was SIADH that was quickly revised to RSWS based on high urine sodium, hypovolemia and polyuria. The patient was able to be transitioned to salt tablets once polyuria resolved over the next 36 hours. Urine sodium remained elevated. A repeat CT head showed resolution of cerebral edema.

**Discussion:** RSWS post SCT is rarely reported. Among the few reported cases an underlying CNS complication or a post-transplant hyponatremia inducing medication exposure that predated acute hyponatremia was present. Moreover the reported cases appeared to be non autologous transplants. SIADH and RSWS (including CSWS) are similar in the sense that both present with similar urine studies. Volume status and urine output are the key factors to help differentiate between the two entities. Clinically differentiating between these two entities is important as fluid restriction is the key management in the one and solute plus volume replacement in the other. Based on our case report we recommend that hyponatremia post SCT should be carefully evaluated and RSWS be considered in the differential even if there is no obvious underlying cause.
Cerebral Salt Wasting in a Renal Transplant Patient
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Introduction: Hyponatremia is a common occurrence in patients with cerebral injury and is usually thought to be secondary to SIADH. Though cerebral salt wasting is documented in literature it has been debated on if it is truly a phenomenon. Among patients with CNS disease, CSW is a much less diagnosed cause of hyponatremia and remains underdiagnosed owing to the challenge of proving its existence. Here we present a patient with a CNS injury who showed clear benefit from treatment not centered around SIADH, thus pushing us to diagnose him with CSW.

Case Description: A 63yo Male with a PMHx of DDKT presented with nausea/vomiting. A cerebellar abscess from a previous biopsy site was found and he underwent a debridement and washout. On POD#2 the patient had a drop in sodium to 131. Urine studies [urine osmolality: 789, urine Na: 72]. With continued drop in sodium and orthostatic hypotension he was started on NS 75cc/hr. The sodium continued to drop to a low of 123. At that time the NS was increased to 125cc/hr. This resulted in an upswing in urine osmolality. The patient was eventually transitioned to a dose of salt tabs close to the equivalent to the amount of fluids he was receiving [5g Q4H]. He was also started on Fludrocortisone 0.1mg daily. This resulted in our ability to drop the Salt tabs to 4g Q6H with stability in serum sodium noted. He was discharged on this regimen and was noted to have stable serum sodium on follow up a few weeks later.

Discussion: CSW is difficult to diagnose due to the similarities in laboratory diagnostic markers with SIADH. One major difference is that in CSW patients are usually hypovolemic. Another aspect that differs from SIADH is the approach to treatment. In SIADH a combination of fluid restriction, lasix, and salt tabs are used. What makes our case unique is the successful use of NS to correct the patient’s sodium. If this was SIADH, continuous administration of NS would have dropped the sodium level. We believe we met the burden of proof to diagnose this patient with CSW. Though there may still be debate about the existence of CSW, we believe that with the difference in treatment approach it should always be considered in the differential in patients with CNS injury.

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PO1150
On the Correction of Plasma [Na] in Hyperglycemia
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Background: The effect of hypertonic states on metabolism was first considered by Seldin et al in 1949. An empirical equation to correct the plasma [Na] for hyperglycemia was put forth by Katz (NEJM, 1975). About 25 years later, Hillier et al (JAM, 1999) presented another equation based on normal volunteers with experimentally induced hyperglycemia. Both equations assume a linear relationship with current plasma glucose (mM) (mEq/L Na × 100 mg/dL [glucose]) of -1.6 (Katz) and -2.4 (Hillier). Non-linearity, however, is apparent in the original data of Hillier, which are better fit by a second-order correction (corrected plasma [Na] = -3.49 × 10^-6 × (plasma [glucose])^2 - 3.91 × 10^-5 × (plasma [glucose]) + 140). Previous equations also assume normonatremia prior to hyperglycemia and a constant volume of distribution for glucose.

Methods: Here, a new model is proposed that also provides a reasonable fit to the measured value of 110 mM. The program starts by calculating the number of effective osmoles in the ICF and ECF based solely on current plasma [glucose], this program takes weight, sex, the presence of edema, and the apparent volume of distribution (aVd) of glucose into consideration. The latter is especially important because the aVd of glucose may change in hyperglycemia.

Results: For example, consider a patient from the 1951 JCI study by Seldin et al: a 59.1 kg edematous patient with cirrhosis who initially had a plasma [Na] of 130 mM when the plasma [glucose] was 126 mg/dL. The program starts by calculating the number of effective osmoles in the ICF and ECF based solely on current plasma [glucose], this program takes weight, sex, the presence of edema, and the apparent volume of distribution (aVd) of glucose into consideration. The latter is especially important because the aVd of glucose may change in hyperglycemia.

Conclusions: Now that making numerous calculations can be done easily and efficiently with apps most physicians have on their phones, it is proposed that equations with linear correction factors be replaced by this new program when clinicians would like to predict or correct the measured serum [Na] in the presence of hyperglycemia.

PO1151
Extreme Hyponatremia with Serum Sodium Less Than 100 mEq/L: A Case Report and Review of the Literature
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Introduction: Hyponatremia is the most common electrolyte abnormality in hospitalized patients and is associated with increased mortality, hospital length of stay and cost. Rapid correction of hyponatremia can increase the risk of osmotic demyelination syndrome (ODS) which can have debilitating and often fatal consequences. Extreme hyponatremia with serum sodium concentration less than 100 mEq/L is rare, but is associated with high a rate of morbidity and mortality.

Case Description: A 52-year-old woman presented with a one-week history of weakness and fatigue. She was cachectic and had signs of severe hypovolemia and critical hyperkalemia. Additionally, she was found to have oliguric acute kidney injury and critical hyperkalemia. Her serum sodium concentration was less than 100 mEq/L, which in this case was +1.9 L. Following infusion of hypertonic glucose, the plasma [Na] fell to 110 mEq/L at the peak plasma [glucose] of 666 mg/dL. The corrected plasma [Na] predicted are (in mM): 130.9 (Katz), 126.4 (Hillier), and 124.5 (quadratic fit of Hillier’s data); all of which do not predict the change in ECF volume measured by the investigators, which in this case was +1.9 L.

Discussion: Herein we present a case of severe hyponatremia induced by urinary retention, especially given the high prevalence and predisposition of geriatric populations to develop hyponatremia. The proposed mechanism of urinary retention induced hyponatremia involves bladder distension and/or pain-mediated ADH release.

PO1152
SIADH and Postoperative Urinary Retention
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Introduction: Hyponatremia is a common electrolyte abnormality in hospitalized patients with increased prevalence noted in geriatric populations. The increased susceptibility is multifactorial from age-related OGR reduction in addition to medication effects (diuretics, antidepressants), decreased glomerular filtration rate, decreased intake and endocrine polisions (SIADH). Herein we present a case of severe hyponatremia induced by urinary retention, an infrequently described and often overlooked etiology of hyponatremia in elderly patients.

Case Description: A 58-year-old male with past medical history of hypertension on amiodipine and losartan presented with nausea, emesis and abdominal pain. The patient was recently discharged 2 weeks earlier s/p uncomplicated distal pancreatectomy with splenectomy for pancreatic adenocarcinoma. Post-operative course was stable with no complications and patient was discharged home on oxycodone/acetaminophen for pain. At home, the patient noticed constipation with worsening abdominal distension with bilateral lower extremity swelling. He had been oliguric for the past week, performing manual suprapubic compression to void. On readmission patient was noted to be severely dehydrated with a large, distended abdomen. Vital signs were BP 102/53, HR 87, SpO2 97%. Notable labs include (mEq/L): Na 111, BUN 132, Cr 4.4, HCO3 18. Urine studies noted (mEq/L): Na 8, Cl -10, K 25, serum osmolality 366 mOsm/kg. Abdominal CT noted a large LUQ fluid collection, distal colonic distension with fecal retention and mild bilateral hydrenephrosis. Subsequent Foley insertion immediately drained 2.5L. Repeat labs 12 hours later were (mEq/L): Na 118, BUN 118, Cr 2.89. Hyponatremic fluids were started to prevent Na overcorrection. Over the next several days the patient’s Serum Na (135) and renal function improved (BUN 21, Cr 0.9) back to baseline.

Discussion: During the post-operative period urinary retention is commonly noted due to anesthesia, analgesics, pain and constipation. This can be exacerbated in elderly male patients due to the ubiquity of BPH. Therefore physicians must be aware of common post-operative complications of urinary retention like hyponatremia, especially given the higher prevalence and predisposition of geriatric populations to develop hyponatremia. The proposed mechanism of urinary retention induced hyponatremia involves bladder distension and/or pain-mediated ADH release.
PO1154

Point-of-Care Ultrasound-Assisted Management of Hyponatremia
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Introduction: Point of care ultrasound (POCUS) is emerging as a valuable adjunct to conventional physical examination in patients with complex fluid and electrolyte disorders. Herein, we present a case of hyponatremia where nephrologist-performed focused cardiac ultrasound (FoCUS) aided in accurate diagnosis.

Case Description: A 73-year-old woman was admitted for the treatment of fractures after sustaining a fall. Nephrology was consulted for decreased in serum sodium level (to 123 mmol/L; baseline 130s). Laboratory data was significant for a urine sodium level of 46 mmol/L, urine osmolality 257 mOsm/kg, serum creatinine 0.5 mg/dL and BUN 9 mg/dL. As the patient was exertional dyspnea and cracks at lung bases, IV diuretic was administered by the rounding physician prior to urine studies. No active pain or thiazide use. X-ray showed a huge hiatal hernia with bowel contents in the chest, which was possibly mimicking cracks on auscultation and causing dyspnea. Systolic BP was in 140s. Urine sodium, though suggestive of euvoletic state, was confounded by diuretic. We performed a FoCUS exam. Left ventricular outflow tract velocity time integral (LVOT-VTI), which is a surrogate for stroke volume was lower than expected (~13 cm [normal 18-22]) suggestive of hypovolemia. Flow changes precede drop in BP. We recommended to administer normal saline and the serum sodium improved to 130 mmol/L in 2 days; VTI normalized to ~22 cm [Fig 1]. Fig 2 illustrates stroke volume estimation using LVOT diameter and VTI. As the diameter is constant for a given person, VTI alone can be used to monitor response to therapy.

Discussion: POCUS is a valuable bedside diagnostic tool in day-to-day nephrology practice.

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PO1155

Polyethylene Glycol-Induced Pseudohyponatremia
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Introduction: Pseudohyponatremia due to Polyethylene glycol (PEG) is poorly described and goes unrecognized. We describe a case of hyperosmolar pseudohyponatremia due to PEG absorption into the systemic circulation.

Case Description: An 84-year-old lady with hypertension and CKD stage 4 was admitted with an asymptomatic serum sodium of 121. Initially thought be due to SIADH. She was started on 1-liter fluid restriction, sodium chloride tablet and torsemide. Nephrology was consulted on day 3 as her serum creatinine was 2.9 (baseline 2.3 mg/dl) and sodium improved to only 124. Patient complained of increased thirst and had dry mucus membrane on examination. Labs on admission revealed a serum sodium of 121 mEq/L, a serum osmolality of 286 mOsm/kg, urine osmolality of 230 mOsm/kg and urine sodium of 40. Serum creatinine was 2.3 mg/dL, BUN 50 mg/dL, glucose of 100mg/dL, uric acid 8.1 mg/dL. Thyroid function tests and cortisol were within normal range. An osmolar gap of 22 was noted. In the absence of hyperglycemia and other potential causes of an osmotic gap, such as mannitol or alcohol, a careful review of medication showed that she was on 3 weeks of PEG for constipation. PEG was held, fluid restriction and torsemide discontinued. Resolution of osmolar gap was confirmed in two weeks with return in sodium to 134 and creatinine to 2.3.

Discussion: The prevalence of hyponatremia is reported at 7% in bowel prep patients. Etiology in these cases was due to increased free water intake. Hyperosmolar hyponatremia is caused by the addition of an ‘effective solute’ (e.g. glucose, mannitol or sucrose) to the serum. Commonly used as an osmotic laxative, PEG is described as ‘a nonabsorbable, nonmetabolized polymers’ that when administered orally acts as a ‘pure osmotic agent’ in the gastrointestinal tract. Systemic absorption can occur in rare cases. When PEG absorption occurs, most of its clearance occurs via renal filtration, this process is likely impaired in a patient with CKD such as seen in our patient. When a patient presents with hyponatremia, the expectation of a low-serum osmolality needs to be confirmed with the actual measurement of serum osmolality. This case highlights the importance of detecting the etiology of hyponatremia without which treatment of the same can be impossible and expands the understanding of normal to high serum osmolality can go beyond the commonly known mannitol, paraproteinemia and lidiemia.

PO1156

Identifying Hypernatremia Subgroups with Differing Survival by Machine Learning Among Hospitalized Patients
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Background: The objective of this study was to characterize patients with hypernatremia on hospital admission into clusters using an unsupervised machine learning approach and to evaluate the mortality risk among these distinct clusters.

Methods: We performed consensus cluster analysis based on demographic information, principal diagnoses, comorbidities, and laboratory data among 6,297 hospitalized adult patients with hypernatremia present at admission. We calculated the standardized difference of each variable to identify each cluster’s key features. We assessed the association with each hypernatremia cluster with in-hospital and one-year mortality.

Results: There were three distinct clusters of hypernatremia: 1,570 patients (25%) in cluster 1; 2,648 (42%) in cluster 2; and 2,079 (33%) in cluster 3. Figure 1 is a plot of standardized mean differences to visualize key features for each cluster. Compared to cluster 2, the odds ratios for in-hospital mortality were 5.73 (95% CI 3.13-9.90) for cluster 3, whereas hazard ratios for one-year mortality were 3.38 (95% CI 3.31-4.25) for cluster 1 and 4.71 (95% CI 3.38-5.80) for cluster 2.

Conclusions: The characteristics and outcomes of hospitalized patients admitted with hypernatremia were heterogeneous. Our cluster analysis identified three clinically distinct phenotypes with differing mortality risks. Identification of heterogeneity in hypernatremic patients using this approach may provide guidance for the management of hospitalized patients with hypernatremia at the time of hospital admission.
A Case of Ketamine-Induced Diabetes Insipidus
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Introduction: To our knowledge there have been six previously published case reports describing central diabetes insipidus (DI) related to ketamine. We present a unique case of central DI associated with ketamine infusion in a critically ill patient with acute respiratory failure.

Case Description: A 52-year-old African American man with medical history of bipolar disorder, polysubstance abuse, chronic obstructive pulmonary disease, hypertension, and deep vein thrombosis was admitted to the medical intensive care unit with hemoptysis and acute respiratory failure. Due to agitation and refractory hypoxemia he required multiple sedating agents. Within hours of starting a ketamine infusion his urine output increased from a mean of 71 mL/hr to 305 mL/hr. Over 48 hours serum sodium (Na⁺) rose from 142 to 159 mmol/L. Urine osmolality (Uosm) was 132 mOsm/kg. 4 mcg intravenous (IV) desmopressin was administered. 90 minutes later Uosm had increased to 646 mOsm/kg. Urine output fell to 49 mL/hr. About 28 hours after the initial dose of desmopressin polyuria recurred and Uosm fell to 272 mOsm/kg. IV desmopressin was re-administered at 2 mcg with a similar response to the first dose. SNA normalized with free water replacement. Ketamine was stopped. Urine output, Uosm, and SNA remained stable without further intervention. Alternative etiologies for central DI such as hypoxic brain injury were considered but felt to be less likely due to the strong temporal relationship with ketamine. The Naranjo adverse drug reaction (ADR) likelihood score was 5 indicating a probable ADR.

Discussion: This case reinforces the association between ketamine and central DI which has been described in prior case reports. A hypothesized mechanism is ketamine’s antagonism of N-methyl-D-aspartate receptors in the posterior pituitary thus inhibiting arginine vasopressin production. Ketamine is being used with greater frequency in critical care. It is important to recognize this rare but potentially serious complication. Monitoring of SNA, Uosm, and urine output should be considered. When central DI related to ketamine is identified, withdrawal of the drug appears to be corrective.

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Higher Risk of Incident Kidney Stones in Patients with Metabolic Acidosis and CKD

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Background: Epidemiological studies have shown an association between kidney stones and risk for CKD and its progression. Some types of stones are less likely to form at higher urine pH. Metabolic acidosis is a risk factor for CKD progression, but the association of serum bicarbonate with risk of incident kidney stones is not well understood.

Methods: Optum’s de-identified Integrated Claims-Clinical dataset of US patients (2007-2019) was queried to identify patients with non-dialysis CKD stages 3-5 with 2 consecutive serum bicarbonate values of 12 to <22 mEq/L (metabolic acidosis) or 22 to <30 mEq/L (normal serum bicarbonate) with data a3 years pre-index. The first qualifying serum bicarbonate test established the index date. Primary exposure variables were baseline serum bicarbonate and change in serum bicarbonate over time. Adjusted time-dependent Cox Proportional Hazards models were performed to evaluate time to first occurrence of kidney stones (by ICD-9 or ICD-10 diagnosis codes) during an average 3.6 year follow-up period. Other covariates included age, sex, race-ethnicity, and income status, history of kidney stones, pre-index comorbidities associated with kidney stones, bariatric surgery, obesity, smoking history, baseline eGFR.

Results: 142,904 patients qualified for the study cohort. Patients with metabolic acidosis at index experienced kidney stones at greater frequency than those with normal serum bicarbonate (HR 1.07 vs 95% CI: 1.06-1.07 vs 95% CI: 1.06-1.07). Other significant factors associated with incident kidney stones included male sex, history of kidney stones, hyperoxaluria, gastroparesis and osteoporosis. Both higher serum bicarbonate at baseline (HR 0.956, 95% CI: 0.948-0.964) and higher serum bicarbonate over time (HR 0.968, 95% CI: 0.961-0.974) were associated with reduced risk of kidney stone development. The observed associations were unchanged in analyses examining death as a competing risk.

Conclusions: In patients with CKD, metabolic acidosis (vs. normal serum bicarbonate) was associated with a higher incidence of kidney stones and shorter time to incident stone formation. Future investigations should evaluate these associations by study design.

PO1165
Anion Gap Metabolic Acidosis on Continuous Renal Replacement Therapy: Are You Missing Something?
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Introduction: Anion gap metabolic acidosis is a common metabolic abnormality seen in the clinical practice. Causes includes Lactic acidosis, Ketoacidosis, Renal failure, volatile acid toxicity and salicylate poisoning. Ketoacidosis is due to decreased glucose and insulin availability leading to starvation ketosis and diabetic ketoacidosis respectively. Ketoacidosis is uncommonly seen in patients on prolonged continuous renal replacement therapy. We present 2 cases at Grady Hospital admitted with Acute hypoxic Respiratory Failure due to COVID 19 pneumonia, developed euaglycemic ketoacidosis on Continuous Renal Replacement Therapy.

Case Description: case 1: 73 male with the history of HTN, DM, CKD III admitted for acute hypoxic respiratory failure due to COVID 19 pneumonia. He was intubated on admission day 9. Course got complicated by hypotension during intubation leading to Acute Renal Failure on day 11. Patient was started on Renal Replacement Therapy on day 12 due to volume overload and acidosis. Day 19, Anion gap worsened and betahydroxybutyrate was elevated. Patient was started on insulin drip with resolution of acidosis on day 20. Case 2: 48 yo male with the history of HTN, DM II, CKD stage III admitted for Altered mental status, Hypertensive emergency and cough. He was diagnosed with COVID 19 Pneumonia. Patient had non oliguric acute kidney injury on admission. Hospital day 11, patient was oliguric, volume overloaded and hyperkalemia prompted Renal replacement therapy initiation. Day 14, Anion gap worsened and betahydroxybutyrate was elevated. Tube feed were initiated and Dialysate prescription was changed leading to resolution of anion gap on day 12.

Discussion: Diabetic ketoacidosis is a medical emergency commonly in patients with Type I DM but also in Type II DM patients as well. It occurs due to decrease insulin concentration or increase insulin resistance with or without decreased glucose availability leading to release of counterregulatory hormone and fatty acid metabolism producing ketocids. Diagnostic criteria include pH<7.3, Serum HCO3<18, Serum glucose>250mg/dl and positive urinary ketones. Euglycemic DKA is a subtype of DKA with serum glucose of <200 mg/dl. Incidence of Euglycemic DKA varies from 2.6-3.2%. Continuous renal replacement therapy is an under-recognized cause of Euglycemic DKA in patients with Diabetes Mellitus.
PO1166
A Wide-Awake Patient with Severe Hypoglycemia and Lactic Acidosis
Sarah Abdelsalam, Madhumita J. Mohanthy, Mili J. Shah. Wayne State University, Detroit, MI.

Introduction: Severe hypoglycemia is associated with altered mental status or loss of consciousness. We report an intriguing patient who had advanced liver disease and presented with severe hypoglycemia and lactic acidosis without any alteration in mental status.

Case Description: 57-year-old female with severe decompensated alcoholic liver cirrhosis, ascites and recurrent hepatic hydrothorax presented to the Emergency Room with worsening shortness of breath. She had poor oral intake except for actively consuming ethanol. Chest X ray revealed worsening right hydrothorax. Routine blood tests revealed severe hypoglycemia (serum glucose 28 mg/dL; severe anion gap metabolic acidosis (arterial pH 7.11, serum bicarbonate 6 mmol/L, anion gap 40 mmol/L) and acute kidney injury with elevation of serum creatinine to 2.2 mg/dL. Subsequent laboratory investigations revealed serum lactate acid level of 23 mmol/L. Serum ethylene glycol, methanol, salicylate and acetonitrile levels were undetectable. She had no seizures, malignancy or hypoxia. The patient was alert and oriented. She was hemodynamically stable. There was no evidence of sepsis, tissue hyperperfusion or bowel ischemia. She was not taking any medications which may have led to hypoglycemia or lactic acidosis. The patient was administered intravenous glucose with rapid improvement of her serum glucose and lactate level.

Discussion: This patient had no alteration in mental status despite severe hypoglycemia. Under normal circumstances, the brain primarily depends on glucose as the primary fuel. Studies have shown that under conditions of hypoglycemia and elevated serum lactate acid levels, lactate may serve as an alternative source of energy for the brain. We hypothesize that hyperlactatemia, by providing an alternate energy source, prevented mental status changes in this patient with severe hypoglycemia. Correction of hypoglycemia led to rapid correction of hyperlactatemia suggesting that perhaps lack of glucose may have contributed to hyperlactatemia. We did not identify any obvious cause of hypoglycemia or hyperlactatemia except for her end stage liver disease, continued ethanol use and perhaps also her oliguric acute kidney injury. This patient illustrates that hyperlactatemia may be neuroprotective in severely hypoglycemic patients.

PO1167
Sleeping Beauty: Hypersomnolence and Hyperammonemia in a Patient with Multiple Myeloma
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Introduction: Metabolic encephalopathy in a patient with multiple myeloma is commonly reported in association with prevalent biological syndromes such as uremia, hypercalcemia, and or hyperviscosity due to immunoglobulin, but very rarely hyperammonemia has been described as another cause of encephalopathy.

Case Description: The patient is a 45 year old woman with a prior diagnosis of multiple myeloma in July 2020. A bone marrow biopsy confirmed plasma cell neoplasm. She presented with confusion and hypersomnolence over two weeks. Labs included hemoglobin 7.3 g/dL, white blood cell 21.9 x10^3/ul, platelets 276,000/ul, serum creatinine 0.7 mg/dL, urea 61 mg/dL, albumin 3.7 g/dL, serum calcium 10.3 mg/dL, phosphate 2.7 mg/dL, sodium 133 mEq/L, potassium 3.7 mEq/L, chloride 108.9 mEq/L, bicarbonate 16.4 mEq/L, arterial pH 7.25, pCO2 32.3 mmHg, pO2 63.3. Hypercalcemia was as the primary fuel. Studies have shown that under conditions of hypoglycemia and elevated serum lactate acid levels, lactate may serve as an alternative source of energy for the brain. We hypothesize that hyperlactatemia, by providing an alternate energy source, prevented mental status changes in this patient with severe hypoglycemia. Correction of hypoglycemia led to rapid correction of hyperlactatemia suggesting that perhaps lack of glucose may have contributed to hyperlactatemia. We did not identify any obvious cause of hypoglycemia or hyperlactatemia except for her end stage liver disease, continued ethanol use and perhaps also her oliguric acute kidney injury. This patient illustrates that hyperlactatemia may be neuroprotective in severely hypoglycemic patients.

PO1168
Renal Outcomes and Safety Profile of Direct Peritoneal Resuscitation (DPR)
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Background: DPR is a novel technique used after damage control surgery where peritoneal dialysis fluid is continuously irrigated and drained from the peritoneal cavity in a open abdomen. This has been shown to improve intestinal perfusion, leading to faster abdominal closure. We analyzed the safety profile in terms of changes in the electrolyte profile.

PO1169
Pyroglyutamic Acidosis: Gaps in the Gaps
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Introduction: Prolonged use of acetaminophen can lead to an acquired form of pyroglyutamic acidosis, a form of anion gap metabolic acidosis (AGMA) from increased production of 5- Oxoprolin (pyroglyutamic acid). 5- Oxoprolin accumulates in the body due to the failure its breakdown by 5- Oxoprolinase and is excreted in urine causing positive anion gap (AG).

Case Description: Case 1: First patient is a 59 y/o man with normal prior renal function with baseline creatinine (Cr) of 0.7 mg/dL with severe pancreatitis. At the time of presentation his serum calcium 15 mg/dL (8.5-10.5) and his serum Cr level was 2.2 mg/dL. His hospital course was complicated by sepsis due to multiple intra-abdominal infections and required iv pressor and ventilator support. He was later started on continuous veno-venous hemofiltration (CVVH) temporarily with recovery of renal function. Acetaminophen 1 gram three times daily was administered for pain control. On the 65th day of hospitalization, his bicarb was 15 with an AG of 14, but when corrected for low albumin 1.8, it increased to 20. HE had a positive urine AG and his urine 5-Oxoprolin was 1583 mmol/mol Cr (range < 62). Case 2: Second patient is a 74-year-old man with a history of stage 4 CKD admitted with sepsis due to perforated viscus. He had long hospital course due to ischemic gut with continued bleeding and sepsis due to perforation. He was on Acetaminophen 1 gram four times daily for pain control. His serum bicarbonate started trending down to a nadir of 11 mmol/L on the 43rd day of admission. He had an anion gap of 12, but corrected anion gap was 18 and had a positive urine AG. His urine 5- Oxoprolin was 631 mmol/mol creatinine (range <62).

Discussion: Both patients in our case series had critical illness, were malnourished, and was recovering from prolonged infection and sepsis which are risk factors for pyroglyutamic acidosis and low serum albumin levels. Their AG might appear to be within normal range if not corrected for albumin. Urine albumin gap is an indirect method of measuring urine ammonia excretion and it is elevated in renal tubular acidosis and from excretion of organic anions like 5-Oxoprolin and ketone bodies. Correction for AG is proposed as measured AG + 2.5 x (serum albumin = 4.2 – measured albumin /g/dL). This is not a “normal AGM” as there is a positive urine AG due to pyroglyutamic acidosis can mimic renal tubular acidosis and can be easily missed.
Diffuse Large B Cell Lymphoma and Synchronous Colon Adenocarcinoma Presenting with Type B Lactic Acidosis Secondary to the Warburg Effect in a Hispanic Man

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Introduction: Lactic acidosis is a major metabolic dysregulation characterized by hyperlactatemia and acidemia that is commonly associated with tissue hypoperfusion. In very rare circumstances, hematological malignancies have been associated with a paraneoplastic syndrome characterized by the modification of the metabolism of cancerous cells from aerobic to anaerobic glycolysis.

Case Description: A 61-year-old man presented to the hospital due to generalized body weakness. He was recently admitted to the hospital due to left knee pain; at that time incision, drainage, and tissue sample were done. The patient was discharged to home with wound care and antibiotics. On presentation, patient was found to be tachypneic, hypotensive with Kussmaul breathing. A warm erythematous lesion was seen on left lower extremity. Laboratory results showed WBC 20000/mm3, Hemoglobin 10 g/dL, Platelets 340 /mm3, creatinine 7.9 mg/dL, Bicarbonate 5 mmol/L, Lactate 6.21 mg/dL, and Ferritin 326 mg/dL, blood cultures positive for Enterobacter. Broad-spectrum antibiotics were administered. Nephrology consulted and dialysis started emergently. The pathology report showed Diffuse Large B-Cell Lymphoma. During the hospital stay, patient acidosis was persistent despite adequate renal replacement therapy and resolution of the septic process. ABG was done showing serum pH of 7.2, Bicarbonate 9 mmol/L, Lactic acid 17.5 mg/dL. Bowel ischemia was ruled out with CT angiogram however imaging showed neoplastic infiltration of peritoneal abdominal structures associated with multiple small nodules. Colonoscopy demonstrated synchronous colon adenocarcinoma. The decision was made to treat the patient with chemotherapy. One week after chemotherapy lactic acid trended down to 1.1 mg/dL. The metabolic acidosis and renal function improved and RRT was stopped.

Discussion: Usually, lactic acidosis is a sign of hyperfusion and septic shock. In this case, the source of lactic acidosis was not hyperfusion but rather a paraneoplastic syndrome that leads to anaerobic metabolism of malignant cells, known as the Warburg effect. This condition can be fatal. Prompt initiation of chemotherapy is recommended.

Distal Renal Tubular Acidosis in Patients with Autoimmune Diseases

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Background: Distal renal tubular acidosis (DRTA) is reported in association with autoimmune diseases. DRTA can evolve without symptoms and systemic acidosis, this form being defined as incomplete DRTA. The incomplete form necessitates the use of a urinary acidification test like the Furosemide and Fluorocitrone test for establishing the diagnosis.

Methods: We conducted a prospective observational study in a selected cohort of 48 patients diagnosed with autoimmune diseases (SLE, SJögren syndrome, ANCA vasculitis, cryoglobulinemic vasculitis), who presented in our clinic from December, 2020 until May, 2021. The patients were submitted to Furosemide and Fluorocitrone test.

Results: The study included 48 patients (36 females, mean age 41.92 ± 15.7 years), diagnosed with SLE (33 patients), pANCA vasculitis (7 patients), cANCA vasculitis (1 patient), SJögren syndrome (3 patients) and cryoglobulinemic vasculitis (4 patients). There was a significant difference regarding age (p=0.001) and eGFR (p=0.001) between the groups with vasculitis (mean age 60.752 ± 20.03 years, eGFR 20.03 ± 11.74 years) and 20.03 ± 11.74 years groups with vasculitis a (standard base excess: -10.4 [−12.5, −9.5] mEq/L in group 20, ± 79 [63, 85] mmHg in group 40 (P<0.05). Despite the increased infusion of bicarbonate in group 40, the blood CO2 content did not change during the experiment. The 12-hour survival rate was higher in group 40 (67% vs. 0, P=0.032).

Conclusions: A higher bicarbonate concentration in the dialysate of animals undergoing hypercapnic respiratory failure was associated with improved blood pH control increasing the PaCO2 levels.

Effect of Continuous Dialysis on Blood pH in Acidemia Hypercapnic Animals with Severe AKI: A Randomized Experimental Study Comparing High vs. Low Bicarbonate Afluent

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Background: Controlling blood pH during acute ventilatory failure and hypercapnia in individuals suffering from severe acute kidney injury (AKI) and undergoing continuous renal replacement therapy (CRRT) is of paramount importance in critical care settings. In this situation, the concentration of sodium bicarbonate in dialysate is still an unsolved question in critical care since high concentrations may worsen carbon dioxide levels and low concentrations may not be as effective in controlling pH.

Methods: We performed a randomized, non-blinded, experimental study. AKI was induced in twelve female pigs via renal hilum ligation and hypoventilation by reducing the tidal volume during mechanical ventilation with the goal of achieving a pH between 7.10 - 7.15. After achieving the target pH, animals were randomized to undergo isovolemic haemodialysis with one of two concentrations of bicarbonate dialysate (40 mEq/L [group 40] vs. 20 mEq/L [group 20]).

Results: The haemodynamic, respiratory, and laboratory data were collected. The median pH value at CRRT initiation was 7.14 [7.12, 7.15] in group 20 and 7.13 [7.09, 7.14] in group 40 (P<0.05). The median baseline PaCO2 was 74 [72, 81] mmHg in group 20 vs. 79 [63, 85] mmHg in group 40 (P<0.05). During the last hour of CRRT, the pH value was 7.05 [6.95, 7.09] in group 20 and 7.12 [7.1, 7.14] in group 40 (P<0.05), with corresponding values of PaCO2 of 85 [79, 88] mmHg vs. 81 [63, 100] mmHg (P<0.05). The difference in pH after three hours was due to a metabolic component [standard base excess: -10.4 [-12.5, -9.5] mEq/L in group 20 vs. -7.9 [-9.2, -5.1] mEq/L in group 40 (P<0.05). Despite the increased infusion of bicarbonate in group 40, the blood CO2 content did not change during the experiment. The 12-hour survival rate was higher in group 40 (67% vs. 0, P=0.032).

Conclusions: A higher bicarbonate concentration in the dialysate of animals undergoing hypercapnic respiratory failure was associated with improved blood pH control increasing the PaCO2 levels.
PO1174
A Patient with Combined Metformin-Induced Lactic Acidosis and Euglycemic Diabetic Ketoacidosis

Introduction: Metformin is a small, non-protein-bound molecule that can cause lactic acidosis in 6 out of 100,000 patients with a mortality rate of 30-50%. Concurrent euglycemic diabetic ketoacidosis (DKA) from sodium-glucose co-transporter-2 (SGLT2) inhibitor has been reported in one case. We report a unique case of a patient with acute kidney injury (AKI) in the setting of metformin-induced lactic acidosis and osmotic diuresis due to euglycemic DKA complicated by celecoxib use.

Case Description: A 66-year-old female with a past medical history of type 2 diabetes mellitus for 21 years on metformin 1000 mg twice daily and emaplatin 25 mg daily with baseline eGFR 51 mL/min/1.73m² 5 months prior, who was also on celecoxib 200 mg daily for 40 days presented for elective cervical discectomy which was canceled due to AKI. On exam, blood pressure was 119/59 mmHg, pulse was 92 beats/min, and the temperature was 36.1°C. She was tachypneic at 24 breath/min. Labs showed sodium 136 mg/dL, potassium 9.5 mg/dL, bicarbonate 14 mg/dL, BUN 83 mg/dl, creatinine 8.78 mg/dL, and glucose 117 g/dL. Lactic acid was 13.5 mmol/L, beta-hydroxybutyrate 5.9 mmol/L, serum osmolality 336 mOsm/kg with no osmolar gap. She underwent conventional hemodialysis (HD) for 3 hours followed by 18 hours of continuous kidney replacement therapy (CKRRT). She required an insulin drip with 5% dextrose in normal saline for 24 hours. Lactic acid was 3.8 mmol/L after 24 hours. Creatinine improved to 2.46 mg/dL on day 4 without further intervention. She was discharged off metformin, emaplatin, and celecoxib.

Discussion: Metformin is readily dialyzable but has a large volume of distribution. There is no specific antidote available to reverse the toxic effects of metformin or consensus on the modality of renal replacement therapy. Previously demonstrated biphasic elimination pattern of metformin intoxication suggests that a brief HD session within the subsequent 3 months.

PO1175
Mind the Gap: An Anion Gap of 52 Fully Explained
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Introduction: The Anion Gap (AG) remains the main clinical tool to elucidate acid-base disturbances in patients with metabolic acidosis. We present a case with an extremely elevated AG of 52 mmol/L, and describe our search for its biochemical explanation.

Case Description: A 66-year-old female was admitted with loss of consciousness, shock, and severe acute kidney injury. She had type 2 diabetes mellitus, treated with metformin. At presentation, she had an AG of 52 mmol/L and osmolar gap of 34 μmol/kg. Her arterial blood gas showed: pH <7, HCO3 7.5 mmol/L, pCO2 16 mm/Hg. Phosphate level was unusually high, 21.3 mm/dL, with unknown etiology. There was no history of enema or laxative use. A significant contributor of AG was lactate at 14.5, given her history of metformin use. Urine drug screen was positive for amphetamines. The volatile alcohol panel was positive for acetone; methanol, ethanol, ethylene glycol and isopropyl alcohol were not detected. Continuous venovenous hemofiltration (CVVH) was initiated. After 3 days, renal function started recovering, lactate and phosphorus levels normalized and AG closed. The patient did not need CVVH thereafter. Two months later, the patient was discharged to a nursing facility in a stable condition.

Discussion: Extremely elevated AG of 52 in this patient can be explained by a rise in concentrations of organic acid anions, lactate, ketoacids, hyperphosphatemia, and retention anions.

Explanation of the high AG: The Figure describes the calculation of AG. In this patient, phosphate was a major contributor to the AG.

PO1176
Is an Increase in Anion Gap a Predictor of Hemodialysis Initiation in Patients with Advanced CKD?

Background: Because uremic symptoms and manifestations vary among patients with advanced chronic kidney disease, it is sometimes difficult to decide on the timing of dialysis initiation only from uremia, we attempted to investigate whether anion gap (AG) that may reflect the accumulation of total organic acids in uremia can be a marker of uremia and may predict the timing of dialysis initiation.

Methods: This study included pre-dialysis patients who attended to our hospital for more than six months prior to the beginning of hemodialysis (HD), and retrospectively analyzed the relationship between their serological data, AG, and various uremic symptoms. The AG was calculated as the corrected AG (cAG) = Na−Cl−HCO3 [mmol/L]×2.5 + (4-serum albumin concentration [g/L]). The statistical analysis was performed by logistic regression analysis, correlation analysis, and factor analysis using SPSS®.

Results: A total of 283 patients [diabetes mellitus: 136 (48.1%), nephroclerosis: 66 (23.3%), glomerulonephritis: 36 (12.7%)] were included in this study. The most common clinical symptom before dialysis initiation was fluid overload, which was seen in 134 patients (47.3%), followed by anorexia 104 patients (36.7%) and general malaise 96 patients (33.9%). The cAG began to increase 3 months before the initiation of HD (14.2 mmol/L), which showed a rapid increase just before the initiation, and was correlated with uremia and fatigue, better than fluid retention. Of note is that cAG was most significantly associated with dialysis initiation among various factors. The ROC of cAG for dialysis initiation showed the highest value of AUC 0.979 (95% CI=0.972 to 0.85, p<0.05), with a cutoff value of adjusted cAG 15.975 (sensitivity 0.689, specificity 0.786).

Conclusions: Uremic symptoms and some serological markers including azotemia, metabolic acidosis, and hyperphosphatemia have been usually used to predict the magnitude of uremia and the timing of dialysis initiation. In our study, it is suggested that a rapid increase in cAG over 16 mmol/L may also be a good predictor of dialysis initiation within the subsequent 3 months.

PO1177
Mysterious Case of Recurrent Life-Threatening Lactic Acidosis
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Introduction: Patients living with diabetes are prone to type-B lactic acidosis, often presenting with profound acid-base derangements. The reason for lactate production is not obvious hence management can be challenging. We present a case of life-threatening recurrent lactic acidosis in a diabetic patient.

Case Description: A 67-year-old man with type 2 diabetes, hypertension, presented to the hospital with malaise for 2 days. He had been on metformin in the past but had recently switched to insulin. There was no history of alcohol ingestion nor use of herbal supplements. The lactic acid level was 34.2 mmol/L with Ph of 6.82, PCO2 of 27 mmHg, serum bicarb of 7 mmol/L, anion gap of 28, and serum Cr of 1.4 mg/dL with baseline of 1 mg/dL. No evidence of infection or ischemia found. Toxicology screen was negative and serum metformin level was undetectable. Lactic acidosis resolved with continuous renal replacement (CRRT) for 24 hours. A month later he returned with similar complaints.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
and its lactate level was 14.8 mmol/L. This was treated with supportive care alone. Six months later the patient returned with lactate of 13.5 mmol/L, worsening to 18.6 mmol/L. He improved after treatment with CRRT and supportive care. Alcohol levels, liver function tests, pyruvate, glutamate, metformin levels were all negative or normal. The thiamine level was not checked during his first admission. During the second visit, the value was normal but this was drawn after thiamine had been given. During the third visit, the thiamine level was noted to be less than 6 mmol/L. The patient was started on thiamine and has not had further episodes of lactic acidosis.

Discussion: Patients with diabetes are prone to excess lactic acid generation due to the decreased conversion of pyruvate to lactic acid and increased conversion of pyruvate to lactate. This is due to the absence of thiamine and pyruvate kinase deficiency. In the absence of thiamine, pyruvate cannot enter the Krebs cycle and is converted to lactic acid predisposing diabetics to type-B lactic acidosis. Thiamine is filtered in the glomerulus and is reabsorbed in the proximal tubule through the thiamine H+ antiporter. Long term use of diuretics has been associated with thiamine deficiency. However our patient was not taking any nor did he have chronic kidney disease or any evidence of malnutrition.

Methods: This was a single-center retrospective chart review of CKD patients with acidosis from 2010-2017. Inclusion criteria were adult patients receiving NaHco3 for CKD-associated acidosis with baseline estimated glomerular filtration rate (eGFR) ≥25 and < 60 ml/min/1.73 m² when starting NaHco3. Patients with glomerulonephritis, kidney transplant, acute kidney injury (not back to at least 75% of eGFR baseline) were excluded. Four groups were identified for comparison based on mean serum Co2 (in mmol/L), from outpatient measures during 3 years follow-up, group A (< 22), group B (22 - < 24), group C (24 - < 25), and Group D (≥ 25). Albumin, urine protein-creatinine ratio (UPCR), PTH, and eGFR were compared, p-values are calculated by a one-way ANOVA model.

Results: There were 383 patients with CKD-associated acidosis receiving NaHco3, 93 patients qualified for the study. Group A (n=21), group B (n=41), group C (n=13), and Group D (n=18). Racial demographics: 35=black (38%), 57=white (61%), 1=Other. Females 49 (53%). Median age 69 years. Follow-up 3 years. At baseline mean eGFR, UPCR, and albumin, and diuretics use and osteoporosis diagnosis in the four groups were similar (p = 0.46, 0.32, 0.15, 0.09, 0.36 respectively). Mean hemoglobin A1C in each group did not exceed 8.2. At 3 years of follow-up, changes in eGFR, UPCR, and osteoporosis status between the four groups were similar (p = 0.14, 0.27, 0.19 respectively). Change of albumin was significantly worse in group A comparing to groups B, and C (p = 0.007, 0.049 respectively), and average PTH was significantly worse in group A comparing to group C (p = 0.045).

Conclusions: In our cohort, all groups of treated CKD-associated acidosis (B, C, and D) showed no statistical difference in CKD progression, the severity of parathyroidism, developing osteoporosis, or nutrition status assessed after 3yes follow-up. Hence, higher Co2 targets don’t carry worse outcomes.
Pseudo-Hypobicarbonatemia with Severe Hypertriglyceridemia

Case Description:
A 42-year-old male patient with a past medical history significant for diabetes mellitus type 2, obesity, and hyperlipidemia. The patient presented with nausea, vomiting and epigastric pain. Physical examination was significant for tenderness in the epigastrium and xanthelasma. The basic metabolic profile (BMP) was significant for Na+ 127meq/L, Cl - 94meq/L, BUN 10mg/dL, creatinine 0.87mg/dL and AGAP 24. A lipid panel showed a cholesterol 461mg/dL, and triglycerides 4061mg/dL. Lipase and amylase were 1183U/L and 202U/L respectively. Urinalysis revealed trace ketones. CT abdomen revealed peripancreatic stranding. The patient was diagnosed with AGMA due to diabetic ketoacidosis and pancreatitis secondary to hypertriglyceridemia. An arterial blood gas analysis (ABG) subsequently revealed a pH 7.39, PCO2 40, PaO2 73 and a HCO3- 24. A significant dissociation between the calculated and measured bicarbonate was noted. Following aggressive lowering of the triglycerides, with Insulin infusion there was an immediate resolution of the pseudo- bicarbonatemia and anion gap metabolic acidosis.

Discussion:
This measurement error is due to the mechanism by which the analyzer interprets the bicarbonate level in the serum. Most analyzers utilize either anion-selective electrode (ISE) or function via an enzymatic/photometric method. High amounts of lipid particles may cause light scattering altering the photometric analysis. This likely caused the discrepancy between the enzymatic/photometric measured serum bicarbonate and the calculated bicarbonate of the aqueous phase ISE analyzer used by the ABG. Clinicians should be able to recognize that its essential to obtain a blood gas sample for determination of the acid-base status to avoid expensive work up.

Pseudohypocarbonatemia in a Patient with Paraproteinemia

Introduction:
The first step in acid-base disorders’ diagnosis is obtaining measurement of blood bicarbonate (HCO3-), pH and partial pressure of carbon dioxide (pCO2) levels. Blood HCO3- levels are estimated via two methods: direct measurement of serum total carbon dioxide (TC02), or via Henderson-Hasselbalch equation using arterial blood and directly measuring pH and pCO2 levels. With the enzymatic method, there have been reported cases of falsely low serum HCO3- due to interference by elevated triglyceride levels, but only two cases have been reported of spuriously low serum HCO3- due to interference by paraproteins.

Case Description:
A 74-year-old male with a history of bladder carcinoma in situ and hypertension presented with complaints of malaise after a recent bladder irrigation. Basic metabolic panel (BMP) was unremarkable except for a HCO3- of 8 mmol/L measured using a Siemens Vista (SV) enzymatic chemistry analyzer. He was hospitalized for high anion gap metabolic acidosis with anion gap of 22. He was started on intravenous NaHCO3 (150 mEq/L) after nephrology was consulted. Repeat serum HCO3- was 11 mmol/L the next day with transition to oral NaHCO3 650 mg therapy thrice daily. On outpatient follow-up, he had low serum HCO3- ranging from 8-11 mmol/L (using SV analyzer) despite his reported compliance with NaHCO3. He was evaluated by another nephrologist with repeat BMP and an arterial blood gas (ABG). The results revealed a serum HCO3- of 8 mmol/L in contrast with ABG pH of 7.41 and HCO3- of 25 mmol/L. Due to the discrepancy, his serum HCO3- was analyzed at a different facility using a Beckman Coulter analyzer which revealed a normal serum HCO3- level of 21 mmol/L. Further work up was pursued with SPEP and SIFE revealing an M-spike and presence of IgM and IgA kappa monoclonal proteins respectively, which led to a diagnosis of monoclonal gammopathy.

Discussion:
Paraproteins have been reported to cause interference with multiple laboratory test results. Paraproteins in our case may have resulted in artifactual error of serum HCO3- by direct interaction with assay reagents, binding of paraproteins to an assay reagent, or turbidity caused by the precipitation of the monoclonal proteins. Our case highlights the importance of being aware of this phenomenon of pseudohyperbicarbonatemia that can occur with certain chemical analyzers.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

PO1181

PO1183

Proton Pump Inhibitor (PPI) for the Treatment of Metabolic Alkalosis due to Gastric Losses

Introduction:
Gastric losses of hydrochloric acid can result in severe metabolic alkalosis (met alk). We describe two cases where patients with significant losses of gastric secretions presented with severe met alk and AKI. In both cases, PPI therapy was used to reduce the volume of the gastric secretions with excellent effect.

Case Description:
Patient 1: A 44 year-old woman with Gardner Syndrome with near-total enterectomy and colostomy on total parenteral nutrition with a venting gastric tube (G-tube), presented with met alk (HCO3- 50 meq/L) and AKI (Scr 4 mg/dL from baseline 1.3 mg/dL). Met alk persisted despite normal saline (NS) administration and gastric tube losses ranged from 4-8 liters per day. Twice daily intravenous PPI was started with immediate decrease of gastric losses and normalization of HCO3-. This patient was admitted one year later (off PPI therapy) with a similar derangements and resuming PPI therapy caused similar improvement. Patient 2: A 59 year-old man with gastric outlet obstruction and venting G-tube presented with met alk (HCO3, 47 meq/L) and acute kidney injury (Scr 4.5 mg/dL from 1.3 mg/dL). Met alk persisted despite NS administration and his gastric tube losses ranged from 4-11 liters per day. Daily intravenous PPI was started with decrease of gastric losses and normalization of HCO3-. This patient presented again to the hospital one month later with normal HCO3- on PPI therapy. Both patients’ bicarbonate and gastric fluid output trend relative to PPI therapy is detailed in figure 1.

Discussion:
There are few reported cases of PPI therapy for metabolic alkalosis due to gastric losses. Generally, met alk that occurs due to gastric losses is readily rectified by increased renal bicarbonate excretion, but this compensatory mechanism is limited in the setting of AKI. We report two cases in which PPI therapy successfully decreased the quantity of gastric fluid losses and rapidly improved metabolic alkalosis.

PO1184

A Case of Extreme Metabolic Alkalosis

Introduction:
Metabolic alkalosis results from an increase in serum bicarbonate concentration due to loss of hydrogen ions and/or gain in bicarbonate ions. We present a case of extreme metabolic alkalosis due to multiple etiologies rarely co-existing.

Case Description:
A 30-year-old male with Duchenne muscular dystrophy, chronic respiratory failure on mechanical ventilation with tracheostomy, gastrojejunostomy (G-J) tube dependent and genetic cardiomyopathy presented with drowsiness and lethargy for last 2 days per mother. His tube feed regimen was Nutren 1 can with 120 cc free water 4 times/day. He was recently started on Lasix 20 mg daily. Initial labs showed blood pH of 7.81, bicarb 66 and PC02 53. He had AKI with Creatinine (Cr) of 2.66, BUN 266 and Cystatin C 11. His baseline Cr was 0.9-1.1. UA showed 3+ protein and no sediment. Urine (Ur) sodium 87, Ur chloride <15, Ur Cr <10 and Ur Ph was 9. Chest Xray showed cardiomagically with mild venous congestion and kidney ultrasound showed bilateral small echogenic kidneys. He was treated with normal saline (NS) IV @100 ccr/h, acetazolamide IV, potassium IV, proton pump inhibitor to decrease gastric acid and minute ventilation was increased to allow for compensatory hypercapnia. AKI improved with adequate diuresis and PH normalized (Image 1) by day 5. He had hypernatremia after 24 hours of IV NS and fluid were changed to hypotonic + free water via G-J tube. High daily output of ~700cc was recorded from the G-J tube. He was discharged home without diuretics and tube feeds were changed to Suplena + increase free water but was re-admitted in 1 week with hyponatremia and severe metabolic alkalosis. He underwent G-J tube exchange during 2nd admission followed by persistent normalization of blood PH.

Discussion:
This is a unique case of extreme metabolic alkalosis primarily due to the loss of gastric acid in the G-J tube, but volume depletion, hypokalemia, AKI, high protein tube feeds, lack of respiratory compensation due to ventilator dependence and loop diuretics contributed to the development and maintenance of metabolic alkalosis.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
We corrected his metabolic alkalosis and AKI with cautious use of IV fluids and Acetazolamide without needing dialysis, although metabolic alkalosis relapsed until the G1 tube was changed.

Daily PH and Cr

**PO1185**

Hypercalemia and Metabolic Alkalosis Induced by the Novel Potassium Binder Patiromer: Report of Rare Event

Kathryn J. Suchow, Swetha Rani Kandula, Juan Carlos Q. Velez. Ochsner Medical Center - New Orleans, New Orleans, LA

**Introduction:** Patiromer is a calcium (Ca)-potassium (K) exchange resin approved for treatment of hyperkalemia. Disorders of Ca or acid base balance were not reported in pre-approval clinical trials. Post-marketing, only 2 case reports of hypercalemia associated with the use of patiromer have been recently published. We present a case of a patient with chronic kidney disease (CKD) with an unusual picture of hypercalemia, metabolic alkalosis and hyperkalemia upon intensification of patiromer dosing.

**Case Description:** A 56-year-old white man with CKD stage 4 (baseline creatinine 2.8 mg/dL) due to type 1 diabetes mellitus, proteinuria (1.5 g/g) and persistently high serum potassium (sK, 5.5 – 5.9 mEq/L) attributed to type 4 renal tubular acidosis was evaluated in clinic. Due to high risk of CKD progression, patiromer 14.4 g qd was prescribed to enable RAS blockade. Five months later, sK remained elevated at 5.0 mEq/L. Patiromer dosage was thus increased to 16.8 g. Three months later, sK fell to 4.1 mEq/L. Hence, patiromer was maintained at 16.8 g and ibesartan initiated. At that time, corrected serum calcium (sCa) was 9.3 mg/dl and serum bicarbonate (sHCO3) was 26 mEq/L. Five months later, routine laboratory tests revealed a sK 2.5 mEq/L, sCa 12.6 mg/dL and sHCO3 34 mEq/L. The patient denied recreational or over-the-counter drugs, diuretics or calcium supplements. Patiromer was discontinued. Thorough investigation (PTH, PTH-related peptide, 1,25-OH-vitamin D, 25-OH-vitamin D, TSH, drugs, diuretics or calcium supplements. Patiromer was discontinued. Thorough investigation (PTH, PTH-related peptide, 1,25-OH-vitamin D, 25-OH-vitamin D, TSH, drugs, diuretics or calcium supplements. Patiromer was discontinued.

**Discussion:** Patiromer promotes gastrointestinal elimination of potassium by binding the molecule to potassium in exchange for calcium. Increased in intestinal absorption of calcium results in hypercalciuria but not sustained hypercalcemia. The clinical course of our patient suggests that the increased dose of patiromer led to a reduction in iCa (↓iCa) by adjusting iCa for Alb and the anion gap’s 3 components, Na, Cl, and CO2. It was likely better than sCa in detecting low iCa (↓iCa) on internal validation (Yap, JALM 2020).

**Background:** The popular adjustment of serum total calcium (sCa) for albumin (Alb) yields a corrected value (cCa) that doesn’t detect abnormal ionized calcium (iCa) well in critical care patients (pts), possibly because it ignores the fraction of iCa complexed by small anions. To account for such anions, we derived a model that estimates iCa (Ci_A2, sCa) by adjusting iCa for Alb and the anion gap’s 3 components, Na, Cl, and CO2. It was likely better than sCa in detecting low iCa (↓iCa) on internal validation (Yap, JALM 2020).

**Methods:** From the MIMIC III v1.4 database, we paired chemistry panel iCa (mg/dL), Alb (g/dL), Na, Cl, and iCa values with gap panel iCa values (ref range: 1.21-1.32 mM) measured up to 20 min. apart. Limiting each pt. to the most closely-timed pair left 4105 pairs (median 10 min apart). We calculated cCa (sCa .012×Alb) and ICaEST (.091×sCa −.034×Alb −.0042×Na −.0073×Cl +.0047×sCO2) and compared their ROC curves (area/SE) for detecting ↓iCa (iCa<1.10; rate=33.1%), and high iCa (↑iCa) (sCa>1.12; rate=5.8%).

**Results:** ICaEST was better than cCa by ROC analysis for both ↓iCa (0.334±0.007 vs 0.752±0.008, p<10^-6) and ↑iCa (0.975±0.004 vs 0.963±0.006, p<.0006). The table compares the sensitivity and specificity (SENS/SPEC) and positive and negative predictive values (PPV/NPV) of ICaEST and iCa at similar cutoffs. ICaEST overestimated iCa by 0.04 mEq/L (1.17±0.002 vs 1.137±0.002, p<10^-6), a bias that was fairly consistent across the full prediction range.

**Conclusions:** The ICaEST model is superior to cCa in ranking critically ill pts for both ↓iCa and ↑iCa. It can help clinicians decide when to directly measure iCa. ICaEST overestimated iCa but applying a local correction of -0.04 would make its absolute predictions accurate, on average, in the ICU setting.

**PO1186**

Beads of Calcium

Nityasree Srilalluri, Karla G. Carias Martinez, Elizabeth Kienman, Jose M. Monroy-Trujillo. Johns Hopkins Nephrology Johns Hopkins Medicine, Baltimore, MD.

**Introduction:** Hypercalemia is a common disorder that can cause acute kidney injury (AKI) and result in significant morbidity and mortality.

**Case Description:** A 50-year-old male with diabetes and hypertension presented with left knee septic arthritis. He had an AKI from volume depletion and vancomycin toxicity (trough level 35.1). Incision and drainage (I&D) was done on day 13 for refractory knee infection. Postoperatively, serum creatinine (Cr) and Calcium (Ca) rose to peak Cr of 2.8 mg/dL and Ca 2.8 mg/dL due to type 1 diabetes mellitus, proteinuria (1.5 g/g) and persistently high serum calcium (sCa) was 9.3 mg/dl and serum bicarbonate (sHCO3) was 26 mEq/L. Five months later, routine laboratory tests revealed a sK 2.5 mEq/L, sCa 12.6 mg/dL and sHCO3 34 mEq/L. The patient denied recreational or over-the-counter drugs, diuretics or calcium supplements. Patiromer was discontinued. Thorough investigation (PTH, PTH-related peptide, 1,25-OH-vitamin D, 25-OH-vitamin D, TSH, drugs, diuretics or calcium supplements. Patiromer was discontinued.

**Discussion:** Patiromer promotes gastrointestinal elimination of potassium by binding the molecule to potassium in exchange for calcium. Increased in intestinal absorption of calcium results in hypercalciuria but not sustained hypercalcemia. The clinical course of our patient suggests that the increased dose of patiromer led to a reduction in iCa (↓iCa) by adjusting iCa for Alb and the anion gap’s 3 components, Na, Cl, and CO2. It was likely better than sCa in detecting low iCa (↓iCa) on internal validation (Yap, JALM 2020).

**Background:** The popular adjustment of serum total calcium (sCa) for albumin (Alb) yields a corrected value (cCa) that doesn’t detect abnormal ionized calcium (iCa) well in critical care patients (pts), possibly because it ignores the fraction of iCa complexed by small anions. To account for such anions, we derived a model that estimates iCa (Ci_A2, sCa) by adjusting iCa for Alb and the anion gap’s 3 components, Na, Cl, and CO2. It was likely better than sCa in detecting low iCa (↓iCa) on internal validation (Yap, JALM 2020).

**Methods:** From the MIMIC III v1.4 database, we paired chemistry panel iCa (mg/dL), Alb (g/dL), Na, Cl, and iCa values with gap panel iCa values (ref range: 1.21-1.32 mM) measured up to 20 min. apart. Limiting each pt. to the most closely-timed pair left 4105 pairs (median 10 min apart). We calculated cCa (sCa .012×Alb) and ICaEST (.091×sCa −.034×Alb −.0042×Na −.0073×Cl +.0047×sCO2) and compared their ROC curves (area/SE) for detecting ↓iCa (iCa<1.10; rate=33.1%), and high iCa (↑iCa) (sCa>1.12; rate=5.8%).

**Results:** ICaEST was better than cCa by ROC analysis for both ↓iCa (0.334±0.007 vs 0.752±0.008, p<10^-6) and ↑iCa (0.975±0.004 vs 0.963±0.006, p<.0006). The table compares the sensitivity and specificity (SENS/SPEC) and positive and negative predictive values (PPV/NPV) of ICaEST and iCa at similar cutoffs. ICaEST overestimated iCa by 0.04 mEq/L (1.17±0.002 vs 1.137±0.002, p<10^-6), a bias that was fairly consistent across the full prediction range.

**Conclusions:** The ICaEST model is superior to cCa in ranking critically ill pts for both ↓iCa and ↑iCa. It can help clinicians decide when to directly measure iCa. ICaEST overestimated iCa but applying a local correction of -0.04 would make its absolute predictions accurate, on average, in the ICU setting.
Hypercalcemia in a Patient with Visceral Leishmaniasis (VL) and Mineral Homeostasis and Acid-Base Disorders: Clinical PO1189

Lubin, Juarez1, Jacob M. Winograd, Jie Tang2,1 Lifespan Health System, Providence, RI; 2Brown University Warren Alpert Medical School, Providence, RI.

Introduction: Hypercalcemia is a relatively common clinical problem with a wide range of etiologies. We report an unusual case of hypercalcemia due to visceral leishmaniasis triggering immune reconstitution inflammatory syndrome in a patient with AIDS.

Case Description: A 45-year-old male with history of previously treated VL complicated by a relapse now on suppressive amphotericin presented with 2 weeks of poor appetite, weight loss, and malaise. Recent history was notable for AIDS restarted on Triumeq in the preceding 2 months with slow recovery of CD4 count to 18 but robust reduction in HIV viral load. He denied other infectious symptoms. Labs were notable for AKI, calcium of 13.1, and pancytopenia. Work up revealed low PTH, low calcidiol, elevated calcium levels and high-normal calcitriol levels with bone marrow biopsy revealing non-necrotizing granulomas. Remainder of infectious work up including mycobacterium, histoplasma, and fungal cultures all remained negative. Of note, CD4 count rebounded to 354 during his month-long stay. He was ultimately diagnosed with IRIS secondary to VL leading to granulomatous hypercalcemia. Initial therapy consisted of fluids which resolved AKI and improved calcium. However, he proved to be fluid dependent as attempts at weaning would result in rise in calcium and creatinine. Definitive therapy consisted of steroids which resolved his hypercalcemia allowing him to come off fluids. Appetite improved and fatigue resolved over course of his stay with stabilization of calcium levels and creatinine returning to baseline. He was continued on suppressive Amphotericin B for VL.

Discussion: Granuloma formation is a known effect of leishmania infection to combat the invading parasites. Presumably, such inflammation could lead to hypercalcemia via increased conversion of calcidol to calcitriol. To our knowledge, this is the first case of hypercalcemia caused by VL in humans. It was likely triggered by the reconstitution of his immune system given recent re-initiation of anti-retroviral therapy and rebound of CD4 cell count. Initial management consisted of fluids and bisphosphonates with definitive management consisting of steroids and amphotericin. We report this novel case of hypercalcemia in hopes of expanding the literature on the various potential manifestations of VL, particularly in the setting of IRIS and AIDS.

PO1190

Systemic Sarcoidosis Presenting with Hypercalcemia


Introduction: Sarcoidosis is an idiopathic autoimmune illness that typically presents with pulmonary involvement but can affect virtually any organ. This often makes it challenging to diagnose as its manifestations can be quite varied. We report an interesting case of systemic sarcoidosis presenting with hypercalcemia of unclear mechanism.

Case Description: A 53-year-old Caucasian male presented to the clinic with polyuria, forgetfulness and weight loss. Medical history included hypercalcemia with recurrent nephrolithiasis, diabetes and positive ANA (titer 1:160) without any prior history of constitutional, respiratory or joint symptoms. Serum calcium returned 13 mg/dL. The patient also had an AKI and an elevated ALP. Furtherworkup revealed a suppressed PTH, normal 25-OH and 1,25-OH vitamin D, but a borderline elevated PTHp (2.5 pmol/L [0-2.3 pmol/L]). This prompted a CT CAP with contrast to rule out malignancy that instead showed mediatinal lymphadenopathy, heterogeneous liver enhancement suggestive of cirrhosis and an enlarged, nodular spleen. Transbronchial lymph node biopsies were normal and an extensive infectious and malignancy workup remained negative. The patient was given fluids followed by zoledronate with resolution of hypercalcemia and AKI. A liver biopsy was ultimately pursued which showed non-caseating granulomas. The patient was prescribed steroids with improvement in symptoms and normalization of ALP.

Discussion: In patients with sarcoidosis, the development of hypercalcemia is thought to be mediated via aberrant activation of vitamin D leading to calcitriol excess. Our patient’s calcitriol level was normal and hypercalcemia may also occur in the absence of elevated levels. Possible described mechanisms include “inadequate normal” calcitriol concentration without elevation in systemic levels, elevated PTHp and direct action of pro-inflammatory cytokines causing osteolysis.

PO1191

Disseminated Histoplasmosis Presenting as Severe Hypercalcemia

Sushma Medikayala, Carla S. Mcwilliams, Shane A. Bobart, Silvia T. Bunting, Dianne T. Sandy, Mauro Braun, Surafel K. Gebreselasie. Cleveland Clinic Florida, Weston, FL.

Introduction: Hypercalcemia (HC) is a significant complication of Disseminated Histoplasmosis (DH). While there are case reports on DH causing HC in immunosuppressed patients including HIV and chemotherapy, there are very rare case reports on DH causing HC in Non-immunosuppressed hosts. The diagnosis of DH may be delayed due to other differential diagnoses such a Sarcoidosis leading to prolonged and worsening hypercalcemia and subsequent renal failure. We report a case of HC in a patient who presented with generalized skin ulcers and bilateral adrenal masses. The initial manifestation of DH with HC, painful skin ulcers, bilateral large lobulated adrenal masses, prompted an initial concern for sarcoidosis. After presenting to our institution 5 months later, a diagnosis of DH was made as the cause of his Hypercalcemia.

Case Description: A 58-year-old male with new onset generalized skin rash was diagnosed with HC, empirically treated with prednisone for sarcoidosis due to elevated 1,25 di hydroxy Vitamin D, 5 months ago at an outside hospital. After starting prednisone, his skin lesions progressed to disseminated painful ulcers and was referred to our institution after developing AKI with a serum creatinine of 4.6mg/dl (Cr 1.6mg/dl, 5 months ago) calcium 14mg/dl, PTH 2pg/ml CT abdomen revealed large lobulated bilateral adrenal masses. Bone marrow biopsy revealed non-necrotizing granulomas with yeast form fungal organisms on GMS stain. A Shave skin biopsy of an abdominal ulcer revealed Fungal yeast forms consistent with histoplasmosis, associated with ulcers on GMS stain. Urine Histoplasma antigen positive. Adrenal mass biopsy revealed necrotic material and fibroconnective tissue. DH was initially treated with IV liposomal amphotericin and transitioned to oral Itraconazole. At the time of discharge, calcium was 9.8 mg/dl and serum creatinine was 2.9mg/dl.

Discussion: Hypercalcemia, in the setting of elevated 1,25 di hydroxy Vitamin D levels, prompts concern for granulomatous disease. Sarcoidosis is a common etiology, however, other causes must be entertained. The cluster of findings of adrenal non-caseating granulomas coupled with diffuse skin ulcers with hypercalcemia should prompt the provider to consider infectious etiologies such as disseminated histoplasmosis as early diagnosis and prompt treatment can result in improved outcomes.
PO1193

Resistant Hypophosphatemia with Vitamin D Deficiency
Yasmin N. Mahmoud,1 Akbar H. Hamid,2 Ammar N. Mohamed,2 Mary C. Mallappallil,1,2 Man S. Oh,1,2 Moro O. Salifu,1,2 SUNY Downstate Health Sciences University Department of Medicine, New York, NY; 3Kings County Hospital Center, Brooklyn, NY.

Introduction: The renal regulation of phosphate homeostasis is mediated mainly by reabsorption of P by NaPi-IIc in the proximal tubule, whereas intestinal absorption is mediated by NaPi-IIb. Normally, about 2/3 of dietary intake (1500 mg/day) is absorbed, but when given by mouth as Na or K phosphate, absorption is nearly 100% in a normal person. We report here a patient with severe hypophosphatemia due to phosphate malabsorption caused by prior gastric bypass surgery along with vitamin D deficiency.

Case Description: A 34 year old African American female with past medical history of benign carcinoid syndrome, pernicious anemia, Hashimoto thyroiditis, and gastric sleeve surgery causing rapid emptying of the gastric content, simulating the dumping syndrome, resulting in diarrhea by unabsorbed Na and K phosphate. Further impairment in intestinal P absorption may have been caused by vitamin D deficiency due to the inadequate dosing (800 units daily) and the inappropriate vitamin D type (Vitamin D2 instead of D3).

PO1194

Severe Hypophosphatemia Induced by Oncogenic Osteomalacia
Abdullah Jalal, Ryan P. Brown. Overlook Medical Center, Summit, NJ.

Introduction: Oncogenic Osteomalacia (Oncom) is an uncommon paraneoplastic syndrome characterized by FGF-23 overexpression from benign mesenchymal tumors causing severe hypophosphatemia. Very few cases of Onc with concomitant paraneoplastic syndromes have been described. Herein we present a rare case of carbofuran-associated hypophosphatemia in the setting of SiADH-induced chronic hyponatremia unmasking an even rarer secondary paraneoplastic syndrome; oncogenic osteomalacia.

Case Description: A 52 year old male with past medical history of chronic hyponatremia on salt tablets secondary to recently diagnosed metastatic small cell lung cancer was admitted for initiation of chemotherapy with carbofuran/etopside. Two days after completing cycle 1 the patient developed acute hypophosphatemia; serum Na decreased from 141 to 129 mEq/L. Serum electrolytes were (mEq/L): K 3.9, Cl 94, HCO3 28, BUN 30, Cr 0.47. Coriisol (17.8 ug/dl) and TSH (2.28 uIU/ml) were within normal limits. Urine studies noted (mEq/L): Na 75, Cl 69, K 43.5, elevated osmolality 860 mOsm/kg. Etiology of acute hyponatremia was attributed to platinum chemotherapy in the setting of SCC-associated SiADH and patient was treated with tolvaptan after several days of non-response to fluid restriction and urea. Patient’s hypophosphatemia subsequently corrected but was incidentally noted to have severe hypophosphatemia (<1 mEq/L) refractory to IV and PO phosphate repletion. ALP was elevated 279 U/L, corrected Ca 10 mEq/L, low 25(OH) vitamin D 23.8 ng/ml, normal PTH 45.6 ng/ml and PTHrP <0.4 pmol/L. Urinary fractional excretion of phosphorus was increased at 24%. An FGF-23 level obtained 12 days after completing cycle 1 of carbofuran-etopside was considerably elevated at 219 pg/ml. Thus, the patient was diagnosed with oncogenic osteomalacia.

Discussion: This case highlights a unique and diagnostically challenging patient presentation of severe hypophosphatemia in the setting of dual paraneoplastic syndromes. Onc should be considered in the differential for severe refractory hypophosphatemia. This occurs via FGF-23 mediated downregulation of PCT Na-Pi transporters and 1a-hydroxylase causing renal phosphate wasting and reduced 1,25-hydroxyvitamin D levels. Over time chronic hypophosphatemia impairs bone mineralization causing osteomalacia. Measurement of the fractional excretion of phosphorus is critical and FGF-23 levels should be obtained to confirm diagnosis.

PO1195

Phenotypes of Patients with Abnormal Phosphate on Admission by Consensus Clustering and Associated Mortality Risks
Carissa Y. Dumanescu,1 Charat Thongprayoon,2 Andrea G. Kattah,1 Michael A. Mao,3 Stephen B. Erickson,4 John J. Dillon,5 Vestia D. Garovic,6 Wiwat Wisitcoutporasert.1,4 Mayo Clinic Minnesota, Rochester, MN; 2Mayo Clinic; 3ISDH; 4SUNY Downstate Medical Center; 5Yale University; 6Mayo Clinic’s Campus in Florida, Jacksonville, FL.

Background: Hospitalized patients with abnormal phosphate are heterogeneous and clustering approaches may identify specific homogeneous groups. This study aimed to cluster patients with abnormal phosphate on admission using unsupervised machine learning approach and to evaluate the mortality risk among these distinct clusters.

Methods: Consensus cluster analysis was performed on hospitalized adult patients with abnormal phosphate on admission, based on clinical and laboratory data. We determined each cluster’s key features using the standardized mean difference. We assessed the association of the clusters with hospital and one-year mortality.

Results: Cluster 2 patients with hypophosphatemia had older age, higher comorbidity burden, hypertension, diabetes, coronary artery disease, lower eGFR, and more acute kidney injury (AKI) (Fig 1a). Cluster 2 patients with hyperphosphatemia had older age, more admission for kidney disease, hypertension, end-stage kidney disease, AKI, and higher admission K, Mg 2+, or PO levels (Fig 1b). Both cohorts in cluster 2 had higher one-year mortality while hyperphosphatemic cluster 2 patients had higher hospital mortality (Fig 2).

Conclusions: The cluster analysis identified clinically distinct phenotypes with differing mortality risk in hospitalized patients with abnormal phosphate on admission. The age, comorbidities, and kidney function were key features.
Annatto Leaf Tea Intoxication: An Unusual Cause of Green Urine

Introduction: The roots and leaves of the annatto (“urucu”) tree (*Bixa Orellana*) are used by the lay population in the treatment of many diseases. We describe a case of AKI with severe fluid and electrolyte (F+E) imbalance due to annatto leaf tea use. In our patient, AKI was aggravated by the diarrhea and greenish urine (Figure). He received fluid resuscitation and underwent two sessions of hemodialysis. He reported having ingested annatto leaf tea to treat his diarrhea. Blood and urine cultures were negative and there was no history of drug use. He was discharged from the hospital without needing hemodialysis. He was diagnosed with severe fluid and electrolyte (F+E) imbalance due to annatto leaf tea use. In our patient, AKI was aggravated by the diarrhea and the diuretic effect of the tea.

Discussion: The diuretic effect of annatto leaf extracts has been shown in experimental models. To our knowledge, this is the first report of severe AKI and F+E imbalance due to annatto leaf tea use. In our patient, AKI was aggravated by the diarrhea and greenish urine (Figure). He received fluid resuscitation and underwent two sessions of hemodialysis. He reported having ingested annatto leaf tea to treat his diarrhea. Blood and urine cultures were negative and there was no history of drug use. He was discharged from the hospital without needing hemodialysis. He was diagnosed with severe fluid and electrolyte (F+E) imbalance due to annatto leaf tea use. In our patient, AKI was aggravated by the diarrhea and the diuretic effect of the tea.

Table 1.

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO1198

Development of AL01211, a Novel Glucosylceramidase Synthase Inhibitor, to Treat Autosomal Dominant Polycystic Kidney Disease (ADPKD)
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Background: ADPKD is a common genetic disease affecting ~1:1000 individuals and is characterized by progressive renal cysts growth, kidney enlargement and renal dysfunction. Glycosphingolipids (GSL) are elevated in the kidneys of ADPKD animal models and ADPKD patients where they promote renal epithelial cell growth and kidney inflammation. Glucosylceramide synthase inhibitors (GCSIs) reduce GSL production, slow cyst growth, and preserve kidney function in multiple animal models. Clinical development of other GCSIs have shown that this enzyme can be safely targeted therapeutically. We are developing AL01211, a potent and selective GCSI with excellent drug-like properties, for the treatment of ADPKD.

Methods: The IC50 of AL01211 against GCS was determined in cells and cell-free activity assays. PK, PD, tissue distribution and clearance studies were conducted in mice, rats and dogs. AL01211’s pharmacological profile was characterized in vitro including off-target selectivity panels, plasma protein binding, transporter assays, cyp inhibition and induction, and other assays. Disease model efficacy studies were conducted in several murine models including pkd1 eKO and jck models.

Results: AL01211 binds the active site of GCS and has an IC50 toward GCS of ~7 nM with limited off-target activity. PK studies support once daily, oral administration. AL01211 has low renal clearance in rats. AL01211 readily distributes to peripheral tissues (such as kidney) but does not cross blood-brain-barrier. Thus, it efficiently reduces GSL production in mouse, rat and dog kidney (reduced by >85% of control levels) with minimal effects in brain GSL. Importantly, AL01211 reduces cyst growth and kidney weight and preserves kidney functions in murine models.

Conclusions: Relative to other GCSI’s in development, AL01211 is more potent with single digit nanomolar potency, has greater reduction of GSL (>85%), is not subject to kidney clearance, and does not enter the brain. Phase I clinical trials, consisting of Phase IA (single ascending dose study in healthy volunteers), Phase IB (14-day multiple dose study in healthy volunteers) and Phase IC (28-day biomarker study in ADPKD patients) are underway.

Funding: Commercial Support - AceLink Therapeutics

PO1199

Keynote: KidneyNetwork Uses Kidney-Derived Gene Expression Data to Predict and Prioritize Novel Genes Involved in Kidney Disease
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Background: Genetic testing in patients with suspected hereditary kidney disease does not always reveal the genetic cause for the patient’s disorder. Pathogenic variants can reside in genes that are not yet known to be involved in kidney disease. To help identify candidate genes for kidney disease we have developed KidneyNetwork, in which tissue-specific expression is utilized to predict kidney-specific gene functions.

Methods: KidneyNetwork is a co-expression network built upon 878 kidney RNA-sequencing samples and a multi-tissue dataset of 31,499 samples. It uses expression patterns to predict which genes have kidney-related functions and which phenotypes might result from variants in these genes. As proof of principle, we applied KidneyNetwork to prioritize rare variants in exome-sequencing data from 13 kidney disease patients.

Results: We assessed the prediction performance of KidneyNetwork by comparing it to GeneNetwork, our previously developed multi-tissue co-expression network. In KidneyNetwork, we observe significantly improved prediction accuracy of kidney-related HPO-terms and an increase in the total number of significantly predicted kidney-related HPO-terms (figure 1). Applying KidneyNetwork to exome-sequencing data allowed us to identify ALG6 as candidate gene for kidney and liver cysts.

Conclusions: KidneyNetwork is a kidney-specific co-expression network that predicts which genes have kidney-specific functions that can result in kidney disease. Gene-phenotype associations of genes unknown for kidney-related phenotypes can be predicted. We show its added value by applying it to kidney disease patients without a molecular diagnosis. KidneyNetwork can be applied to clinically unsolved cases, but it can also be used by researchers to better understand kidney physiology and pathophysiology.

PO1201

Modeling Gene-Targeted Strategies for Therapeutic Correction of PKD1 Loss-of-Function Mice
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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease and is characterized by progressive growth of fluid-filled cysts in the kidneys. Growth factor binding to receptor tyrosine kinases (RTKs) are known to stimulate cell proliferation and cyst growth in PKD. In the current study we tested the effect of Nintedanib, an RTK inhibitor and FDA approved drug for non-small cell lung carcinoma and idiopathic lung fibrosis, in mouse models of ADPKD. Nintedanib is a triple RTK inhibitor which targets vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (FGFR).

Methods: The effect of Nintedanib on renal cyst growth and fibrosis was tested in two orthologous models of ADPKD, the Pkd1+/Pkd1+/ mouse, and Pkd1f/f mouse. Nintedanib treatment (20 mg/Kg on alternate days by intraperitoneal injections) was from postnatal day P10 to P18 in Pkd1+/Pkd1+/ mice and in for 8 weeks starting at the age of 3 months in Pkd1f/f mice. In vitro studies were performed using primary culture human ADPKD renal cyst epithelial cells and renal myofibroblasts.

Results: Nintedanib treatment significantly reduced kidney-to-body weight ratio, cyst renal index, cystic epithelial cell proliferation and blood urea nitrogen levels compared to vehicle treated Pkd1+/Pkd1+ and Pkd1f/f mice. Western blot data indicates reduction in the phosphorylation of ERK1/2, AKT, STAT3 and mTOR activation and pro-fibrotic factors, including Yes associated protein (YAP), c-Myc and Cyclin D1 protein levels. Moreover, nintedanib treatment significantly reduced renal fibrosis in Pkd1f/f mice, however, fibrosis in Pkd1+/Pkd1+ mice remained unaffected. In vitro data suggests that nintedanib significantly reduced proliferation and cyst size of human ADPKD cystic epithelial cells as well as cell viability and migration of human ADPKD renal myofibroblasts.

Conclusions: The results suggest that Nintedanib is effective in reducing cyst growth and may be repurposed to treat ADPKD.

Funding: NIDDK Support
collecting tubular origin and survived until P12-15. While Srebp reached Pkd1 therapeutic levels in the mild Srebp1c/-/-, the additional Tg copies suggest the presence of regulatory region within Pkd1 gene-body. Renal cysts in Srebp1c/-/+-Srebp1c/-/+ and Srebp1c/-/+ detected by RNAscope and IF, arise likely from insufficient and chimeric Pkd1 re-expression. These analyses also shed light on Pkd1 spatio-temporal expression patterns with highest expression in collecting tubules during renal maturation that shifts to distal tubules following maturation.

Conclusions: Pkd1 is regulated by elements both upstream for spatio-temporal pattern and intragenic sequences for expression levels. The renal-specific Srebp minimal regulatory region is sufficient for therapeutic correction in one copy Tg. Our study demonstrates that Pcl re-expression can substantially delay cystogenesis and markedly extend lifespan.

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PO1202
Wheat-Gluten Diet Attenuates Ccl2-Mediated Immune Response and Slows Polycystic Kidney Disease

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Background: Disease severity of autosomal-dominant polycystic kidney disease (ADPKD) is highly variable, even among families with the same gene mutation. A high protein diet is a well-recognized ADPKD progression-accelerating factor. Dietary protein composition is important, as pre-clinical studies have shown a soy protein-based diet slows kidney cyst formation in rodent PKD models. Recruitment of macrophages in the kidney are known to promote cystogenesis in PKD. We hypothesize that type of protein in the diet may serve as a potential environmental stimulant to immune response and cyst growth.

Methods: Using tamoxifen-inducible Pkd1-global knockout mice, we fed the mice with either a high casein-protein (animal-based protein: 60%), a low casein-protein (6%) or a regular wheat-gluten (plant-based protein: 60%) for a total of 1 week or 6 weeks. Some mice fed a high casein protein diet were treated with liposomal clodronate or saline for a total of 5 weeks. Mice were euthanized and kidney cyst area, number of macrophages and chemokine/cytokine levels were measured.

Results: Pkd1-knockout mice fed a high casein diet increased the number of kidney macrophages, expression of macrophage-recruiting chemokine Ccl2 (but not chemokines Csf1 or Ccl5), pro-inflammatory cytokine (Ilf6, Tnf-a) and accelerated cyst growth compared to counterparts fed an iso-caloric high wheat-gluten (WG) diet or a low casein diet. Cyst growth was significantly lower in very early stages during dietary casein load (1 week after diet modification), cyst expansion precedes macrophage recruitment in the kidney, indicating that diet per se triggers early cyst growth rather than as a consequence of macrophage recruitment and inflammation. High casein diet fed Pkd1-knockout mice treated with liposomal clodronate, resulted in decreased number of macrophages, cytokine, and fewer cysts.

Conclusions: Wheat-gluten diet fed Pkd1-knockout mice resulted in decreased the number of macrophages, suppressed levels of kidney Ccl2, but not Csf1 or Ccl5, and slowed cyst growth compared to counterparts fed an iso-caloric casein based diet. Dietary protein modification may suppress immune response and cyst growth in PKD.

Funding: NIDDK Support

PO1203
High Prevalence of Kidney Cysts in Hereditary Hypophosphatemic Rickets with Hypercalciuria

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Background: Hereditary Hypophosphatemic Rickets with Hypercalciuria (HHRH) is a rare monogenic disorder caused by SLC34A3 mutations. Patients present with infantile rickets with hypercalciuria and secondary hyperparathyroidism, which can evolve into hereditary hypophosphatemic rickets with hypercalciuria (HRH). HHRH is caused by biallelic and HRH by monoallelic mutations. Despite the large differences in disease expression, there is no clear consensus on the best treatment for HHRH. We characterized cystic kidney disease (CKD) in HHRH to help determine if a similar cystic kidney disease pattern also exists in HHRH.

Methods: Medical records from Mayo Clinic and Rare Kidney Stone Consortium (RKSC) were queried for all patients with genetically confirmed HHRH diagnosis. Underline represents presenting author.

Results: Among 12 patients with SLC34A3 pathogenic variants (7 monoallelic, 5 biallelic), 42% (5/12) were males. Median age at clinical presentation was 17 yrs (range 8-46) and at genetic confirmation 42 yrs (range 9-66). None had a family history of kidney cysts. Median age at clinical presentation was 17 yrs (range 8-46) and at genetic confirmation 42 yrs (range 9-66). At least 2 cysts ≥ 5 mm in size were found in 100% of children. At least 2 cysts ≥ 5 mm in size were found in 100% of children. 5 biallelic), 42% (5/12) were males. Median age at clinical presentation was 17 yrs (range 8-46) and at genetic confirmation 42 yrs (range 9-66). None had a family history of kidney cysts. Median age at clinical presentation was 17 yrs (range 8-46) and at genetic confirmation 42 yrs (range 9-66). At least 2 cysts ≥ 5 mm in size were found in 100% of children. At least 2 cysts ≥ 5 mm in size were found in 100% of children. Table 1.

Conclusions: Our data highlight tryptophan metabolism as a novel dysregulated pathway in vivo in mouse and human ADPKD and suggest that tryptophan metabolites are biomarkers of disease progression. Further, inhibition of the pathway presents a new therapeutic strategy for PKD.

Funding: NIDDK Support, Private Foundation Support

PO1204
Dysregulated Tryptophan Metabolism Promotes Polycystic Kidney Disease Progression

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Background: Metabolic reprogramming is a feature and modifier of autosomal dominant polycystic kidney disease (ADPKD) progression. Moreover, immune cells regulate cyst growth. In cancer, a disease with parallels to PKD, the metabolic landscape created by tumors significantly impacts immune cell function and tumor growth. Yet, this link is unexplored in PKD. Here, we study tryptophan metabolism, a known immunosuppressive pathway, in cyst growth.

Methods: Metabolites were profiled in ADPKD patient plasma and kidneys of an orthologous ADPKD model (C57Bl/6 Pkd1(-/-)). We also crossed the ADPKD model to Ido1-/- mice, the enzyme metabolizing tryptophan to kynurenines, and inhibited IDO1 using the tryptophan analog 1-MT (400mg/kg, twice daily, orally). From these mice, kidney immune cells were profiled via flow cytometry.

Results: Tryptophan metabolites were significantly increased in Pkd1(-/-) mice at 3-, 6-, and 9-months compared to age- and gender-matched controls with disease progression. Plasma levels of kynurenines significantly associated with HtTKV at baseline, and positively correlated with annual percent change of HtTKV in adult ADPKD patients. IDO1 levels were significantly increased in kidneys of Pkd1 mice and patient cells lines. At 6-months age, Pkd1-/-; Ido1-/- mice had significantly milder PKD compared to Pkd1(-/-) mice as measured by % KW/BW and cystic/lobular index. Similarly, treatment of 1-month-old Pkd1(-/-) mice with 1-MT for 3 weeks slowed cyst growth; overall providing functional evidence of the pathway’s relevance to PKD. Kidney immune profiling of Pkd1(-/-); Ido1-/- and 1-MT-treated mice revealed a significant reduction of resident macrophages, regulatory T cells, and immune checkpoint protein expression (PD-1/CD4, 1), while the percentage of CD8+ T cells/total T cells increased.

Conclusions: Our data highlight tryptophan metabolism as a novel dysregulated pathway in vivo in mouse and human ADPKD and suggest that tryptophan metabolites are biomarkers of disease progression. Further, inhibition of the pathway presents a new treatment approach. IDO1 inhibitors are FDA approved for various cancers. Our data suggest a link between metabolic reprogramming, immune cell function, and disease progression, as IDO1 loss/inhibition impacted immune cell populations/pathways shown to regulate cyst growth.

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PO1205

Creatine Kinase Elevation in Patients with Autosomal Dominant Polycystic Kidney Disease on Tolvaptan Treatment
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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease worldwide. Studies such as the TEMPO 3:4 and 4:4 have demonstrated tolvaptan’s (vasopressin V2 receptor antagonist) effectiveness in slowing the progression of this disease. The best described adverse effect seen with this treatment is drug-induced liver injury, however, creatine kinase (CK) elevation has also been described anecdotally in a couple of case reports.

Methods: This is a prospective observational study of adult patients with rapidly progressive ADPKD on tolvaptan treatment under follow-up at Hospital Clinic de Barcelona from October 2018 to March 2021. Quantitative variables are described as mean and standard deviation, while qualitative ones are reported as absolute and relative frequencies.

Results: A total of 37 patients started treatment with tolvaptan during this period. In 34 of them, serum CK levels were measured as part of the monthly biochemical follow-up. A total of 29.11% (10 of 34) of the patients elevate this parameter with a mean of 3519 ± 5016.36 U/L. In one of them due to concomitant drug-induced liver injury and in the other two due to persistent CK elevation despite dose reduction or temporary treatment interruption. CK elevation was usually less related to exercise, although one patient performed a weekly intensity cycling exercise with increased myalgia afterward) and was not significantly correlated with LDH levels, liver enzymes, calcium, potassium, urinary or plasma osmolality.

Conclusions: By performing a general screening, we found that CK elevation is more frequent than previously described in the literature, reaching significantly increased levels or producing symptomatology requiring definitive treatment interruption. Based on these results, although the studied sample is small, we suggest adding this parameter as a part of tolvaptan treatment’s follow-up, at the beginning of treatment and when increasing its dosage as it may promptly detect undesirable adverse effects and gain a better understanding of this phenomenon.

PO1206

Protein Kinase A Downregulation Delays the Development and Progression of Polycystic Kidney Disease
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Background: Upregulation of cAMP-dependent as well as -independent PKA signaling is thought to promote cystogenesis in polycystic kidney disease (PKD). We have shown that the PKA-I regulatory subunit RIα is increased in kidneys of orthologous mouse models and that kidney specific knockout of RIαR1 or inhibition compared to EPAC or PKA-II inhibition on ex vivo mIMCD3 cystogenesis and ex vivo cystogenesis. Genetic and of TricB in adult-onset kidney-specific Pkd2-inactivated mice ameliorates cystogenesis. Double deletion of TricB and Pkd2 in mice reveal synergistic genetic interactions. However, the ciliary proteins in this process are not well understood.

Methods: Upregulation of cAMP-dependent and PKA-I activation promoted, and inhibition prevented, cystogenesis using Pkd1 CK elevation despite dose reduction or temporary treatment interruption. However, treatment had to be interrupted in the remaining three patients (mean 3519 ± 5016.36 U/L). In one of them due to concomitant drug-induced liver injury and in the other two due to persistent CK elevation despite dose reduction or temporary treatment interruption. CK elevation was usually less related to exercise, although one patient performed a weekly intensity cycling exercise with increased myalgia afterward and was not significantly correlated with LDH levels, liver enzymes, calcium, potassium, urinary or plasma osmolality. Based on these results, although the studied sample is small, we suggest adding this parameter as a part of tolvaptan treatment’s follow-up, at the beginning of treatment and when increasing its dosage as it may promptly detect undesirable adverse effects and gain a better understanding of this phenomenon.

PO1207

Protein 4.1O Links Polycystin 1 to the Actin Cytoskeleton and Modulates Hippo Signaling
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Background: The majority of ADPKD patients have a PKD1 gene mutation. PKD1 codes for Polycystin-1 (PC-1). Cyst formation is caused by altered renal tubular cell proliferation. Protein 4.1 family members are actin adaptors, which link plasma membrane receptors to the actin cytoskeleton. Polypeptide of the FRMD3 family (FRMD3) is a candidate gene for diabetic nephropathy. Furthermore, protein 4.1O has properties of a tumor suppressor. This study investigates the molecular and cellular properties of protein 4.1O as a potential ADPKD modifier and therapeutic target.

Methods: PC-1 full-length and truncation mutants were transiently expressed. PC-1 interaction with protein 4.1O and its truncation mutants were investigated. Truncation mutants cover the N- and C-terminal domains of protein 4.1O (Band 4.1, FERM, actin-binding domain and coiled coil domain). Communoprecipitations of protein 4.1O with PC-1 in IMCD cell lysates were performed. Pulldown experiments with bacterial recombinant protein 4.1O and F-actin were performed. The modulation of the PC-1 signaling properties by protein 4.1O were investigated in luciferase assays for c-myc and TEAD. FRMD3 core promoter regions were cloned into luciferase reporter.

Results: Communoprecipitations show an interaction of protein 4.1O full-length with the C-terminus of PC-1 interacts with four isoforms of protein 4.1O (201, 202, 204, 207). The truncation mapping and isoform alignment identifies a potential leucine zipper domain in protein 4.1O as the C-terminal binding domain to PC-1. The N-terminal domain of protein 4.1O is also sufficient to mediate PC-1 interaction. Protein 4.1O C-terminus binds to F-actin and links the PC-1 C-terminus to the cytoskeleton. Protein 4.1O silences the PC-1 mediated transactivation of c-myc and hippo signaling (TEAD). Furthermore, F-actin destabilization influences the PC-1 induced hippo signaling. PC-1 activates the protein 4.1O pro-angiogenic activity.

Conclusions: Both, the FERM domain and leucine zipper containing coiled coil domain of protein 4.1O interact with the PC-1 C-terminus. The interaction of protein 4.1O links PC-1 to the actin cytoskeleton. The protein 4.1O interaction inhibits the PC-1 mediated activation of c-myc and hippo signaling. Furthermore, protein 4.1O provides a F-actin based sensitivity to the PC-1 mediated hippo signaling. In summary, protein 4.1O shows features of an anti-cystogenic protein.

PO1208

Polycystin 2 Mediates Endoplasmic Reticulum K+–Ca2+ Exchange to Protect Against Polycystic Kidney Disease
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Background: Prevailing view is that PKD is a ciliopathy. Yet, PC2 is most abundantly expressed in ER. Early studies showed that PC2 is involved in agonist-induced ER Ca2+ release. Decrease in ER Ca2+ release in PC2-deficient cells is believed to contribute to AMP overproduction and cystogenesis. Recent patch-clamp experiments reveal that PC2 channel consists of 40X more selective to K+ than Ca2+, raising the question regarding how PC2 mediates ER Ca2+ release and role of ER-localized PC2 in PKD pathogenesis. To avoid potential polarization impeding ion fluxes, Ca2+ release from ER lumen to cytosol requires coupled counter cation exchange and/or parallel anion movement.

Methods: ER Ca2+ release is assayed by far2-fluorimetry stimulated by ATP. PC2-deficient morphant zebrafish and doxycycline-inducible adult-onset PC2-deficient mice are used for in vivo PKD model.

Results: (Table).

Conclusions: Our results provide compelling support for the notion that ER resident PC2 plays an important role in anti-cystogenesis of PKD. The mechanism of action is likely through mediating cystosol-to-ER lumen K+ flux to facilitate Ca2+ release via IP3R.

Funding: NIDDK Support

PO1209

Interactions Between TUL13 and ARL13B in Lysinipid Protein Translocation to Cilia and Regulation of Renal Cystogenesis
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Background: Signaling outputs from cilia maintain renal tubular homeostasis preventing cystogenesis; however, the ciliary proteins in this process are not well understood. The tubby family protein–TUL13 coordinates with the intracellular transport machinery to regulate transport of proteins required for ciliary function and signaling. TUL13 and ARL13B regulate transport of PKD1 and PKD2 to cilia. However, the underlying mechanisms are poorly understood.

Results: We have previously characterized the interaction between TUL13 and ARL13B and have shown that TUL13 promotes transport of PKD1 and PKD2 to cilia. Furthermore, we have shown that ARL13B interacts with TUL13 and that this interaction is required for PKD1 and PKD2 transport to cilia. In this study, we have extended these findings by characterizing the interaction between TUL13 and PKD1 and PKD2 and by characterizing the interaction between TUL13 and RAB7 in cilia.
Results: The transmembrane cargoes have short motifs that are necessary and sufficient for TULP3-mediated cystogenesis. We now show that TULP3 is required for transport of the atypical GTPase ARL13B into cilia, and for cilary enrichment of ARL13B-dependent farnesylated and myristoylated proteins. ARL13B transport requires TULP3 binding to IFT-A core but not to phosphoinositides, unlike transmembrane cargo transport that requires binding to both by TULP3. A conserved lysine in TULP3 mediates binding to TULP3 and directs trafficking to cilia. Tulp3 trafficked lipidated ARL13B and directed transport that requires binding to both by TULP3. A conserved lysine in TULP3 mediates binding to TULP3 and directs trafficking to cilia. Tulp3 trafficked lipidated proteins are depleted with distinctive temporal kinetics from kidney epithelial cilia during Tulp3 deletion-induced cystogenesis.

Conclusions: We conclude that TULP3 transports transmembrane proteins and ARL13B into cilia by capture of short sequences through a shared tubby domain site. Drugging this interaction domain could provide therapeutics in polycystic kidney disease. The depletion of lipidated cargoes with distinct kinetics from kidney epithelial cilia following Tulp3 deletion suggests their differential roles in cilia in regulating renal cystogenesis.

Funding: Other NIH Support - NIGMS, Private Foundation Support

Conclusions: Our experiments establish the direct link between TRPV4 function and directly reprogrammed mammalian cells (iRECs) we investigated transcriptional modules and identified novel direct and indirect targets of the transcription factor HNF1B, which are linked to signaling pathways associated with renal morphogenesis, cilia and organic anion transport.

Conclusions: In conclusion, the combined use of directly reprogrammed mammalian cells and Xenopus renal organoid experiments allow us to gain a unique perspective into evolutionary conserved mechanisms of renal development and HNF1B associated kidney disease.

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Autophagy Inhibition Ameliorates Polycystic Kidney Disease

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Background: We found that there is a decrease in autophagy proteins in Pkd1<sup>RC/Rc</sup> mouse kidneys. Our study aimed to determine the mechanistic role of suppressed autophagy in causing cyst growth using pharmacological and genetic autophagy inhibition.

Methods: Male Pkd1<sup>RC/Rc</sup> (RC) mice were treated with 2-Deoxycholeosine (2DG) or Chloroquine (CHLQ) from 50-120d of age. Kidney specific Pkd1<sup>-/−</sup> Agt7 double knockout mice were generated by Kepl3-Cre-lox recombination. Relative densitometry units (RDU) were determined on immunoblot. Autophagic flux was measured by the change in LC3-II (autophagosomes) +/− Bafilomycin (Baf).

Results: Autophagic flux was present in wild type (WT) and 120 d old RC but suppressed in 150 d old RC kidneys. LC3-II (RDU) +/− Baf was 0.1 vs 0.7 in WT (p<0.01), 0.6 vs 1.0 in 120 d old (p<0.05) and 2.4 vs 2.1 (NS) in 150 d old RC. 2DG resulted in a decrease in ATG12-5 complex and suppressed autophagic flux in RC kidneys. LC3-II (RDU) +/− Baf was 0.5 vs 0.8 in VEH (p<0.05), 0.7 vs 0.7 in 2DG (NS). 2DG significantly reduced cyst growth and improved kidney function. Cystic index (%), count +/− 2DG: 7.7 vs 3.7 (p<0.01), 211 vs 161 (p<0.05). BUN (mg/dl) +/− 2DG: 3.5 vs 27 (p<0.01). Next, RC mice were treated with CHLQ, a specific autophagy inhibitor. CHLQ resulted in suppressed autophagic flux, less PKD and improved kidney function in RC mice. LC3-II (RDU) +/− Baf was 1.2 vs 1.2 (NS) in CHLQ treated kidneys. Cyst index (%), count +/− 2DG: 7.7 vs 3.7 (p<0.01), 211 vs 161 (p<0.05). BUN (mg/dl) +/− 2DG: 3.5 vs 27 (p<0.01). Next, autophagy was inhibited in PKD kidneys by generating double Pkd1<sup>-/−</sup> Agt7 KO mice. The 2 kidney BW (%WV) was improved in Pkd1<sup>-/−</sup> Agt7 KO vs single Pkd1<sup>-/−</sup> KO mice (32 vs 39 p<0.05). Agt7<sup>-/−</sup> kidneys had a massive increase in p62 indicating a build-up of autophagic cargo. p62 in WT vs Agt7<sup>-/−</sup> KO (RDU) 0.1 vs 1.8 p<0.001. Interestingly Agt7<sup>-/−</sup> KO kidneys were filled with tertiary lymphoid organs (TLO): large condensed infiltrates of T and B cells. pAMPK<sup>α2</sup> was increased in Agt7<sup>-/−</sup> KO kidneys. AMPK activation is known to reduce PKD.

Conclusions: Both 2DG and CHLQ suppressed autophagic flux in RC mice and resulted in less PKD and improved kidney function. Double Pkd1<sup>-/−</sup> Agt7 KO mice had significantly lower kidney weight than single Pkd1<sup>-/−</sup> KO mice. Both pharmacological and genetic autophagy inhibition resulted in less PKD.

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ARL13B Negatively Regulates Kidney Cysts from Within Cilia

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Background: Polycystic kidney disease (PKD) is intricately linked to the primary cilium. Polycystin proteins localize to cilia and loss of cilia leads to renal cysts. PKD mouse models often disrupt ciliary genes, removing both ciliary and cellular pools of these gene products; however, the molecular pathway(s) that drive cyst formation is unknown. ARL13B is a regulatory GTPase highly enriched in cilia due to a VxPx localization motif near its C terminus. ARL13B is also localized to extraciliary sites within the cell. We engineered mice in which we mutated the valine to alanine within ARL13B’s VxPx cilia-localization motif so the mice express cilia-excluded ARL13BV358A with the tethered agonist mechanism.

Methods: We used mouse inner medullary collecting duct (mIMCD3) cells with the T1G (TIG cells) or T2c (T2J cells) gene disrupted by CRISPR/CAS9 methodology. EVs were isolated from the cell culture media by size-exclusion column chromatography followed by detailed physical and chemical characterization. Physical characterization of EVs was achieved by tunable resistive pulse sensing and dynamic light scattering, electron microscopy, and western blot analyses.

Results: Physical characterization of EVs revealing similar average sizes and zeta potentials (at pH 7.4) for EVs from mIMCD3 (123.5 ± 5.7 nm and −16.3 ± 2.1 mV), TIG cells (131.5 ± 8.3 nm and −19.8 ± 2.7 mV), and T2J cells (127.3 ± 4.9 nm and −20.2 ± 2.1 mV). EVs derived from parental mIMCD3 cells and both mutated cell lines were heterogeneous (>90% of EVs < 150 nm) in nature. Immunoblotting detected chicken Hemoglobin signaling protein Arl13b; intercellular proteins TSG101 and Alix; and transmembrane proteins CD63, CD9, and CD81. Compared to T2J deletion, T1G deletion cells had reduced EV production and release rates. EVs from T1G mutant cells altered mTORC1, autophagy, and β-catenin pathways differently than EVs from T2c-mutated cells. Quantitative PCR analysis revealed the down regulation of miR-212a-3p and miR-99a-5p in EVs from T2c-mutated cells compared to EVs from T1G-mutant cells.

Conclusions: EV-derived miR-212-3p and miR-99a-5p axes may represent therapeutic targets or biomarkers for TSC disease.

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ADPKD Mutations in the Stalk/Tethered Agonist of Polycystin-1 CTF Affect Signaling and GPS Cleavage

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Background: Like Adhesive G protein-coupled receptors (aGPCRs), the N-terminal ectodomain of polycystin-1 (PC1) contains a membrane-proximal GAIN domain that catalyzes self-cleavage at its embedded GPCR proteolysis site (GPS), dividing these proteins into extracellular N-terminal (NTF) and membrane-embedded C-terminal (CTF) fragments. PC1 GPS cleavage is required for JAK/STAT signaling, PC1 maturation/ trafficking and for prevention of renal cystogenesis in mice. ADPKD mutations that map within the GAIN domain inhibit GPS cleavage. We previously reported that the PC1 CTF utilizes an aGPCR-like tethered agonist mechanism to activate G-protein signaling to an NFAT reporter, which involves the short, N-terminal, extracellular stalk of the CTF serving as the tethered agonist. Deletion of the stalk dramatically inhibited signaling, while synthetic stalk-derived peptides could rescue signaling by the stalkless CTF and inhibit cystogenesis in metanephric organ cultures of hypomorphic Pkd1<sup>RC/Rc</sup> kidneys. Here we assess the effect of stalk-localized ADPKD missense mutations on signaling by the dissociated CTF subunit and on GPS cleavage of full-length (FL) PC1 to gain additional insight for this regulatory mechanism.

Methods: Wild type (WT) or mutant, FL or CTF forms of PC1 were expressed in HEK293T cells and compared for activation of an NFAT promoter-luciferase reporter, levels of total and cell surface expression and GPS cleavage. Homology modeling of the PC1 (A3) domain was also performed.

Results: Of 11 substitutions throughout the stalk, the 6 significantly reduced, 2 increased, and 3 had no effect on signaling by PC1 CTF. Total and surface expression levels of the CTF mutants ranged from 62-125% of WT CTF. Most mutations had no effect on GPS cleavage. We then constructed a mutant CTF that included inhibited signaling or GPS cleavage mapped to the N-terminal portion of the stalk, while the 2 mutations that increased signaling were in the latter half.

Conclusions: PC1 stalk has more than one region important in regulation of CTF signaling, perhaps as part of the agonistic sequence or for its proper orientation. This study underscores the importance of PC1 GPS cleavage and suggests disruption of a tethered agonist mechanism may also contribute to renal cystogenesis. Better understanding of the tethered agonist mechanism is necessary for development of PKD1 mutation-specific therapies.

Funding: NIDDK Support, Other NIH Support - NIGMS
Metabolic Analysis of Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD): Associations with Disease Progression and Treatment

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Background: ADPKD is characterized by epithelial proliferation and cyst growth. Metabolic abnormalities have been identified in murine models, but little is known about alterations in metabolic pathways in human ADPKD. We evaluated plasma metabolomic profiles in ADPKD subjects prior to and after exposure to tolcapron (T) as compared to healthy controls to better understand metabolic alterations in ADPKD and potential associations with disease progression and treatment response.

Methods: Plasma samples were collected and analyzed at baseline and month 12 in 100 ADPKD subjects (50 in T and 50 in placebo [P] arms) enrolled in TEMPO 3:4 (NCT00428948). The protein fraction was removed, and the remaining extract split into equal parts for analysis on the same tandem mass spectrometry and gas chromatography mass spectrometry platforms. Proprietary software (Metabolon, Inc., Durham, NC) matched ions to an in-house library of standards for metabolite identification and quantitation. Forty age- and sex-matched healthy subjects were analyzed as a control group. Linear mixed effect modeling identified associations of metabolites with ADPKD vs control, height-adjusted total kidney volume (htTKV), Mayo Imaging Classification (MIC), and T vs P.

Results: Baseline metabolic profiles differed between ADPKD and controls, with significant differences in lipid metabolism, TCA cycle, and amino acid metabolism. Baseline MIC 1C, 1D, 1E (vs 1B) were associated with accumulation of the uremic toxin pseudouridine, elevated fatty acid synthesis, and altered tryptophan metabolism, with similar findings when baseline hTKV was analyzed. Thyroxine, urea, and dimethylsulfone were decreased in T vs P at month 12, as well as other metabolites involved in lipid and amino acid metabolism.

Conclusions: We identified novel associations of amino acid and lipid metabolic pathways with ADPKD vs control and with measures of disease severity (MIC and hTKV). These metabolic changes may be due to altered protein turnover, increased kidney-body weight ratio, and tandem mass spectrometry analysis of specific metabolic pathways. Further work is necessary to elucidate potential metabolic pathways involved in ADPKD progression and treatment response.

Funding: Commercial Support - Otsuka Pharmaceutical Development & Commercialization, Inc.

Short-Term Ketogenic Interventions Are Feasible and Effective in Cystic Kidney Disease (ADPKD): Results from the RESET-PKD Study

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by cyst formation deriving from collecting ducts. Pluripotent stem cells associated with the formation of renal structures have been used in vitro studies of nephrogenesis or cystogenesis related to ADPKD. However, the association between transcripts integrating pathways involved in stem cells pluripotency and cystogenesis deserves further investigation. The microRNAs (miRNAs) that participate in the regulation of these transcripts in kidney tissues of mouse models orthologous to ADPKD have not yet been validated. To identify regulatory miRNAs and differently expressed transcripts associated with stem cell pluripotency in kidney tissues of Pkd1-deficient mouse models.

Methods: A transcriptomic computational identification and validation of the expression level of regulatory miRNAs and genes by RT-qPCR, normalized by their respective housekeeping, mir-26a and Ppia was performed. The analyses were performed on kidneys from 10- to 12-week-old cystic mice (Pkd1−/−; Nestin−/− or Pkd1−/−; Nestin−/−, CY, n = 10) and their non-cystic controls (Pkd1+/+/ or Pkd1−/−, NC, n = 10); mice haplinsufficient for Pkd1 (Pkd1−/−, HT, n = 6) and their wild controls (Pkd1−/−, WT, n = 6); and 15-day-old severely cystic mice (Pkd1−/−, SC, n = 7) and their controls (CO, n = 5).

Results: The validation of the computational analyses performed in three to animal models with reports from the literature in other Pkd1-deficient models, identified 10 differently expressed genes associated with the regulation of stem cells pluripotency. Increased expression of Sts3 and Map3k1 genes and decreased regulatory miRNA Let-7a were observed in SC versus CO kidneys. On the other hand, Mapk14 gene showed decreased expression while its potential regulator, miR-21, revealed increased expression in SC versus CO kidneys. Fgf10 expression was decreased in SC versus CO kidneys whereas a trend of increased expression in the CY versus NC group has been observed.

Conclusions: Present results support a potential regulatory effect of miR-21 on Mapk14 expression and of miR-let-7a on the expression of Sts3, Map3k1 and Fgf10, namely transcripts involved in stem cells pluripotency and cystogenesis in kidney tissues of Pkd1−/− mouse models.

Funding: Government Support - Non-U.S.

Investigation of LAD1 as a Candidate Modifier of Polycystic Kidney Disease in Pkd1 Mouse Models


Background: Polycystic Kidney Disease (PKD) is a monogenic disease caused by mutations in either Pkd1 or Pkd2, which encode polycystin-1 (PC1) and polycystin-2 (PC2), respectively. One proposed function for PC1 is to regulate cell migration and cell-cell interaction, possibly through modulation of the cytoskeleton. In prior transcriptomic studies of Pkd1 mutant kidneys, we had identified Lad1 as one of the few genes whose expression was dysregulated early in the course of the disease. The limited available literature suggests LAD1 may encode a cytoskeleton protein that acts as an anchoring filament to the basement membrane of epithelial cells. The goal of this study is to investigate the role of LAD1 in mediating modifying PKD phenotypes.

Methods: We quantified LAD1 gene and protein expression in the tissues of Pkd1 conditional mutant mice, kidney epithelial cell lines derived from Pkd1 conditional mice and human keratinocyte HaCat cells by quantitative polymerase chain reaction (qPCR) and western blot analyses. We used CRISPR technology to generate two LAD1 mutant mouse lines that have large deletions spanning most of the coding region of LAD1 and characterized the phenotype of homozygous mutants. LAD1 mutants were crossed with Pkd1 conditional mice with Ksp-Cre and tamoxifen-Cre to test for genetic interaction in early and late onset PKD models.

Results: We confirmed that Pkd1 mutant kidneys and epithelial cells have lower LAD1 expression levels compared to wild type samples. Mice with homozygous deletion of LAD1 exons 3 to 8 were born at normal Mendelian ratios and lacked obvious abnormalities up to 1 year of age. Histopathologic analyses of the kidney and organs with the highest expression of LAD1 also were normal. Pkd1/Lad1 double mutants were born at expected ratio, but showed distinct phenotypic features. However, early data suggest that Pkd1/Lad1, Ksp-Cre/+ LAD1 homozygous mutants have increased kidney-body weight ratios with worse cystic disease. Further analysis, including LAD1 CRISPR knock-out animals crossed with late-stage conditional Pkd1 knock-out animals, is ongoing.

Conclusions: LAD1 expression is reduced in Pkd1 mutant kidneys. CRISPR knock-out of LAD1 alone shows no obvious phenotype. Loss of LAD1 may worsen disease in the early onset Pkd1-cystic model.

Funding: NIDDK Support

Analysis of MicroRNAs as Regulators of Expression of Transcripts Associated with Stem Cell Pluripotency in Pkd1-Deficient Mouse Models

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by cyst formation deriving from collecting ducts. Pluripotent stem cells associated with the formation of renal structures have been used in vitro studies of nephrogenesis or cystogenesis related to ADPKD. However, the association between transcripts integrating pathways involved in stem cells pluripotency and cystogenesis deserves further investigation. The microRNAs (miRNAs) that participate in the regulation of these transcripts in kidney tissues of mouse models orthologous to ADPKD have not yet been validated. To identify regulatory miRNAs and differently expressed transcripts associated with stem cell pluripotency in kidney tissues of Pkd1-deficient mouse models.

Methods: A transcriptomic computational identification and validation of the expression level of regulatory miRNAs and genes by RT-qPCR, normalized by their respective housekeeping, mir-26a and Ppia was performed. The analyses were performed on kidneys from 10- to 12-week-old cystic mice (Pkd1−/−; Nestin−/− or Pkd1−/−; Nestin−/−, CY, n = 10) and their non-cystic controls (Pkd1+/+/ or Pkd1−/−, NC, n = 10); mice haplinsufficient for Pkd1 (Pkd1−/−, HT, n = 6) and their wild controls (Pkd1−/−, WT, n = 6); and 15-day-old severely cystic mice (Pkd1−/−, SC, n = 7) and their controls (CO, n = 5).

Results: The validation of the computational analyses performed in three to animal models with reports from the literature in other Pkd1-deficient models, identified 10 differently expressed genes associated with the regulation of stem cells pluripotency. Increased expression of Sts3 and Map3k1 genes and decreased regulatory miRNA Let-7a were observed in SC versus CO kidneys. On the other hand, Mapk14 gene showed decreased expression while its potential regulator, miR-21, revealed increased expression in SC versus CO kidneys. Fgf10 expression was decreased in SC versus CO kidneys whereas a trend of increased expression in the CY versus NC group has been observed.

Conclusions: Present results support a potential regulatory effect of miR-21 on Mapk14 expression and of miR-let-7a on the expression of Sts3, Map3k1 and Fgf10, namely transcripts involved in stem cells pluripotency and cystogenesis in kidney tissues of Pkd1−/− mouse models.

Funding: Government Support - Non-U.S.
Sildenafil Inhibits ADPKD-Derived Cyst Growth in 3D Culture and Induces Apoptosis in the Han/SPRD Cy+/+Cy Rat Model of Renal Cyst Disease
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Background: In prior studies we found that human renal cyst cells express high levels of GMP phosphodiesterase 5, 6 and 9 as compared to normal human kidney cells. In breast cancer, inhibition of cGMP phosphodiesterases induces apoptosis. We tested the hypothesis that sildenafil blocks cell proliferation and/or induces apoptosis in cyst epithelia.

Methods: PKD Q4004X cells were grown in Matrigel and treated with vehicle or sildenafil for 7 days. Cyst size was assayed by light microscopy. Differences in cyst area were analyzed by two-way ANOVA. In separate experiments, male cy+/+ rats were given either vehicle or sildenafil in their water supply for 7 or 28 days. Kidneys were harvested and apoptosis was assayed by staining with anti-M30, a monoclonal antibody that binds to apoptosis mediated cleavage of cytokeratin 18 in epithelial cells.

Results: In 3D cultures of PKD Q4004X cells, cultures treated with sildenafil (1, 2 and 4 µg/ml) are significantly smaller than vehicle-treated cultures (p=0.05 for all doses). Further analysis showed that cysts larger than 150 µm were not observed in any sildenafil-treated cultures. Figure 1 shows M30 staining in sildenafil (20 µg/kg/day x 7 to 40 days). Arrows point to cytokeratin 8/18 positive (red cytosolic stain) in cyst epithelia.

Conclusions: Sildenafil inhibits human kidney cyst growth in 3D culture. In male cy+ rats, sildenafil at a dose of 20 mg/kg/day for 7 or 40 days results in apoptosis of cyst epithelia.

Funding: Private Foundation Support

Rab GTPase Regulation in Ciliogenesis and Polycystic Kidney Disease
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Background: Primary cilia are sensory organelles with widespread roles in development and epithelial function. Mutations resulting in isomorphic cilia and ciliary dysfunction are associated with renal ciliopathies such as polycystic kidney disease (PKD), yet primary cilia remain enigmatic in terms of their molecular and functional characterisation. Rab GTPases are central regulators of vesicular trafficking that have been shown to regulate ciliary protein transport and cilia composition, with downstream effects on ciliary function and signalling. Rab GTPases are therefore poised to vary or modify primary ciliary function, by working in conjunction with key cilia proteins, including those mutated in ciliopathies.

Methods: Our data show that Rab13 localises to the primary cilia of mouse kidney cells and Rab13 loss of function affects ciliaogenesis in a variety of in vitro and in vivo models including zebrafish embryos. Characterisation of Rab13 knockout epithelial cells reveal altered cilia, the perturbation of ciliopathy-associated protein localisation, and the formation of dysorphic renal spheroids. Rab13 knockdown zebrafish embryos display a range of cilia-associated developmental defects and Rab13 expression is diminished in mouse PKD cells.

Conclusions: Here we reveal a novel cilia-associated role for Rab13 GTPase. Investigating the genes and molecules that contribute to the ciliome of disease is important to improve knowledge, for potential translation and discovery of new therapeutic approaches for renal ciliopathies including PKD.

Funding: Private Foundation Support, Government Support - Non-U.S.
POI1227  Efficacy and Adverse Effects of a Novel Mesoscale Nanoparticle-Guided Sirolimus Delivery Strategy in a Phkd1Pck Cyst Rat Model
Michal Mrug,1 Daniel A. Heller,2 Chintan H. Kapadia,3 Ryan Williams,4 Phillip H. Chunley,1 Sean Mullen,2 Ronald E. Roye,1 Gabriel Rezonewicz,5 Juling Zhou,2 Edgar A. Jaimez.2 The University of Alabama at Birmingham, Birmingham, AL; 3Memorial Sloan Kettering Cancer Center, New York, NY; 4Goldolphin Therapeutics, New York, NY; 5The City College of New York, New York, NY.

Background: Pre-clinical studies have shown that mTOR inhibition attenuated renal cystic disease progression but it did not improve outcomes in patients with autosomal dominant polycystic kidney disease (ADPKD). This was attributed to the dose limitations in humans due to mTOR inhibitor toxicity. To increase the mTOR inhibition efficacy and reduce its toxicity in renal cystic diseases, we studied mesoscale nanoparticle (MNP)-guided delivery of an mTOR inhibitor, sirolimus (mTOR-sirolimus), in Phkd1PckCys rats. We used recently developed MNPs that selectively and with high affinity target the renal tubular epithelium.

Methods: We synthesized Empty-MNPs or MNP-sirolimus and used them in an experiment that resembled seminal pre-clinical studies of tolvaptan, the only FDA-approved ADPKD therapeutic. Newly outbred Phkd1PckCys rat males were divided into 3 groups (each N= 8-9) and treated for 8 weeks (p22 to p77) with: Empty-MNP (50 mg/kg IV q6h), Free-sirolimus (0.15 mg/kg IV q48h) and MNP-sirolimus (50 mg/kg IV equivalent to 0.3 mg/kg sirolimus q6h). Pre- and post-treatment cyst volumes were assessed by MRI at p21 and p78.

Results: The MNP-sirolimus or Free-sirolimus both inhibited renal mTOR activity in Phkd1PckCys rats. The mean p56/total S6 ratios were: 7.9 for MNP-sirolimus vs 19.1 for Free-Rapa and 10.1 for Empty-MNP (p<0.001) while total S6 levels did not differ (p=0.806). Similarly, an 8-week mTOR inhibition reduced mean renal cyst volumes: 39.9 mm3 for MNP-sirolimus vs 59.3 mm3 for Free-sirolimus vs 148.4 mm3 for Empty-MNP (overall p=0.005). However, pairwise comparisons showed that Empty-S6 levels were significantly reduced in MNP-sirolimus Rats (p=0.017) while for Free-sirolimus treatment the significance was marginal (p=0.052). The pre-treatment renal cyst volumes at 3 weeks were not significantly different (p=0.772). Among side effects, mTOR inhibition reduced body weight and heart weight (p<0.001). In both cases, their averages were less severely reduced in MNP-sirolimus as compared to Free-sirolimus treated rats.

Conclusions: Together, our studies support the concept that a novel MNP-guided sirolimus delivery increases renal mTOR inhibition and therapeutic efficacy in renal cystic diseases, while reducing systemic toxicity.

Funding: NIDDK Support, Other U.S. Government Support

POI1228  Biomarkers Reflecting Extracellular Matrix Turnover Are Prognostic for Kidney Function Decline in Patients with ADPKD
FedERICA Genovesi,1 Judith E. Heida,1 Nadja Sparding,1,2 Morten A. Karsdal,1 Ron T. Ganshevoort,1 Daniel Guldager Kring Rasmussen.1 Nordic Bioscience, Herlev, Denmark; 2Biomedical Sciences, Faculty of Health and Medical Science, University of Copenhagen, Copenhagen, Denmark; 3Dept. Nephrology, University Medical Center Groningen, Groningen, Netherlands.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common inherited disorders in humans and is caused by mutations in the PKD1 and PKD2 genes. The disease is characterized by development and growth of cysts leading to kidney dysfunction. Previous findings suggest that ECM is a driving force in progressive kidney disease in ADPKD and is characterized by an impaired turnover of extracellular matrix (ECM). Here, we investigated the association of ECM biomarkers with rate of kidney function decline in patients with ADPKD.

Methods: We measured four markers of ECM turnover in serum and urine from 305 patients with ADPKD from the DIPAK-1 study (NCT01616927): three markers of interstitial collagen turnover (C3M, PRO-C3 and PRO-C6) and one laminin degradation marker reflecting basement membrane turnover (LG1M). The association of the biomarkers with kidney function decline was investigated with a linear mixed model (change in eGFR/year) and logistic regression (decline in eGFR of >30%). Data was log-transformed if appropriate.

Results: All four markers of kidney fibrosis in serum were associated with eGFR at baseline when adjusting for sex, age, height adjusted total kidney volume (hTKV) and PKD mutation in serum (C3M, P<0.05; PRO-C3, P=0.001; PRO-C6, P=0.001; LG1M, P=0.001). In urine, only C3M and PRO-C6 (C3M, P=0.001; PRO-C6, P=0.001) and not PRO-C3 and LG1M (PRO-C3, P=0.07; LG1M, P=0.31) were independently associated with eGFR. Serum C3M (P=0.005) as well as urinary PRO-C3 (P=0.001) and PRO-C6 (P=0.001) were associated with the rate of eGFR decline per year when adjusting for sex, age, baseline eGFR, hTKV and PKD mutation. A total of 60 patients had a decline in eGFR of >30% and when adjusting for sex, age, baseline eGFR hTKV and PKD mutation, only serum C3M (OR=4.18, P=0.02) was independently associated with a decline in eGFR of more than 30%.

Conclusions: Serum C3M as well as urinary PRO-C3 and PRO-C6 were associated with the rate of kidney function decline when adjusting for known determinants of disease severity. Also, serum C3M could identify fast progressors (decline in eGFR of >30%). These markers hold promise that components from the ECM may be used as prognostic markers in ADPKD, but should be validated first in an independent ADPKD cohort.

POI1229  Magnetic Resonance Fingerprinting (MRF) Identifies Potential Imaging Biomarkers for Autosomal Recessive Polycystic Kidney Disease (ARPKD)
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Background: Autosomal Recessive Polycystic Kidney Disease (ARPKD) is an important cause of morbidity and mortality in children with chronic kidney disease (CKD). Novel therapies have shown efficacy in ARPKD animal models, but clinical trials in ARPKD patients have not been possible due to the lack of sensitive measures of kidney disease progression. Non-invasive Magnetic Resonance Imaging (MRI) techniques, including novel MRF Fingerprinting (MRF), show promise in addressing this unmet need. We previously identified MRF-based T1 and T2 mapping as potential biomarkers of ARPKD kidney disease in animal models and initial human studies. In the current study, we evaluated the relationship between these imaging parameters and renal function in ARPKD fluoresce in mild to moderate CKD.

Methods: ARPKD subjects (age 6-25 yrs) with estimated glomerular filtration rate (eGFR) >60ml/min/1.73m2 were scanned on a Siemens 3T MRI scanner utilizing novel MRF technology to simultaneously generate mean kidney T1 and T2 maps in 15 secs/imaging slice with no sedation or injectable contrast agent. The relationship between eGFR (U25 eGFR formula) and imaging parameters was assessed by Pearson correlations with significance set at <0.05.

Results: 7 subjects (2M/5F, age=12±5 years) were imaged. eGFR was 87±21, range=52-109 ml/min/1.73m2; 5 had hypertension. Mean kidney T1 (94±10 msec) showed a significant negative correlation with eGFR (R=-0.86, p<0.013). Mean kidney T2 (216±37 msec) also showed a strong negative correlation (R=-0.69) but did not yet reach significance (p=0.086). Mean T1 and T2 values for the right and left kidneys also demonstrated a significant correlation (T1: R=0.99, T2: R=0.79).

Conclusions: This is the first study to establish a relationship between MRF-derived imaging biomarkers (T1 and T2) and kidney function (eGFR) in ARPKD subjects. Despite the small cohort, data clearly demonstrate that mean T1 and T2 both increase with decreasing eGFR. These findings suggest that MRF-based T1 and T2 mapping may provide a safe, non-invasive, quantitative, and reproducible measure of kidney disease severity to support future clinical trials to identify subjects at high risk for disease progression and monitor response to treatment.

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Underline represents presenting author.

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Suppressed Autophagy Drives Increased Cellular Metabolic Activity in Human ADPKD Cells

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Background: We published that the autophagy phenotype in Pkd1CSC mouse kidneys is characterized by decreases in crucial autophagy proteins (Cell Signal 2020). We attempt to determine the mechanistic role of suppressed autophagy as it relates to cell metabolism, viability (viability and proliferation) in ADPKD cells.

Methods: Human primary immortalized cultured cells were used: normal renal cortical tubular epithelium (RCTE, Pkd1+/+ and ADPKD cyst-lining epithelium (9-12, Pkd1-/-). To measure autophagic flux, cells were treated with lysosomal inhibitor chloroquin (C) and LC3-luminal labeling, a marker of autophagosomes or mCherry LC3 (fluorescence) were analyzed. MTT assay was used to measure cellular metabolic activity (cell viability and proliferation). Relative densitometry units (RDU) were measured on immunoblots.

Results: There was an increase in MTT and a decrease in Anx in 9-12 vs RCTE (P<0.05). In MTT OD was 0.36 in RCTE vs 0.44 in 9-12 (p<0.001). Anx in MTT (Anx (% gated) marker of apoptosis, was 67 in RCTE vs 18 in 9-12 (p<0.001). The increase in LC3-II in C was not seen in 9-12 indicating suppressed autophagy. LC3-2 (RDU) C/-/+ C was 0.6 vs 1.4 in RCTE (P<0.01) and 0.9 vs 1.1 (NS) in 9-12. mCherry (% gated) C/-/+ C was 6 vs 6 (p=0.05) in RCTE and 6 vs 13 (NS) in 9-12 cells, p62 marker of autophagic cargo, was increased in 9-12 vs RCTE. p62 (RDU) was 0.7 in RCTE and 1.2 in 9-12 (p<0.05). Cells were treated with an ATG7 shRNA (SH) to inhibit a crucial autophagy protein. There was a 50% decrease in LC3-II and ATG7 protein in SH-treated 9-12 cells. SH resulted in an increase in MTT and a decrease in Anx in MTT indicating that suppressed autophagy drives MTT and inhibits apoptosis. MTT OD was 0.7 with scrambled shRNA (SCR) and 0.9 with SH (p<0.05). AnnexinV was 26 with SCR vs 13 with SH (p<0.05). Tat-Beclin peptide (TAT), a specific autophagy inducer, resulted in a decrease in MTT in 9-12 suggesting that autophagy decreases MTT. MTT OD was 0.9 with Veh vs 0.2 with TAT (p<0.001). TAT did not affect Anx.

Conclusions: In ADPKD cyst lining epithelial cells there is increased MTT, suppressed autophagic flux, and decreased apoptosis. Autophagy inhibition increased MTT and suppressed MTT. Autophagy or suppressed autophagy drives increased cellular metabolic activity in ADPKD cells. The effect of autophagy induction/inhibition on cyst growth in vivo merits further study.

Funding: Veterans Affairs Support, Other U.S. Government Support

Species-Specific Differences in FPC-CTD Trafficking: Implications for Differential Activation of Intracellular Signaling Pathways

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Background: ARPKD (MIM 263200) is caused by mutations in PKHD1, which encodes FPC. But, orthologous mouse Pkd1 mutants either have no renal cystic disease or very mild PCT dilatation. We previously showed that MYC/Myc is overexpressed in human ARPKD and mouse Cys1/resc Pkd1 mutant kidneys, but not in several Pkd1 mutants. We also showed that expression of the intracellular carboxy-terminus of mouse FPC (mFPC-CTD), but not human (hFPC-CTD), activates the Myc/Myc1 promoter (J Am Soc Nephrol 2020). The current study focused on: 1) the intracellular trafficking of mFPC-CTD and hFPC-CTD, and 2) activation of the Src/STAT3 signaling pathway, linked to hFPC-CTD (Abulh, 2020), in a mouse Pkd1 mutant lacking FPC-CTD and in the cpl mouse model of ARPKD, with and without Cys1 rescue.

Methods: Comparative immunoblot analysis. Immortalized mouse CCD (mCCD) and human (hCCD) cell lines stably expressing mFPC-CTD and hFPC-CTD, respectively. Kidneys from cpl, Cys1-rescued cpl, and Pkd1tm1del67 mutant mice; western blot and immunofluorescence.

Results: FPC-CTD is the least conserved domain, with 55% identity between human-mouse CTDs, compared with 73% identity across the full-length FPC. The CTD is unique, with an AA-sequence not found in other terrestrial vertebrate proteins. In stable cell lines, mFPC-CTD localized to both nuclei and cilia, whereas h-FPC-CTD primarily localized to the apical membrane. In non-cystic del67 kidneys (lacking FPC-CTD), PSTAT3Ph and e-Myc were similar to wild-type controls. In cpl kidneys, pSTAT3Ph and e-Myc were upregulated, but their levels in Cys1-rescued cpl kidneys (Iang 2021) were comparable to wild-type.

Conclusions: Differences in intracellular trafficking of mFPC-CTD and hFPC-CTD may explain the species-specific differences in Myc/Myc1 promoter activation. Distinct subcellular localizations may reflect differential in the functional evolution of human and mouse FPCs, with mFPC-CTD trafficking to nuclei and hFPC-CTD to the cytoplasm, whereas hFPC-CTDs functions as a membrane-associated signaling regulator of Src-STAT3. Activation of Src-STAT3 signaling and Myc upregulation are signatures of cystic epithelia, suggesting that renoprotective mechanisms in FPC-deficient mouse kidneys remodel in response to Pkd1 mutation.

Funding: NIDDK Support, Private Foundation Support

Cystic Kidney Disease - I

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Underline represents presenting author.

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**Results:** We found that full length oKlotho was decreased in collecting duct cells, macrophages, fibroblasts and T/NK immune cells in Pkd1 homozygous kidneys. Transgenic oKlotho delayed cyst growth in Pkd1 conditional knockout mice by normalizing the expression of genes associated with a number of diverse functions, including the genes associated with the transitions between collectig duct cell subtypes and those involved in epithelial-mesenchymal transition. In addition, we found that the genes associated with the epithegenic clock (DNA methylation age) were dysregulated in those cells in cystic kidneys, and that they could be normalized by transgenic oKlotho, suggesting that transgenic oKlotho might slow down the process of epithegenic age acceleration in cystic kidneys. The dysregulation of the epigenetic age-acceleration genes, Apoe, Cldn4, Mge and S10c38a2, might contribute to PKD pathogenesis and might serve as potential biomarkers for ADPKD. Finally, transgenic oKlotho affected a large number of genes associated with metabolic and oxidative signaling, suggesting that oKlotho might act by gene expression and signaling pathways to extend the life span of mice.

**Conclusions:** Reduction of oKlotho regulates cyst growth through diverse signaling pathways. Pkd1 mutation accelerates epithegenic age in ADPKD. Transgenic oKlotho not only delayed cyst growth but also slowed down epithegenic age acceleration.

**Funding:** NIDDK Support

PO1236

Mechanistic Interaction Between Cystin and Fibrocystin/Polyductin in Model Cell Lines and cpk/cpk Kidneys

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**Background:** Cystin cpk (cpk) mice exhibit ARPKD-like renal phenotype due to a mutation in the Cys1 gene and loss of cystin. ARPKD (MIM 263200) is caused by mutations in PKHD1, encoding FPC. Both cystin and FPC are present in the primary cilium, but no physical interaction has been reported. Using mouse CCD cell lines, we have shown that FPC levels were reduced in cpk cells by 75% relative to wt. Cystin deficiency is specifically linked to FPC reduction and did not affect cilia development, but altered ciliary architecture (ASN 2020). The current study focuses on cellular mechanisms driving FPC reduction in cystin-deficient cells, and the consequences of FPC loss. We show that FPC is necessary for proper E3 ubiquitin ligase function and consequently cellular proteome management (Kaimori 2017).

**Methods:** Immortalized wt and cpk mouse CCD cells. Wt and cpk mouse kidneys. sRNA silencing of Cys1: qRT-PCR, western blot, confocal microscopy, morphometry, patch clamp.

**Results:** Silencing Cyst1 in wt cells results in a sRNA dose-dependent reduction of both cystin and FPC. Correlative studies showed marked reduction of FPC in cpk kidneys. Similar Pkd1 cpk mRNA levels in wt and cpk cells, and kidneys implicate FPC regulation at the protein level. Proteasome or lysosome inhibition did not recover FPC, but activation of autophagy further reduced FPC levels, suggesting a role for selective autophagy in FPC removal. Diminished FPC levels lead to E3 ubiquitin ligase defects and reduced polyubiquitination of proteins, necessary for proteome management. In cpk cells, we observe altered membrane retention of the epithelial sodium channel and increased sodium transport.

**Conclusions:** Our studies provide the first functional link between cystin and FPC in renal epithelial cells. We propose cystin as a gatekeeper for FPC at the base of the cilium and in the E3 ligase complex. In cystin-deficient cells, FPC is continuously degraded driving FPC reduction in cystin-deficient cells, and the consequences of FPC loss. We speculate that FPC is necessary for proper E3 ubiquitin ligase function and consequently cellular proteome management (Kaimori 2017).

**Funding:** NIDDK Support, Private Foundation Support

PO1237

Tubular Flow Disruption During Cyst Development in Polycystic Kidney Disease

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**Background:** Polycystic kidney disease is an inherited disorder in which clusters of cysts develop within the kidneys, causing the kidneys to enlarge and lose function. Cyst development can be due to functional changes caused by mutations in ciliary localized proteins Pkd1 and Pkd2 or changes in cilia formation/structure (e.g. i888 mutants). It is currently unknown how cysts impact tubule flow and cilia, or whether flow alterations occur prior to or after cyst formation is initiated.

**Methods:** We used inducible Cre conditional mutant mouse models with an optical imaging camera to monitor changes in proximal tubule flow at multiple timepoints during cystogenesis in live kidneys. Additionally, we evaluated dextran absorption into proximal tubules as an indicator of tubule flow in mutant and control mice during cyst development. We determined the number of dextran+ proximal tubule cells by FACS to quantify changes in the percentage of tubules with flow in cystic versus non cystic kidneys. We performed H&E staining to quantify cyst severity and analyzed sections by immunofluorescent microscopy to assess changes in flow.

**Results:** Our results suggest that during the cyst formation, there is a marked decrease in flow through the tubules and that this reduction in flow occurs early during cyst formation. This corresponds to a 56.8% of cells that are both dextran+ and LTA+ (proximal tubule) by flow cytometry and similar results were obtained by IF analysis. We also find an increase in resident and infiltrating macrophages around the forming cysts.

**Conclusions:** The use of intravital imaging approaches allows us to evaluate changes in tubule flow as cysts progress. With the addition of cilia markers, we will examine the responses of the cilium to the changes in flow. Preliminary data suggests that alterations in tubule flow occur at early time points during cyst initiation with larger cysts seldom containing epithelium that are dextran-. These data indicate that loss of tubule flow may be an early event associated with cystogenesis. Our data also suggests that disruption of tubule flow is progressive with fewer tubules with flow at later time points (4-6 months post induction). We are currently assessing whether there is an association between the disruption of flow in a tubule and localized immune responses.

**Funding:** NIDDK Support

PO1238

FoxM1 Promotes Cyst Growth in Autosomal Dominant Polycystic Kidney Disease

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**Background:** Autosomal dominant polycystic kidney disease (ADPKD) is driven by mutations in PDK1 and PDK2 genes and is characterized by renal cyst formation, inflammation and fibrosis. Forkhead box protein M1 (FoxM1) is a transcription factor of the Forkhead box (Fox) protein super family which is defined by a conserved winged helix DNA-binding domain 1. FoxM1 has been reported to promote tumor formation, and disruption of dextran and fibrosis in many organs. However, the role and mechanism of FoxM1 in regulation of ADPKD progression is still poorly understood.

**Methods:** To evaluate the role and mechanisms of FoxM1 in cyst in growth in vivo, we treated early stage and long lasting Pkd1 mutant mice with the FoxM1 specific inhibitor, FDI-6. To identify novel FoxM1 target genes involved in cystogenesis, we performed ChIP-sequence analysis.

**Results:** We found that FoxM1 was upregulated in cyst-lining epithelial cells in polycystin-1-deficient murine kidneys and human ADPKD kidneys. Inhibition of FoxM1 with FDI-6 delayed cyst growth as seen by decreased cystic index, kidney weight (KW)/body weight (BW) ratios, blood urea nitrogen (BUN) levels, cyst lining epithelial cell proliferation, and increased cyst lining epithelial cell apoptosis in Pkd1 mutant mice (all p < 0.01). Targeting FoxM1 also decreased renal fibrosis in long last Pkd1 mutant kidneys. Upregulation of FoxM1 promotes cyst growth through: 1) upregulation of the expression of Akt and Stat3 and activation of ERK and Rb signaling to increase cystic renal epithelial cell proliferation, 2) inhibition of p65-dependent cystic renal epithelial cell death, 3) facilitation of the recruitment and retention of renal macrophages, and 4) upregulation and activation of IL6 markers to promote renal fibrosis. In addition, FoxM1-dependent macrophage recruitment was associated with upregulation of monocytic chemotactic protein 1 (MCP-1) and inflammatory cytokine TNF-α. Further, we identified novel FoxM1 target genes by ChIP-seq analysis, which may connect FoxM1 signaling to the cilopath hypothesis in PKD.

**Conclusions:** FoxM1 promotes renal cyst growth and fibrosis in ADPKD through Akt, ERK, Rb and STAT3 signaling as well as NF-kB and cilopath associated signaling. Targeting FoxM1 in cystic renal epithelial cells may be a viable new therapy for ADPKD.

**Funding:** NIDDK Support

PO1239

Allosteric Mechanism of PC1 Tethered Agonist-Mediated Signaling

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**Background:** Polycystin-1 (PC1) is the 11-transmembrane protein product of the human autosomal dominant polycystic kidney disease (ADPKD) gene Pkd1. PC1 functions as an atypical GPCR and shares multiple features with the Adhesion GPCRs, including a GPCR autoproteolysis-inducing (GAIN) domain that catalyzes cis-cleavage of the receptors into extracellular N-terminal (NTF) and membrane-embedded C-terminal (CTF) fragments. We previously reported that CTF-mediated signaling to an NFAT promoter-luciferase reporter is dependent on the presence of the stalk, is reduced by ADPKD-associated missense mutations within the stalk, and can be rescued by synthetic, stalk-derived peptides, supporting a tethered ligand mechanism of PC1-G protein signaling (JASN 2018;29:671; JASN 2019;30:388).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: We have combined highly complementary experiments and computer simulations to investigate the mechanism of the tethered agonist-mediated signaling of PC1 CTF. A computer model of the human PC1 CTF was generated using the cryo-EM structure of the PC1-PC2 complex with important missing regions added through I-TASSER homology modeling. All-atom enhanced molecular dynamics (GaMD) technique were performed, followed by calculations of residue correlation matrices and free energy profiles. GaMD simulation-predicted residue interactions important for WT stalk-mediated activation of PC1 CTF were further investigated by mutagenesis and cellular assay experiments.

Results: GaMD simulations were consistent with experimental signaling data obtained with PC1 CTF expression constructs encoding wild type and stalk variants of the PC1 CTF. Correlation matrices revealed regions of highly correlated residue motions involving the stalk, TOP and putative pore loop domains. Key residue interactions predicted from the GaMD simulations were validated with newly designed mutation experiments.

Conclusions: Complementary experiments and simulations studies support the function of the PC1 CTF stalk region as a tethered agonist and suggest a mechanism whereby it can induce TOP-pore loop interactions which can be further translated to the GaMD model for G protein activation. This in-depth knowledge is expected to facilitate future drug design efforts targeting this function of PC1 for more effective treatments of ADPKD.

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PO1240

Abstract Withdrawn

PO1241

Analysis of Calcium Signaling in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: ADPKD is an inheritable kidney disease characterized by the development of fluid-filled renal cysts, mainly caused by mutations in the PKD1 and PKD2 genes, leading to loss of renal function. Molecular mechanisms underlying cystogenesis are poorly characterized but it is postulated that disturbed calcium homeostasis is a primary event in cystogenesis. The precise molecular players that cause this disturbance are largely poorly explored, especially in non-cystic cell types. We therefore aim to characterize the profile of calcium-coupled G-protein coupled receptors (GPCRs) in a human renal epithelial cell models, to identify which receptors are present, whether their function is affected in ADPKD and whether they can be used to modulate cyst formation and growth.

Methods: Urine-derived conditionally immortalized proximal tubule epithelial cells (ciPTECs) of ADPKD patients and healthy controls were screened for calcium-coupled GPCRs, using an agonist library on Fura-2 loaded cell populations seeded in 96-well format. Validation of specific hits was done using single-cell measurements with a fluorescence microscope and built-in perfusion system in the ciPTECs as well as in tissue-derived conditionally immortalized cystic cells (ciCCs). Matrikel-based 3D cell culture was used to grow ciCCs to assess their ability to form cystic structures. Structures were stained with nuclear and cytosolic stains and imaged via confocal microscopy.

Results: From a library of 418 GPCR agonists a selective amount of calcium-coupled GPCRs was found functionally active in ciPTECs. ciPTECs from both healthy controls and ADPKD patients were found to functionally express purergic - , histaminergic - , serotonin and dopamine receptors. In single-cell experiments, we did not find any significant differences in functionality between healthy controls and ADPKD patients, but observed that response characteristics are mainly donor-specific, suggesting patient-specific disease mechanisms. ciCCs grown in 3D cell culture were found to form hollow, cell-lined cyst-like structures.

Conclusions: We describe the first thorough characterization of calcium-coupled GPCRs in a human proximal tubule epithelial cell model. We established a 3D cyst growth assay using tissue-derived cystic cells to explore the possibility to use the identification of GPCRs to modulate cyst formation and growth.

Funding: Government Support - Non-U.S.

PO1242

Loss of Polycystin Function in Lymphatic Cells Impair CTP1a Expression and Fatty Acid Uptake

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Background: Homozygous Pkdl or Pkdr null mutant mice die at mid-gestation due to vascular abnormalities including edema and hemorrhage. We have previously shown that edema in Pkdl and Pkd2 knock out mice is due to abnormal lymphatic morphogenesis, with grossly dilated, blood filled dermal lymphatic vessels. Because proper lymphatic development is supported by fatty acid β-oxidation (FAO), we probed fatty acid transport in Pkdl1/Pkd2 lymphotothelial cells (LECs).

Methods: Pkdl1 and Pkd2 mutant LECs were isolated from mouse E14.5 embryos or generated using lentiviral shRNAs against PKD1 or PKD2 in human dermal LECs (HDLCs). Protein levels of PC1, PC2 and CPT1a were determined by western blotting and CPT1a/CPT2 mRNA levels were analyzed by qRT-PCR. Fatty acid uptake was assessed by BODIPY 558/568 C12, staining of control and Pkd1 mutant LECs pre-incubated with or without 50 µM palmitate, and counterstained with mitochondrion. Cells were imaged by confocal microscopy and the relative abundance of lipid droplets were quantified using ImageJ software. Each experiment was repeated 3 times and pairs of means (mutant versus control) were compared using Student’s T-test.

Results: Embryonic Pkdl1- and Pkd2- murine LECs exhibit a robust decrease of CPT1a protein levels. In addition, CPT1a protein levels were significantly reduced in Pkdl1 and Pkd2 deleted HDLCs, suggesting a conserved role of Pkdl1/2 in CPT1a regulation. PC1 and PCD2 depletion in HDLCs results in an accumulation of cytoplasmic lipid droplets which often colocalized with mitochondria, indicative of impaired fatty acid utilization. The ability of PKD1 mutant cells to metabolize fatty acids is further challenged by pre-treatment with 50uM palmitate, which exacerbates the accumulation of lipid droplets.

Conclusions: Our results highly suggest that polycystin function is required to maintain normal levels of CPT1a expression and fatty acid transport to mitochondria in LECs. We thus speculate that a defect in FAO with consequent dysregulation of gene expression is the basis of impaired lymphangiogenesis in Pkd1/2 mutant embryos.

Funding: NIDDK Support

PO1243

Pharmacological Activation of Long-Form PDE4 Enzymes Suppresses Disease Progression in PkdlRC/RC and Pkd1 Knockout (iKspCrePkd1/lox,lox) Mouse Models of ADPKD

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Background: Upregulation of cAMP signalling is thought to promote cystogenesis in ADPKD. Phosphodiesterase 4 (PDE4) enzymes degrade cAMP and contribute to its compartmentalized signaling. We have previously described novel small molecules that allosterically activate long isoforms of PDE4 and lower intracellular cAMP. Here we demonstrate significant efficacy with MR-L22, an advanced PDE4 activator compound, on suppressing cystic burden and preserving kidney health in orthologous models of ADPKD.

Methods: The effects of the long isoform PDE4 activator MR-L22 (administered by oral gavage) were assessed in rapidly (iKspCrePkd1/lox,lox induced at P10, treated from P14 to P27) and slowly progressive (Pkd1/2, treated from 4 to 16 weeks of age) mouse models of ADPKD. Test groups were compared to control groups receiving vehicle alone or vehicle control (results not shown).

Results: Compared to vehicle treated controls, MR-L22 treated Pkd1/-/c mice exhibited reduced kidney cAMP levels, cyst indices, kidney weight/body weight ratios (Kw/Bw) and MRI measured total kidney volumes (TKV) (Table and Figure). Long isoform PDE4 activation significantly protected kidney function and, when compared to tolvaptan, animals receiving MR-L22 produced significantly less urine volume. MR-L22 also suppressed the aggressive cystic disease exhibited by tamoxifen induced (P10) iKspCrePkd1/lox,lox mice, where Kw/Bw and cystic indices were reduced in comparison to vehicle control (results not shown).

Conclusions: Small-molecule activators of long isoforms of PDE4 suppress cystic disease progression in key translational models of ADPKD and may be better tolerated and more effective than vasopressin V1 receptor antagonists.

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Underline represents presenting author.
Heterozygous Variants in NEK8 Kinase Domain Cause an Autosomal-Dominant Ciliopathy

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Background: NEK8 encodes a protein that localizes to the primary cilium. Bilallelic NEK8 variants are known to cause multigorgan developmental defects including renal cystic dysplasia, with heterozygous carrier parents being asymptomatic. This autosomal recessive inheritance is most common for ciliopathies. Complementary to this, we now propose a dominant-negative effect for certain heterozygous NEK8 nonsense variants in the kinase domain.

Methods: We performed genetic testing in patients from several medical centers. To explore the consequences of the identified NEK8 variants we are performing cilia staining assays in patients’ skin fibroblast and kidney cells, as well as in mMCD5 cells overexpressing the identified variants.

Results: We identified three distinct heterozygous NEK8 variants in eight families (table 1), all leading to missense alterations in the kinase domain. The large symptomatic family and the de novo occurrences are also in favor of a dominant mode of inheritance. All patients have a kidney phenotype, varying in severity, age of onset and presence of kidney failure. Interestingly the p.Arg457P variant is a recurrent variant found in six unrelated families. Our preliminary results from functional studies show normal localization of the NEK8 protein to the Golgi region, but abnormal primary cilia formation, in serum starved primary ciliated cells – a finding corroborated with functional assays.

Conclusions: We present the first evidence for a pathogenic effect of heterozygous NEK8 variants. Remarkably our patients present with a renal limited phenotype as compared to the multigorgan defects found in patients with biallelic variants. This reveals a new mode of inheritance for NEK8 variants and expands genotype-phenotype correlations for this gene.
Methods: Co-immunoprecipitation (co-IP) of UMOD and TMDG cargo-receptors was assessed in HEK293 cells transfected with wild type (WT) or mutant (C126R) human UMOD. Next, we performed untargeted Affinity Purification Mass Spectrometry followed by tandem MS to generate a list of UMOD interactors. We also conducted in vivo studies in UMOD−/− mice.

Results: We identified distinct WT and mutant UMOD interactomes using an unbiased AP-MS proteomics approach. Several interactors, including members of the TMED family, were significantly enriched in the mutant UMOD interactome. Targeted co-IP in lysates of HEK293 cells transfected with UMOD and interacting protein candidates confirmed the identification of UMOD interactors in-vitro, suggesting that when pulling down TMEDs, we found abundant immature non-glycosylated UMOD, suggesting entrapment in early secretory compartments. In vivo, treatment with BRD4780 was suggestive of disrupted interactions between mutant UMOD and interacting partners responsible for toxic entrapment in the ER, as assessed by immunolocalization of kidney lysates and immunofluorescence microscopy of tissue from UMOD−/− mice.

Conclusions: Our results suggest that UMOD interacts with TMDG cargo-receptors and other proteins that may mediate the pathogenic quality control mechanisms responsible for toxic ER-retention and accumulation. Shedding light on these new molecular mechanisms may unmask new therapeutic strategies for the treatment of ADTDK-UMOD.

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PO1251

Weight Loss to Slow Cyst Growth in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: Recent studies in animal models of ADPKD suggest that food restriction can profoundly slow cyst growth and maintain renal function. We have also reported that overweight and obesity are strong independent predictors of ADPKD progression. Thus, it is plausible that weight loss, caloric restriction, and/or periods of fasting may slow ADPKD progression in humans; however, the feasibility of these dietary interventions, and whether the driver of therapeutic efficacy is periods of fasting or reduction in body weight, is unknown.

Methods: We conducted a one-year study evaluating feasibility of delivery of a behavioral weight loss intervention based on either daily caloric restriction (DCR) or intermittent fasting (IFM) in adults with overweight/obesity, ADPKD, and eGFR ≥30 mL/min/1.73m2 (targeted weekly energy deficit of ~34% in both groups). We also evaluated the safety, acceptability, and tolerability of each intervention, and obtained exploratory insight into changes height-corrected total kidney volume (htTKV).

Results: 28 participants (16F/12M; 46 ± 9 yrs, body mass index 34.7 ± 5.0 kg/m², eGFR of 69±22 mL/min/1.73m²) were randomized to either DCR (n=15) or IFM (n=13). Clinically significant (~5%) weight loss was achieved in both groups at month 3 (DCR: -7.1±4.2% vs. IFM: -5.5±3.3%). At 12 months DCR lost additional weight while weight loss in IFM plateaued (DCR: -9.1±6.0% vs. IFM: 4.9±5.6%; p=0.05 DCR vs. IFM). Overall, DCR had a more favorable safety, tolerability, and adherence profile than IFM. Annual htTKV %Δ was qualitatively low in both groups in comparison to historical data, and particularly DCR, was feasible interventions over a one-year follow-up. Clinically significant (>5%) weight loss was achieved in both groups at month 3 (DCR: -7.1±3.3% vs. IFM: 1.7±5.6%; p<0.05 DCR vs. IMF). Overall, -7.1±3.3% at 12 months DCR lost additional weight while weight loss in IMF plateaued (DCR: -9.1±5.6%; p<0.05 DCR vs. IMF). Annual htTKV %Δ was qualitatively low in both groups in comparison to historical data, and particularly DCR, was feasible interventions over a one-year follow-up. Clinically significant (>5%) weight loss was achieved in both groups at month 3 (DCR: -7.1±3.3% vs. IFM: 1.7±5.6%; p<0.05 DCR vs. IMF).

Conclusions: We demonstrate that renal tubular peroxisomes are dispensable for normal renal function. This indicates a large flexibility of proximal tubule cells both in terms of lipid membrane composition and metabolic/antioxidant functions. Our data also suggest that renal injuries in ZSD patients are of extrarenal origin.

Funding: Government Support - Non-U.S.

PO1254

Overweight and Obesity Predict Kidney Growth in Children and Young Adults with ADPKD

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Background: We have previously reported that overweight and obesity are independently associated with more rapid progression in adults with early-stage autosomal dominant polycystic kidney disease (ADPKD). We now evaluate whether overweight and obesity are also associated with faster kidney growth in children and young adults with ADPKD.

Methods: 54 non-diabetic children and young adults (6-25 years of age) with ADPKD and estimated glomerular filtration rate (eGFR) >60 mL/min/1.73m² who participated in a 1-year randomized controlled trial and submitted for follow-up. Participants were categorized based on BMI (if ≥18 years; n=27) or BMI percentile for age, sex, and height (if <18 years; age; n=27) as normal weight (n=40 [74%]) or overweight/obese (n=14 [26%]). The longitudinal (1-yr) association of overweight/obesity with change in height-corrected total kidney volume (htTKV) by magnetic resonance imaging was evaluated using multivariate linear regression models.

Results: Mean±sd. age was 18±5 years, annual % change in htTKV was 6.1±9.0%, and eGFR (full-age-spectrum equation) was 112±18 mL/min/1.73m². The annual % change in htTKV was 5.5±9.1% in the normal weight participants and 7.9±8.6% in overweight/obese participants. Mean±sd. height was 169±9 cm, mean±sd. weight was 74±15 kg, and mean±sd. BMI was 24.8±4.1 kg/m². At baseline, 60% of children and young adults were overweight/obese (n=33; 51.9%). The annual % change in htTKV was 5.5±9.1% in the normal weight participants and 7.9±8.6% in overweight/obese participants.
Cystic Kidney Disease - II

PO1255

Metabolic Changes over 1 Year Following Drug or Lifestyle Interventions in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most commonly inherited progressive kidney disease. Studies have shown differences in metabolic profiles in those with ADPKD; however few studies assess change over time.

Methods: We performed metabolomics to assess patterns of change across four groups of participants with ADPKD pooled from 2 randomized clinical trials: placebo control (CON), metformin (1,000 mg/day) (MET), intermittent fasting (IFM; 3 day/weekly) arbitrary restriction (DCR; daily restriction of 34% per day from baseline weight maintenance requirements). Analyzed plasma samples were collected during the trials at baseline and year for each group. A total of 163 metabolites were measured using liquid chromatography-mass spectrometry (LC-MS). Differences in metabolic profiles over time and within study groups were evaluated by a one-way ANOVA and Bonferroni correction for multiple comparisons.

Results: Baseline characteristics for each trial included CON (n=22, 14 female (F), 49±7 yrs of age (means±S.D.), estimated glomerular filtration rate [eGFR] 73±13 ml/min/1.73m², body mass index (BMI) 29.3±4 kg/m²), MET (n=22, 14 F, 48±6 yrs of age, eGFR 69±14 ml/min/1.73m², BMI 29.7±7 kg/m²), MET (n=10, 5 F, 47±6 yrs of age, eGFR 77±16 ml/min/1.73m², BMI 34.6±5 kg/m²); and DCR (n=9, 5 F, 46±13 yrs of age, eGFR 68±21 ml/min/1.73m², BMI 34.1±5 kg/m²). Age and eGFR did not differ between groups but BMI was higher in the IFM compared to CON (p=0.031). Metabolite changes are depicted in Figure 1.

Conclusions: There are changes at one year in metabolites in adults with ADPKD between control, metformin, intermittent fasting, and daily caloric interventions. Further research is needed to identify metabolic profile shifts involving drug and dietary interventions.

Funding: NIDDK Support, Other U.S. Government Support

PO1256

Identification of CLC-5, the Electrogenic 2Cl−/H+ Exchanger, as the Dominant Apical Chloride Secretory Transporter in Kidney Cyst Epithelium in Tuberous Sclerosis

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Background: Cyst expansion in Tuberous Sclerosis Complex (TSC) or PKD requires secretion of chloride into the cyst lumen as the driving mechanism for salt accumulation. In PKD, C1 secretion into the cyst lumen is mediated via the eAMP/PKA-stimulation of CFTR in principal cells consequent to the V2 receptor activation by AVP. Kidney cyst epithelium in TSC differs from PKD in that cyst epithelium in TSC is comprised of genotypically normal A-intercalated cells, which do not exhibit noticeable expression of either CFTR or the V2 receptor. The identity of the Cl- secreting molecule(s) in TSC cyst epithelia remains unknown. Based on RNA Seq analysis in kidneys of Tsc1 KO mice, we hypothesized that the chloride transporter CLC-5 is expressed on the apical membrane of A-intercalated cells in cyst epithelia of humans and animal models of TSC. CLC-5 is a 2Cl−/H+ exchanger that is located in collecting duct A-intercalated cells where it is predominantly localized to endosomes and plays a critical role in dissipating H+ secretion and membrane depolarization by H+-ATPase. This allows parallel movement of Cl− and H+ into the endosomes.

Methods: Double immunofluorescence labeling demonstrated remarkable colocalization of CLC-5 and H+-ATPase on apical membranes of an overwhelming numbers of cyst epithelial cells in all models of TSC, including the human kidney cysts. In contrast, kidney cysts in Pkd1 mutant mice showed no apical CIC-5 expression and very few H+-ATPase expressing cells.

Conclusions: These are the first reports on apical membrane localization of CLC-5 in A-intercalated cells in any disease state, and suggest that similar to late endosomes/lysosomes, CLC-5 and H+-ATPase may function synergistically on cyst epithelia by secreting Cl− and H+ into the cyst lumen. These results strongly point to enhanced translocation of CLC-5 and H+-ATPase from late endosomes/lysosomes to the apical membrane of cyst epithelia in TSC.

Funding: Veterans Affairs Support, Other U.S. Government Support, Private Foundation Support

PO1257

Two Years In: The Development and Basic Characteristics of a National Patient-Powered Registry in ADPKD

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Background: The therapeutic pipeline in autosomal dominant polycystic kidney disease (ADPKD) has grown, generating a need for more patient participation in clinical trials. To facilitate US ADPKD patient enrollment and to encourage the utilization of patient-reported outcomes in trial design, the PKD Foundation (PKDF) designed a national ADPKD Registry.

Methods: The ADPKD Registry is hosted on a secure, online platform (IQVIA, oc-meridian.com/pkdrce). Participants are consented through the online system and complete a series of modules. The Core Questionnaire includes diagnosis, latest kidney function tests, and comorbidities. Family history, diet and lifestyle, quality of life, and complications of liver cysts, and vascular outcomes are queried.

Results: Between 9/4/19 and 5/1/21, 1,580 ADPKD patients have registered and completed the Core Questionnaire. Participants have a median age of 49 years, 73% have not reached ESKD, and 79% reported a family history of the disease. Currently, the cohort is 71% female, 93% Caucasian, 4.8% Hispanic/Latino and 2.5% African American. Strategic efforts are in development to increase diversity in the cohort. Nearly three quarters of participants had not previously participated in research, with only 27% indicating that they had been in another PKD study or clinical trial. All participants have consented to be contacted about future studies. Many will likely qualify for ongoing trials based on completed module data. Thus far, the Registry platform has made over 2,200 patient-contracts contacting about six clinical studies, with some individual overlap due to similar eligibility criteria.

Conclusions: The ADPKD Registry is a longitudinal research tool intended to capture ADPKD patient-reported data and is designed to impact research in multiple ways. It will allow for a range of analyses to be performed on ADPKD early from disease through dialysis and post-transplant outcomes. Additionally, modules on health care access & utilization and COVID-19 impact will help the PKDF better understand the challenges of this community.

Funding: Private Foundation Support

PO1258

Polycystic Kidney Disease and Race

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Background: Racial/ethnic differences in the development of kidney failure (ESKD) and transplant (TX) access are well-documented. ESKD is anticipated in familial autosomal dominant polycystic kidney disease (ADPKD), providing the opportunity for greater ESKD preparation. We sought to define the impact of race on ESKD/TX outcomes in ADPKD.

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Underline represents presenting author.

Percent Δ of metabolites. Values are expressed as mean ± SD.
Methods: White (W), African-American (A), or Hispanic (H) ADPKD patients were identified in USRDS 1(2000-6:2018); demographic and laboratory data were obtained. Median income was derived from US Census. Models included: age at ESKD (linear), pre-emptive TX (logistic), and TX after dialysis initiation (Cox), adjusted for age, sex, albumin, hemoglobin, eGFR, insurance, income, ESKD Network, and employment, with W as reference.

Results: Among 41,485 patients, (77.3% W, 13.3% A, 9.4% H), characteristics/ outcomes are shown in Table 1. AA and H had lower median income and less private insurance, pre-ESKD nephrology care, and employment. For AA and H, peritoneal dialysis and TX were less common than in W. Albumin, hemoglobin, and GFR were lowest in W. ESKD occurred 2.2 ± 0.2 and 4.8 ± 0.3 years earlier in A and H, compared to W. Adjusted odds of pre-emptive TX were 0.38 (0.33, 0.42) and 0.47 (0.40, 0.55) for A and H. Adjusted hazards for TX after dialysis initiation were 0.60 (0.55, 0.65) for A and 0.78 (0.72, 0.85) for H, P=0.001 for all. TX rates for A vs W by network are shown in Figure 1.

Conclusions: Despite the hereditary nature of ADPKD, renal outcomes differ by race, attributed to in part, economic and geographic factors. Health inequity is a contributing factor to patient outcomes in ADPKD that needs to be addressed.

PO1260
Curcumin Therapy to Treat Vascular Dysfunction in Children and Young Adults with Autosomal Dominant Polycystic Kidney Disease (ADPKD)
Kristen L. Nowak,1 Heather Farmer-Bailey,1 Wei Wang,1 Zhiyong You,1 Cortney Steele,1 Melissa A. Cudnaphornchai,1 Jelena Klawitter,1 Nelis Piotel,1 Diana George,1 Anna Jovanovich,1 Danielle Soreno,1 Berenice Y. Gitomer,1 Michel Chonchol,1 2 Rocky Mountain Hospital for Children, Denver, CO; 3 VA Eastern Colorado Health Care System, Aurora, CO; 4 Children’s Hospital Colorado, Aurora, CO.

Background: Clinical manifestations of autosomal dominant polycystic kidney disease (ADPKD) can begin in childhood, including evidence of vascular dysfunction, an important predictor of cardio-vascular events and mortality. Curcumin is a polyphenol found in turmeric that reduces vascular dysfunction in rodent models and humans free from ADPKD. It also slows kidney cystic progression in a murine model of ADPKD.

Methods: We hypothesized that curcumin supplementation would reduce vascular dysfunction (brachial arterial flow-mediated dilation [FMD]) and aortic pulse-wave velocity (aPWV) in children and young adults with ADPKD. In a prospective, randomized, controlled, double-blind trial, n=68 participants 6-25 years of age with ADPKD and an estimated glomerular filtration rate >80 mL/min/1.73 m² were randomized to either curcumin supplementation (25 mg/kg body weight/day) or placebo administered in powder form for 12 months. We also assessed change in circulating and urine biomarkers of oxidative stress/inflammation and kidney function (height-adjusted total kidney volume [htTKV], exploratory endpoint) by magnetic resonance imaging. In a subgroup of participants ≥18 years, we also assessed vascular oxidative stress as the change in FMD at an acute infusion of ascorbic acid.

Results: Fifty-seven participants completed the trial. Participants were 18.5 (means ± SD) years, 55% female, and 85% non-Hispanic White. The co-primary endpoint, FMD (%,), did not change in the curcumin group (baseline: 9.4 ± 4.1; 12-months: 10.6 ± 3.9), as compared to the placebo group (baseline: 8.9 ± 4.0; 12-months: 9.3 ± 4.5; p=0.007) and did not change in the other co-primary endpoint, aPWV (cm/sec) (baseline: 51.7 ± 106; 12-months: 517 ± 18; placebo: baseline: 51.8 ± 82 cm/sec 12-months: 525 ± 95 cm/sec; p=0.53). There was no curcumin specific reduction in vascular oxidative stress, nor any changes in mechanistic biomarkers. htTKV also did not change over the 12-month study with curcumin administration as compared to placebo.

Conclusions: Curcumin supplementation does not reduce vascular dysfunction or slow kidney growth in children/young adults with ADPKD.

Funding: NIDDK Support, Commercial Support - Verdure Sciences (study drug), Private Foundation Support

PO1261
Polycystic Kidney Disease Associates with Increased Myopia and Retinal Breaks

Background: Ophthalmologic manifestations in Polycystic Kidney Disease (PKD) are not known.

Methods: We conducted a retrospective cohort study using EMR data extraction. All adult patients with polycystic kidney disease (“PKD”) and CKD from another cause (“non-PKD/CKD”), seen at our center between 1/1/2000-4/30/2020, and Eye disorders of interest in these 2 cohorts were identified using ICD-9/10 diagnostic codes. The date of the first visit to Nephrology clinic was regarded as “Index date”. The prevalence of Eye disorders at the index date was compared between “PKD” and “non-PKD CKD” cohorts.

Results: A total of 859 patients with “PKD” and 8309 patients with “non-PKD/CKD” were included. Majority of patients in both groups were male (58% [498] and 54% [4457]) and identified as White (88% [758] and 86% [7185]). At the index date, PKD patients were younger (mean age 55 vs 60 years in non-PKD/CKD; p<0.01) and had shorter follow up time (median 901 vs 1311 days; p<0.01). PKD patients had higher eGFR (52 [31-81]; N=795) vs 43 ml/min/1.73m² [29-59; N=7342]; p<0.01) and had shorter follow up time (median 901 vs 1311 days; p<0.01). Myopia and all Retinal breaks (with or without detachment) were found to be higher in PKD as compared to non-PKD/CKD after multivariable adjustment for age, gender, race, diabetes and follow up time (adjusted odds ratio 1.4 [95% CI: 1.1-1.7] and 1.7 [1-2.8]; respectively; p<0.01). Retinal breaks with detachments by themselves were also more frequent in PKD but did not reach statistical significance (Table). Peripheral retinal degeneration was similar between the two groups.

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PO126

TSC2 Loss-of-Heterozygosity Mutations Drive Cystogenesis in Kidney Organoids Generated from Tuberous Sclerosis Complex Patient-Derived Induced Pluripotent Stem Cells

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Background: Kidney cysts are the second most common renal manifestation of TSC, accounting for 50% of kidney lesions. The genetic mechanisms driving TSC-associated cystic kidney disease remain poorly understood.

Methods: We induced nephric differentiation of a series of TSC patient-derived iPSCs into 3D cystic models. All TSC2 hiPSCs developed cystic structures in ~0.5 cysts/well for +/+ and ~4.7 cysts/well for −/− organoids. Of note, 2-D cyst-like structures developed in a spontaneous manner, that is without addition of cAMP as TSC2 containing podocytes expressing podocalyxin 1 (PODXL). By Day-21 of differentiation, organoids sequentially segmented into distal tubules expressing cadherin 1 (CDH1), proximal tubules and glomerular components.

Results: Analysis of Day-21 two-dimensioinal cell cultures showed that nephrons derived from TSC2−/− and TSC2−/− hiPSCs presented normal morphology, and were sequentially segmented into distal tubules expressing cadherin 1 (CDH1), proximal tubules containing brush borders labeled by lotus tetragonolobus lectin (LTL) and glomeruli containing podocytes expressing podocalyxin 1 (PODXL). By Day-21 of differentiation TSC2−/− hiPSC-derived kidney tissues showed cavitated structures resembling cysts. Analysis of nephron segments showed positive signal for both CDH1 and LTL, indicating the cyst lining could comprise distal tubule and/or proximal tubule cells. The observed frequency of cyst formation was ~4.7 cysts/well for TSC2+/- +/+ cultures, compared with 0 cysts/well for TSC2−/− −/− organoids also showed that while individual tubule segments were involved in cyst lining, in certain cases a combination of both proximal and distal tubule cells were detected, suggesting improper segmentation mechanisms in the absence of TSC2. While single-cell lining layers were associated with well-defined tubule segments, mixed-cell lining regions were multi-layered, resembling the columnar epithelium observed in the renal cysts of TSC patients.

Conclusion: TSC2 organoids provided evidence supporting LOH events accounting for 50% of kidney lesions. The genetic mechanisms driving TSC-associated kidney disease remain poorly understood.

Funding: NIDDK Support

PO1265

A Combination Therapy with Two Dietary Supplements Acting on Different Mechanisms Ameliorates Disease Progression in a Rat Model of Polycystic Kidney Disease

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Background: Nephropathies-related cystopathies (NPHP-RC) are a group of autosomal recessive kidney diseases that are characterized by renal cysts, tubulointerstitial fibrosis and basement membrane disruptions. Mutations in ankyrin repeat and sterile alpha motif domain containing 6 (ANKS6) gene were recently identified as causing nephropathies in mice type 16 (NPHP16) in humans. Although, several mouse models with Anks6 mutations have been reported, its function in the kidney remains incompletely understood. In order to investigate the disease mechanisms of nephropathies in the function of Anks6 in kidneys we deleted Anks6 expression in the nephron progenitor population using the S6Cre transgenic mouse line.

Methods: Six2Cre transgenic mice were crossed with Anks6fl/fl mice to generate Six2Cre:Anks6fl/− mice. Gross morphological characterization and tissue histological analysis of mutant mice was performed on E15.5, E18.5 and P1 kidneys. Cysts were embedded in paraffin and sectioned at 5μm for histological staining with hematoxylin and eosin. Immunofluorescence (IF) staining was performed to label neprhenoid segment and glomerular components. Anks6 expression in the kidney was examined using X-gal staining. ANKS6 role in epithelial cell polarity was investigated using a squashed assay after 4X36 sRNAi knockdown in IMCD3 cells.

Results: Six2Cre:Anks6fl/− mice die at birth due to kidney failure. Anks6 expression was ubiquitous in the developing kidney. Histological analysis revealed that deletion of Anks6 in nephron progenitors leads to proximal tubule morphogenesis defects and glomerular hyperplasia. Inactivation of the glomeruli showed reduced recruitment of mesangial cells and decreased podocyte numbers in mutant kidneys. Proximal tubule development was similarly arrested at an early tubular morphogenesis stage resulting in short straight tubules. Knock down of ANKS6 in cell culture resulted in polarization and loss of epithelial phenotype.

Conclusions: Our data demonstrate that Anks6 is required for proximal tubule morphogenesis and glomerular development. Deletion of Anks6 in nephron progenitors leads to severe kidney morphogenesis defects that are incompatible with life. Spheroid analysis revealed that ANKS6 has an important role in epithelial polarity and lumen formation. Future work will address which morphogenic pathway(s) are regulated by Anks6 during nephrogenesis.

Funding: NIDDK Support

PO1264

The Impact of Salt Deficiency on Acid-Base Homeostasis in Autosomal Recessive Polycystic Kidney Disease

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Background: In healthy subjects, dietary salt restriction exacerbates imbalances of acid-base homeostasis. The disease progression of autosomal dominant PKD is associated with increasing serum bicarbonate levels and metabolic acidosis, however very little is known about acid-base imbalance in autosomal recessive (AR) PKD, particularly, in response to dietary restrictions. Here we hypothesized that a salt-deficient (SD) diet leads to electrolytic and acid-base imbalance in ARPKD.

Methods: Male and female PCK/CrljCrjPhdlpc1/crl (PCK) rats were fed a SD (0.01% NaCl, Deyts Inc) diet for 1, 3, 5, 7 and 9 weeks beginning at 4 weeks of age. Before each endpoint, urine was collected, and plasma and tissue samples were harvested. Plasma and urinary creatinine, electrolytes, BUN, and plasma aldosterone levels were measured. Cystic index was analyzed with ImageJ. Statistical analysis was performed with 2-way ANOVA.

Results: Two-kidney-to-body-weight, weight consumption, plasma K+ and urine output decreased over the course of the SD diet in both sexes. Plasma Na+ and Cl- as well as creatinine increased; and BUN did not change. Plasma aldosterone increased from week 1 to week 5 (week 1: 2.6±1.5 mg/mL (M) and 7.7±1.1 (F), p<0.001 (over time)), followed by a return to baseline by week 9 of the SD diet. The frequency of cyst formation was significant in cystogenesis in female rats from week 1 to week 9 of the SD diet (week 1: 142.4±1.9%, week 9: 36.3±2.4%). Further, we observed an increase in plasma pH (week 1: 6.98±0.08 (M) and 6.83±0.03 (F), week 5: 7.16±0.08 (M) and 7.13±0.02 (F), p<0.001 (over time)) and a decline in urine pH (week 1: 7.69±0.42 (M) and 8.75±0.08 (F), week 9: 5.80±0.07 (M) and 5.72±0.08 (F), p<0.001 (over time)) in both sexes throughout the dietary challenge.

Conclusions: PKC rats on a SD diet exhibit acidification of urine pH and an increase in plasma pH. We can speculate that acid base transporters such as NHE1, NBCe2, and pendrin are upregulated to conserve plasma sodium leading to a shift in acid-base homeostasis. Further studies aimed at elucidating the role of these transporters may add to the current knowledge regarding the pathogenesis and dietary management of ARPKD.

Funding: NIDDK Support, Other NIH Support - NHLBI R01 HL148814; NIDDK R08 DK105360, NIH T35 DK074731

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are widely available and classified as safe dietary supplements. These results suggest that a combination of widely available and generally safe diet supplements, when appropriately formulated, demonstrate high promise for supporting kidney health in PKD. **Funding:** Other NIH Support - NIH 1 R01 DK109563-01A1, Private Foundation Support

**PO1266**

A Single-Center Experience of ARPKD in Adults

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**Background:** Autosomal recessive polycystic kidney disease (ARPKD) is an inherited cystic disorder with presentation in infancy or early childhood. ARPKD has an incidence of 1-2/10,000 live births and arises from biallelic variants in PKHD1 encoding for fibrocytin, with variants in DZIP1 accounting for <1% cases. Imaging findings include large echogenic kidneys, poor corticomedullary differentiation, renal cysts or “salt and pepper appearance”. ARPKD-congenital hepatic fibrosis (ARPKD-CHF) complex consists of renal disease with biliary dilatation portal hypertension and splenomegaly. 50% develop ERSD in childhood with limited data on renal prognosis for those that present later.

**Methods:** A retrospective chart review of patients >16 yr of age with cystic kidney disease and/or congenital hepatic fibrosis to identify possible cases of ARPKD. Clinical phenotype (compatible hepato-biliary and renal involvement) and/or genetic testing were used to verify the diagnosis.

**Results:** We identified 29 patients with ARPKD-CHF, out of which 13 were >16 yr (mean 32.4±8 yr). 38% were males, 15% identified as Hispanic and the rest as non-Hispanic white. All had radiographic evidence of renal and/or hepato-biliary involvement and of 5 and 13 patients had biallelic variants in PKHD1. On the most recent imaging study, 92% had renal cysts, 23% large echogenic kidneys, 23% poor renal corticomedullary differentiation, 15% medullary sponge kidney, 23% with salt and pepper pattern. Only 3 (3%) had reached ESRD or received a kidney transplant, while the remaining had a mean eGFR of 46ml/min/1.73m2. Of these, 50% had eGFR >40ml/min/1.73m2. Amongst those with hepato-biliary involvement, 40% had CHF, 53% portal hypertension, 40% splenomegaly, 26% liver cysts.

**Conclusions:** We describe a cohort of patients with ARPKD, the majority presenting as adults, with an eGFR >60ml/min/1.73m2. A significant number of these patients had multiple large renal cysts. Absence of obvious renal phenotype in patients with congenital hepatic fibrosis can make the diagnosis challenging, requiring a high degree of clinical suspicion. We believe that we may have missed a significant number of patients without obvious combined hepatic and renal abnormalities who may have had delayed onset ARPKD. Our small series suggest that some patients with ARPKD present as adults with a more limited phenotype that can easily be mistaken for ADPKD.

**PO1267**

Analysis of Somatic Mosaic Mutations in Nephropathy-Associated Genes Reveal Candidate Disease-Causing Mutations in Previously Germ-line-Negative Cases


**Background:** Somatic mosaic variant (SMV) arises due to postzygotic mutations that results in two genetically distinct populations of cells in the same person. SMVs may be missed by standard search for germline (or inherited) mutations, and the use of dedicated analytic pipelines for SMVs can potentially explain “exome negative” cases.

**Methods:** We searched for SMVs in 248 patients who underwent exome sequencing for congenital kidney anomalies. Somatic mutations were identified through GATK Mutect2 software, and clinically annotated following the American College of Medical Genetics and Genomics (ACMG) guidelines. We focused the analysis on 625 nephropathy-associated genes previously used for the germline analysis.

**Results:** Previous analyses germline variants had identified 52 diagnostic variants in this cohort (20.9% diagnostic rate). In addition, the SMV pipeline identified candidate disease-related SMVs in 4 “exome-negative” patients (1.6% of cases). The SMVs were detected in RET, ENG and COL4A5, and are reported in Table 1. This improved the diagnostic rate of the cohort to 22.5%.

**Conclusions:** Analysis of somatic mosaic variants can increase diagnostic yield in patients with congenital kidney anomalies. Application of the SMV pipeline may increase diagnostic in other forms of kidney disease.

**SVM identified in congenital anomalies kidney patients**

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<td>p.Glu1614Val</td>
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**PO1268**

Comparison of Imaging Approaches for Quantifying Total Kidney Volume (TKV) and Fibrosis in a Mouse Model of Polycystic Kidney Disease (PKD)

Carien R. Sussman, Heather L. Holmes, Ka Thao, Adriana Gregory, Ryan J. Meloche, Yaman G. Mkhairmer, Harrison H. Wels, Slobodan Macura, Peter C. Harris, Timothy L. Kline, Michael T. Romero. Mayo Foundation for Medical Education and Research, Rochester, MN.

**Background:** 3D imaging and histology are critical tools for assessing PKD in patients and animal models. Magnetic resonance (MR) imaging provides an resolution, but is time consuming, expensive, and access to equipment and expertise is limiting. Robotic ultrasonic (US) imaging is lower resolution but fast. Similarly, picrosirius red (PR) staining and standard light microscopy is used to assess fibrosis; however, alternative methods for quantifying PR staining have been shown in other tissues to allow greater sensitivity and more detailed characterization.

**Methods:** Pkd1<sup>−/−</sup> mice were compared to Pkd1<sup>−/−</sup> (WT). TKV was quantified from US and MRI (7T and 16T) at 1, 3, and 4 months old. US measurements of kidney and heart volume were performed using the Vevo and EchoPlex image analysis software. Inter-observer variation for quantifying fibrosis using US was assessed using Bland-Altman analysis. PR-stained kidneys were imaged using standard light microscopy, circularly (c) polarized light with binning into four categories of collagen thickness, and fluorescent imaging with analysis using eFire. Renal cAMP and BUN were measured using standard approaches, and GFR was measured using a transdermal fluorescent sensor (MediBead).

**Results:** US detected increased TKV at 1 month and was similar to MR (7T or 16T). Inter-observer variability (2 observers) was greater for US than MR, but still able to detect differences between genotypes and time points. US allowed scanning in 2-5 minutes/mouse while MR required 20-30 minutes. Cylindrical light showed a greater percentage of the thickest collagen fibers in RC/RC mice, and a corresponding lower percentage of each of 3 categories of thinner collagen fibers. Preliminary data using fluorescence microscopy showed a higher density of collagen fibers in RC/RC mice vs. WT. Analysis of collagen fiber angle, length, straightness, and width is ongoing. RC/RC had a lower GFR, higher BUN, and elevated cAMP vs WT. No differences were observed in cardiac function (ejection fraction, heart rate, or cardiac output).

**Conclusions:** These studies demonstrate the utility of US and alternative approaches of quantifying fibrosis using PR.

**Funding:** NIDDK Support

**PO1269**

Phenotypic Heterogeneity in Type IV Collagen-Associated Nephropathy: The Cystic Phenotype

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**Background:** Exome sequencing (ES) revealed mutations (mut) in type IV collagen (COL4) genes in patients (pt) diagnosed with other forms of chronic kidney disease (CKD), supporting the concept of spectrum of phenotypes for COL4-Nephropathy. Unexpectedly, some pt with CKD presenting with cystic phenotype were identified with COL4-Nephropathy by ES.

**Objectives:** The retrospective study included 130 pt referred to outpatient clinic of genetic kidney diseases of ASST Speziali Civili di Brescia from 2002 to 2021 and diagnosed with COL4-Nephropathy. Based on the presence of multiple and bilateral renal cysts on imaging (fig1), a group of pt with cystic phenotype was selected (27/130,21%).

**Methods:** The study contributes to expand the emerging phenotypic heterogeneity of COL4-Nephropathy and suggests that cystic phenotype could predict progression of kidney disease.
Rare Variants in Syndromic Ciliopathy Genes as Novel Causes of Isolated Renal Disease in Adults

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Background: Renal ciliopathies are among the commonest genetic causes of end-stage renal disease (ESRD). Ciliopathies are caused by defects of the primary cilium, an antenna-like organelle with mechanosensory roles, crucial for organ development and maintenance. Disorders of the cilium present early with multi-organ involvement, but some individuals present as adults with organ-specific phenotypes, potentially due to milder mutations and organ-specific effects.

Methods: We identified rare variants in two ciliopathy genes in two unrelated adults presenting with ESRD. ACMG guidelines did not classify these variants as pathogenic, requiring functional validation to establish a causal genotype-phenotype relationship.

Results: Bi-allelic CC2D3 missense variants were identified in a patient with ESRD, suggestive of an isolated renal ciliopathy. CC2D3 is essential for ciliogenesis, with complete loss of cilia in knockout mice (Development 135:4049 2008). Severe mutations were reported in patients with a syndromic ciliopathy (OPD XIV; OMIM# 615948), but no cases of isolated renal disease have been reported. We detected a moderate but consistent shortened cilia length in skin fibroblasts and renal epithelial cells from our proband, suggestive of a milder ciliary defect. Remarkably, the proportion of ciliated cells was significantly reduced in renal epithelial cells but not in fibroblasts, indicating an organ-specific ciliogenesis defect. Pathogenic variants in CC2D2A cause Joubert and Meckel syndrome, with no isolated renal presentations observed to date (Mol. Genet. Genom. e1603 2021). We identified a novel homozygous nonsense variant (Arg34*) in CC2D2A, classified as not pathogenic due to an alternate start-codon, in a previously healthy 37-year-old male with isolated ESRD of unknown etiology. Using public data (GTEx), we show that protein-coding transcripts harbouring this variant are the predominant transcripts in the kidney when compared to tissues relevant to CC2D2A-related phenotypes (e.g., cerebellum, liver).

Conclusions: Rare variants in known syndromic ciliopathy genes cause isolated renal disease in adults due to potential organ-specific effects. Using variant classification schemes without functional analysis may not accurately capture the genetic contribution to adult ESRD.

Funding: Government Support - Non-U.S.

Targeted Exome Sequencing Application for Genetic Diagnosis of Pediatric Patients with Cystic Kidney Disease

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Background: Detection of a monogenic cause of chronic kidney disease accounts for almost 30% of cases in the pediatric cohort. Of these, the highest yield in the genetic diagnosis is currently seen in cystic kidney disease. Nearly 100 monogenic causes of renal cystic ciliopathies have been identified and the genetic diagnostic yield is reported to be approximately 50%. Here, we report the results of genetic testing in a cohort of Korean pediatric patients with cystic kidney disease.

Methods: From July 2019 to February 2021, children under the age of 18 with three or more cysts in both kidneys on imaging studies were recruited from three pediatric nephrology centers in Korea. Genetic identification was performed by targeted exome sequencing (TES) including 89 genes known as cystogenesis-related or causative-ciliopathy.

Results: A total of 46 pediatric patients with cystic kidney disease were recruited. The median age was 9.2 years (IQR, 5.49-14.53) and 60% were boys. Twelve patients (27.9%) had a family history of cystic kidney disease. The clinical diagnoses of the patients were 10 patients with autosomal dominant polycystic kidney disease, 5 patients with autosomal recessive polycystic kidney disease, 2 patients with multicystic dysplastic kidney, 1 patient with nephronophthisis, and the others were undiagnosed. The mutation detection rate was 52.2% (24 of 46). PKD1 was the most common causative gene (16 patients, 34.8%), followed by HNF1B (3 patients), PAZ2 (2 patients), PKD2 (1 patient), PKD1D1 (1 patient), and NPHP3 (1 patient). Genetic mutations were identified in all patients (12 of 12) with a family history of cystic kidney disease. In patients without a family history, genetic mutations were found in 35.3% (12 of 34).

Conclusions: The mutation detection rate in this cohort of Korean pediatric patients with cystic kidney disease was 52.2% by TES. Mutations in PKD1 were found most commonly, and the mutation detection rate was higher in patients with a family history of cystic kidney disease. For children with cystic kidney disease, molecular genetic testing is essential for an accurate diagnosis, personalized treatment, and prognosis prediction.

Funding: NIDDK Support

The Prognostic Factors of Cyst Infection due to ADPKD

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Background: Renal or hepatic cyst infection is a complication of autosomal dominant polycystic kidney disease (ADPKD), which requires hospitalization and causes death. Cyst aspiration was the gold standard to diagnose this disease. Because of its invasiveness, several diagnostic criteria without using cyst aspiration have been proposed, but prognostic factors of cyst infection have not been analyzed in this setting.

Methods: Inclusion criteria of this retrospective cohort are ADPKD patients who were admitted in Toranomon hospital and Toranomon hospital Kajigaya between 2016 April and 2021 March, and who were diagnosed as cyst infection based on MRI findings, which we previously published. Primary composite endpoint was defined combination of death, septic shock, or hospitalization for more than four weeks, and secondary outcomes were defined by each outcome mentioned above. Logistic analysis was planned to assess the predictors of the outcomes.

Results: One hundred ninety patients were eligible to this study. The average age was 65.0±9.2 years old, 116 (61.1%) were female, and the average height-adjusted total liver volume (htTLV) was 3322±2286 mL per meter, and 164 (86.3%) had hemodialysis therapy. Compositive outcome occurred in 109 (57.4%): 25 death, 36 shock, and 98 longer-hospital-stay. Multivariable logistic regression model after adjusted related variables showed that older age (odds ratio(OR) 1.10 (95% confidence interval: 1.10-2.54), p-value=0.02), male (OR 2.49(1.66-3.53), p-value=0.02), higher htTLV (OR 2.29 (3.39-3.77), p<0.01), lower mean blood pressure at admission (OR 0.735(0.579-0.9319), p<0.01), larger size of infectious cyst (OR 1.42(1.06-1.91), p<0.02) were significantly associated with the composite outcome. Although the culture-positive case or higher white blood cell count were not significantly associated with the primary outcome, they were associated with septic shock due to cyst infection.

Conclusions: Baseline characteristics at admission were associated with the prognosis of cyst infection diagnosed by MRI-based criteria, which was similar to cyst infection diagnosed by cyst aspiration. Culture-positive case or higher white cell count were reported as risk factors requiring more invasive therapies that could lead to septic shock and need longer hospitalization in our study’s cohort.
Uncovering the Role of the Extracellular Matrix in ADPKD Progression

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Background: Polycystic Kidney Disease (PKD) is a genetic disorder due to mutation in either Pkd1 or Pkd2 genes and characterized by bilateral cysts formation. We recently uncovered a direct role of Pkdc1, the protein product of Pkd1 gene as a mechanismosensor of extracellular stiffness. We found that Pkdc1 interacts mediator inhibition of actomyosin contraction that mediates the cellular response to the rigidity of the Extracellular Matrix (ECM). Based on these findings we speculated that Pkd1 cells fail to properly respond to the extracellular mechanical force of ECM leading to excessive matrix deposition and proliferation. In line with this, kidneys of end-stage PKD patients show enhanced fibrosis typical of cystic kidney disease and tumors. We then wondered whether PKD ECM is a part of an active Cyst Microenvironment (CME), exerting a key role in the evolution of the disease.

Methods: We characterized CME in the renal tissue of an aggressive Pkd1Δcre/+; Ksp-Cre and a low aggressive Pkd1Δcre/+; Tam-Cre inducible mouse models. To study the composition and the mechanical properties of the cystic ECM we decellularized cystic kidneys obtaining ECM-derived kidney scaffolds. Furthermore, we isolated matrix from Pkd1Δcre/+ fibroblasts in vitro.

Results: We have characterized the renal tissue microenvironment of two Pkd1 inducible mouse models at a late stage of the disease confirming the presence of fibrosis, immune infiltrates and progressive accumulation of collagen I. In line with an active role of PKD ECM, we showed that ECM-derived kidney scaffolds were able to stimulate pro-inflammatory cytokine expression in PKD fibroblasts in vitro.

Conclusions: ECM plays an active role in the progression of ADPKD disease.

PO1276

Abstract Withdrawn

PO1277

17q12 Deletion Syndrome Presenting as Congenital Diaphragmatic Hernia in a 2-Month-Old Infant


Introduction: 17q12 deletion syndrome results from the loss of as many as 15 genes on the long arm of chromosome 17 including the hepatocyte nuclear factor-I-beta gene (HNF1B). Heterozygous pathogenic variants, whole gene deletion, or duplication in HNF1B are frequently linked to inherited kidney malformations including hyperechoic kidneys, kidney cysts, solitary kidney, and hydrenephrosis as well as extrarenal phenotypic features. 17q12 deletion syndrome has also been linked to congenital diaphragmatic hernia (CDH). We present a case of an infant with hyperechoic and cystic kidneys, diagnosed postnatally with CDH.

Case Description: A 2-month-old female with a history of hyperechoic kidneys on prenatal ultrasound presented to the emergency department with increased work of breathing. A chest x-ray revealed left hemidiaphragm elevation, normal cardiac silhouette, and no focal pulmonary consolidation. Computed tomography of the chest confirmed the diagnosis of CDH. A repeat kidney ultrasound revealed diffuse hypechogenic kidneys and a focal kidney cyst within the right upper pole (Image 1). Genetic workup revealed a 1.9 megabase deletion on the long arm of chromosome 17 consistent with the diagnosis of 17q12 deletion syndrome.

Discussion: Pathogenic variants in HNF1B or whole gene deletion as part of 17q12 deletion syndrome should be considered in infants with hyperechoic kidneys with cysts, particularly in the context of extrarenal manifestations. Studies have examined the link between HNF1B and the development of a CDH. It is proposed that HNF1B is involved in the WNT signaling pathway that is critical to mesodermal differentiation and proper diaphragm formation. Only 4 other cases of HNF1B mutations associated with CDH are reported in the literature. Two cases describe HNF1B deletions, and 2 cases describe HNF1B duplications. It is possible that the high prenatal mortality of CDH could explain the paucity of this association.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

410
PO1278

Recurrent Pneumothorax in a Marfanoid Adolescent with Autosomal Dominant Polycystic Kidney Disease

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Introduction: Pneumothorax may be a rare extra-renal manifestation of autosomal dominant polycystic kidney disease (ADPKD), and may indicate co-inheritance of other genetic diseases.

Case Description: A 21 year-old man with ADPKD and pneumothoraces presented to nephrology clinic. A screening ultrasound in late childhood was completed due to his family history and confirmed ADPKD. The patient was normotensive and had a tall, thin habitus. His musculoskeletal examination was pertinent for several marfanoid findings, including increased arm span ratios, pes planus, and positive thumb and wrist signs. His eGFR was normal and he did not have proteinuria. He was hospitalized several times between ages 13-20 for recurrent pneumothoraces requiring left apical wedge and lower lobe resections with pleurectomy, and right upper lobectomy and pleurectomy.

Discussion: The patient’s lung collapse was attributed to primary spontaneous pneumothorax due to his tall stature and intermittent tobacco use. However, this cannot account for his high rate of recurrence. The extent of pneumothorax burden in this patient should be considered in context of his underlying polycystic renal disease. Pulmonary manifestations of ADPKD are not well understood and have only been described in a handful of case reports. Bronchiectasis and cystic lung disease are thought to occur as a downstream consequence of impaired parenchymal healing. Mutated polycystin-1 in ADPKD prevents normal ciliary function, which is imperative for coordination of cellular repair in bronchial smooth muscle cells. Evolving cystic lung disease in the setting of underlying ADPKD could explain this patient’s recurrent pneumothoraces. The possibility of a co-inherited connective tissue disease should also be considered in patients with ADPKD and pneumothoraces. “Overlap” disorders between ADPKD, Marfan syndrome and Tuberous Sclerosis (TSC) have been examined in linkage studies, and have chromosomal proximity. Marfan syndrome and TSC are associated with pneumothorax. Though our patient did not manifest criteria for TSC, his examination is consistent with a Marfan’s variant phenotype. This patient may be an example of co-inherited disease, and raises the question of whether it is under this circumstance that rare pulmonary complications become apparent. Clinicians should be aware of these overlap disorders in relation to ADPKD.

PO1279

Ruptured Intracranial Aneurysm as the Initial Presentation of ADPKD in a Pediatric Patient

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Introduction: Autosomal dominant polycystic kidney disease (ADPKD) is associated with multiple extra-renal manifestations, most notably intracranial aneurysms (ICA). Approximately 10% of ADPKD patients develop ICA during their lifetime. Subarachnoid hemorrhage (SAH) is a major complication of ICA and usually occurs during the end of the 3rd decade. Aneurysm rupture in children <18 years of age is extremely rare. We report a case of a 9-year-old boy presenting with symptomatic ICA rupture as the initial presentation of ADPKD, despite a negative family history of ICA.

Case Description: A 9-year-old boy presented to the emergency department with an abrupt onset of severe headache and lethargy after a fall. His family history was remarkable for ADPKD in his father and grandfather. None of his affected family members developed ICA or intracranial hemorrhage. Initial non-contrast computed tomography scan of the head showed frontal lobe hemorrhage. Additional imaging studies revealed a ruptured anterior communicating artery with SAH. Urgent aneurysm coiling was performed, his bleeding was controlled, and the patient survived. Due to his strong family history for ADPKD, a kidney ultrasound was performed and showed enlarged kidneys with multiple renal cysts bilaterally confirming the diagnosis of ADPKD. The patient’s father underwent a screening MRI of the brain at the age of 48 years and was negative for ICA.

Discussion: Our case of SAH due to ICA rupture as the initial presentation of ADPKD, in the absence of a positive family history of ICA or hemorrhage, has not been reported in children. Rare cases of subarachnoid hemorrhage in pediatric patients with ADPKD and a positive family history of ICA or hemorrhage have been described. Based upon available data, it is unclear if either widespread or targeted screening for intracranial aneurysms is beneficial for pediatric patients with ADPKD. Screening is reserved for patients with a family history of hemorrhage, migraine, stroke, patients undergoing major surgery, or patients with high-risk jobs. However, we do not screen children <18 years of age because of the extreme rarity of aneurysmal rupture at that age. Though extremely rare, when care physicians and pediatricians should stay aware that ICA rupture occurs in children with ADPKD and can lead to devastating complications, even in the absence of positive family history.

PO1280

Congenital Solitary Kidney in ADPKD: A Genotype-Phenotype Correlation

Romina Bucci, Marta Vespa, Maria Teresa Sciarrebone Alibrandi, Giancarlo Joli, Giulia Mancassola, Giuseppe Vezzoli, Paolo Munanta. IRCCS Ospedale San Raffaele, Milano, Italy.

Introduction: There are a very few cases of ADPKD associated with Unilateral Renal Agenesis (URA). The total amount is currently 9 cases known in the world and their renal function outcome is somewhat undefined.

Case Description: ZG is a pleasant 41-year-old man with a congenital solitary left kidney with multiple cysts and a genetic diagnosis of ADPKD. Familiarity is negative for ADPKD, but positive for URA (present in his sister and her son). Except for hypertension, there are no extrarenal ADPKD manifestations. Poster et al. analyzed 3 patients with a similar phenotype in a cohort of 182 ADPKD subjects, comparing how the volume of the single kidney increased (SKV) over time and how the GFR dropped, stratifying them for sex and age. A greater SKV in time has been recorded in these 3 patients, caused by both compensatory hypertrophy and cyst growth. Surprisingly though, their kidney function was better compared to controls. Late onset kidney failure is probably caused by hyperfiltration, and it is linked with a long-term worse outcome. In our case, ZG’s SKV increased less compared to another subject with same age and sex and with controls found in literature. Same goes for kidney function, which was better and more stable in a 10-year time-lapse compared to controls.

Discussion: The reason for this could be found in the PKD1 mutation: ZG has a missense mutation, while the aforementioned 3 cases had truncating ones. ZG’s increased SKV is probably more related to hypertrophy than cyst growth itself. Therefore, even in an unorthodox situation like this one, long-term outcome seems to depend on the genotype of the subject.

Note: Table shows values of SKV for patient ZG and patient with polycystic solitary kidney. For the matched 2-kidney ADPKD group is reported the SKV mean values with 95% CI. For this last group the volume given is that of the left kidney present in the other 2 cases. SKV is calculated from MRN scans. Creatinine clearance is estimated according to the Cockcroft-Gault formula. In the 2-kidney ADPKD group CCC is estimated by calculating both kidneys.

PO1281

Management of a Patient with ADPKD Who Needs Lithium

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Introduction: N/A

Case Description: A 35-year-old female with borderline personality disorder and schizoaffective disorder presented to nephrology for autosomal dominant polycystic kidney disease (ADPKD). Her biological father had ADPKD and was on dialysis at the time of death. The patient has taken lithium for 10 years, and only lithium allows her to work and live independently. She presented with polydipsia and polyuria, indicating possible nephrogenic diabetes insipidus (DI) from lithium, essential hypertension since age 30, and constant headache; brain MRI was negative for aneurysm. Labs showed a lithium level between 0.3-0.9 mmol/L, creatinine between 0.6-0.75 mg/dL, eGFR of 85-90 ml/min, urine protein:creatinine ratio of 0.27-0.32 g/g, and urine osmolality <100 mOsmol/kg.

She was treated with 2.5 mg lithium, 10 mg amiloride, and 1350 mg lithium daily. Abdominal MRI without contrast showed scattered liver cysts and innumerable bilateral kidney cysts. Kidney volume indicated Mayo Class 1C PKD. Her father developed ESRD in his late 50s, suggesting rapidly progressive ADPKD class. Lithium nephropathy is typically characterized by 1-2 mm renal microcysts (Khan et al., Int J Psychiatr Med 50(3):290-298). The patient’s larger cysts, total kidney volume, and liver cysts suggest ADPKD. Genetic testing showed that the patient has a heterozygous mutation in c.12445+1G>T, expected to cause altered splicing and function of the PKD1 gene.
**Discussion:** Finding an appropriate agent to slow CKD progression is the current strategy to manage PKD. Her condition is complicated by likely lithium nephropathy. The TEMPO trial (Torres et al, N Engl J Med 367:2407–2418, 2012) showed that tolvaptan helps slow rapidly progressive ADPKD by inhibiting vasopressin’s effect, reducing cAMP production, further inhibiting cyst formation and growth (Wang X et al, J Am Soc Nephrol 19: 102–108, 2008; Aihara M et al, J Pharmacol Exp Ther 349: 258–267, 2014). Lithium can also inhibit vasopressin in the kidney, leading to nephrogenic DI (Bokenhauer et al, Nat Rev Nephrol11(10):576-88, 2015). In ADPKD, tolvaptan helps achieve a urine osmolality of less than 300 mOsmol/kg (Torres, Clin J Am Soc Nephrol. 13(11):1765-1776, 2018). Our patient already has polyuria and urine osmolality below 100 mOsmol/kg. Her condition requires agents targeting other pathways. For now, she is on lisinopril, with BP <110/75, and amiloride to limit polyuria.

**PO1282**

**A Case of Mistaken Identity: Alport Syndrome Masquerading as Polycystic Kidney Disease**

**Kana R. Amari, Jennifer A. Tuazon. Northwestern University Feinberg School of Medicine, Chicago, IL.**

**Introduction:** Alport Syndrome (AS) is an inherited nephritis caused by a collagen-IV-related mutation leading to abnormalities in the glomerular basement membrane. Patients may present with unexplained hematuria, proteinuria, with or without renal insufficiency. Here, we describe two cases of patients presenting with multiple bilateral renal cysts, initially diagnosed with autosomal dominant polycystic kidney disease (ADPKD), and who were later found to have Alport syndrome via genetic testing.

**Case Description:** We report two cases of patients followed in our nephrology clinic who were initially thought to have ADPKD. The first patient is a 75-year-old woman who was followed for long-standing hematuria, CKD3aA2, innumerable bilateral renal cysts, few livers cysts, cerebral aneurysms, and a family history of cystic kidney disease. Due to normal kidney sizes, genetic testing was done which revealed a pathogenic COL4A3 mutation, c.1372G>C (p.Gly458Arg). Our second patient is a 64-year-old man with a history of hematuria, CKD3aA2, sensorineural hearing loss, retinal detachment, and family history of hematuria. His genetic testing revealed an X-linked COL4A5 mutation c.367G>C (p.Gly123Arg).

**Discussion:** Very few cases have described an association with AS and cystic kidney disease. The causal mechanism for renal cyst formation and Alport syndrome is unknown. These cases illustrate the importance of considering alternate diagnosis when suspected ADPKD has atypical features such as normal kidney sizes or kidney dysfunction more than expected for the cyst burden.

Case #1 Bilateral renal cysts in COL4A3-related Alport syndrome

**PO1283**

**Heterozygous HSD11B2 Gene Mutations and Apparent Mineralocorticoid Excess (AME) in a Patient with Heterozygous ADPKD1**

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**Introduction:** HSD11B2 gene which locates at Chromosome 16p22.1 and encodes the Type 2 isomorph of 11-beta-Hydroxysteroid Dehydrogenase that interconverts biologically active cortisol and inactive cortisone. Polycystin-1, encoded by the PKD1 gene, which locates at Chromosome 16p13.3. PKD1 gene forms a complex with polycystin-2 (PKD2) that regulates multiple signaling pathways to maintain normal renal tubular structure and function. We present a new finding of HSD11B2 gene in a patient with polycystic kidney disease.

**Case Description:** 58-year-old Chinese male presented with bilateral renal cysts and CKD Stage 3A. PMHx is significant for early onset HTN at the age of 45, Left ICH without residual weakness at the age of 46 years and episode of hypokalemia. Denied Licorice ingestion. Family history is positive for HTN and polycystic kidney disease in his mother and all three siblings. His BP was 145/91 mmHg, not controlled well with daily dose of oral Lisinopril 40 mg and Amlodipine 10 mg. His Na 141, K 4.7, CO2 27, BUN 20, Cr: 1.6, Hb 12.5 and Urine protein/creatinine ratio was 0.22. He was started with low dose of Spironolactone 12.5 mg daily for BP control and proteinuria. Renal ultrasound showed Right kidney was 19.5 cm, left kidney was 18.6 cm and presence of multiple bilateral renal cysts. Abdominal CT without contrast disclosed H1TKV: 1724 ml/m. Mayo clinic class was 1 C; estimated frequency of FRSKD at 10 years was 37.8%. Kidney gene panels detected the gene of PKD1 ( Autosomal Dominant) and HSD11B2 (Autosomal Recessive). BP stable at 125/78 mmHg, 24-hour urine protein was 125 mg per day, Serum cortisol 11 mcg/dl (normal: 8-19 mcg/dl), Serum cortisone: 0.74 mcg/dl (normal: 1.34-2.65 mcg/dl), Serum cortisone/cortisone ratio: 0.74 (normal: 3.9-11), 24 hours Urine free cortisol: 7 mcg/day (normal 5-64 mcg/day), 24 hours Urine cortisol: 31 mcg/day (normal 16-128 mcg/day), 24 hours Urine free cortisol/cortisone ratio: 0.22 after spironolactone. However, it was discontinued upon repeated serum K was at the higher side of normal. He is currently treated with oral Tolvaptan.

**Discussion:** This is an unique case which could be the first case report of HSD11B2 mutations with apparent mineralocorticoid excess associated with heterozygous ADPKD1.

**PO1284**

**A Rare Presentation of Autosomal Recessive Polycystic Kidney Disease in Adulthood**

**Katerina Hysi, Saira Sajid, James Drakakis. NYU Winthrop Hospital, Mineola, NY.**

**Introduction:** Autosomal recessive polycystic kidney disease (ARPKD) belongs to a group of congenital hepatorenal fibrocystic syndromes and causes significant renal and liver related morbidity and mortality in children. Renal cysts, congenital hepatic fibrosis, and recessive inheritance characterize ARPKD. The disorder usually manifests infancy, with a high mortality rate in the first year of life. For the patient who survives the neonatal period, the probability of being alive at age 15 ranges from 50-80%, with the majority requiring renal replacement therapy at that age. This diagnosis is rarely made in the adult years with the clinical course and prognosis much less well defined.
Case Description: 57-year-old male with PMHx of gout and long standing CKD with creatinine 1.6 mg/dL, due to developing GFR to 10 ml/min with little progression presented for evaluation. Urinalysis was without microscopic hematuria or proteinuria. Historic imaging showed small kidneys and medical renal disease. An updated MRI noted bilateral kidneys cysts with areas of atrophy and scarring, which along with an increase in in serum liver transaminases suggested chronic hepatic fibrosis, raised possibility of ARPKD. The patient subsequently underwent whole exome sequencing, which confirmed two pathogenic variants (specifically S3018F and R1624W) in the PKHD1 gene, consistent with ARPKD. His brother was eventually tested as well and found to have the same two variants.

Discussion: The classic presentation for ARPKD is systemic hypertension with progression to ESRD by the age of 15. In a typical presentation, a small number of those with ARPKD live to adulthood with some compromise of kidney function; but with significant liver dysfunction. Due to the wide phenotypic variability, the diagnosis of ARPKD may be made during any stage of childhood; in rare cases, it does not present until adolescence or adulthood. A minority of affected individuals present as older children or young adults with evidence of hepatic dysfunction or otherwise unexplained renal cysts as the prominent presenting feature. This case exhibits the silent menace of ARPKD with a delay in recognition of clinical manifestations and thus an unusually older age at the time of diagnosis.

PO1285

HDR: A Novel Mutation in GATA-3 with Variable Expressivity in an Affected Family
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Introduction: Hypoparathyroidism, deafness, and renal disease (HDR) syndrome, also known as Barakat syndrome, is a rare autosomal dominant disorder caused by heterozygous variants in GATA-3. GATA-3 belongs to a family of dual zinc finger transcription factors that is involved in embryonic development of the inner ear, kidneys, and parathyroids. The exact prevalence of HDR syndrome is unknown, but less than 200 cases have been described. The disease has variable expressivity even within the same family. Making a diagnosis can be challenging, more so in individuals with no laboratory abnormalities. Herein we describe a father-daughter dyad with HDR syndrome with variable disease expression.

Case Description: A 7-year-old female with history of congenital deafness, multicystic dysplastic kidney, reflux nephropathy, and multiple urinary tract infections underwent genetic testing. Exome sequencing revealed a heterozygous missense variant in GATA-3, a three-base change in the mRNA sequence (c.113C>T). The variant in the same sense has been reported with ARPKD syndrome. As the patient carried the same genetic variant, the father’s history was pertinent for sensorineural hearing loss diagnosed at 2 years of age with normal renal function, serum calcium, and PTH.

Discussion: Hypoparathyroidism is the most specific symptom of HDR syndrome, absent in 5-8% of affected patients. Kidney manifestations are variable and may include aplasia, hypoplasia, dysplasia, cysts, vesicoureteral reflux, hematuria, and/or proteinuria. The missense variant described in our patient has not been previously reported, although an alternative serum calcium chain has been reported with HDR syndrome. As the father had isolated deafness, he remained undiagnosed for almost 25 years, until the identification of HDR syndrome in his daughter. Screening family members is important for recognition and treatment of hypoparathyroidism and of renal disease as patients are at risk of symptomatic hypocalcemia and progressive kidney disease.

PO1286

Assessing Genomic Needs
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Background: Interventions must address nephrologists’ knowledge gaps, perceived needs, and preferences in a genomic data to provide personalized patient care. Methods: U.S. Boarded nephrologists were invited to complete an anonymous electronic needs assessment survey on genomic implementation that incorporated multiple themes e.g., objective knowledge, attitudes perceived barriers. Its design was informed by a comprehensive literature review and adapted published tools. Descriptive statistics were used to summarize demographics and baseline characteristics. Results: Between January-May 2021, 319 complete surveys were eligible for analysis by nephrologists across 47 U.S. States, (86% adult vs. 14% pediatric), with 34% community-based (vs. 66% academic) including 36% who perform transplant evaluations and 75% with prior experience ordering genetic testing; 77% responded that genetic test results have meaningful implications for a patient’s care ≤50% of cases. Community nephrologists were more likely to cite limited experience, educational resources and access to experts as perceived barriers to implementation of genomics compared to those in academic practice. Conclusions: Our findings highlight variable levels of experience and comfort using genomics and can inform the design of tailored interventions that address nephrologists’ specific needs, including education, workflow and clinical-decision support tools. Together, such tools can promote wider utilization of genomic resources and empower nephrologists to use genomic data.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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Method:

Results to Children

Background: Pediatric (ped) nephrologists care for children with genetic causes of chronic kidney disease (CKD). While genetic testing (GT) is now more accessible in nephrology, little is known about the utility, clinical application, and relevance of GT in determining underlyng CKD or other actionable secondary genetic findings for ped nephrology patients. We explored ped nephrologists' views regarding GT in clinical and research settings.

Methods: An online 30-item survey was developed and distributed via professional listserves. Inclusion criteria required self-identification as a U.S. licensed nephrologist. Data collection was from 1/22/21-5/4/20 and analyzed by STATA 15.1. Descriptive statistics are reported.

Results: 85 ped nephrologists completed the survey. Respondents range in yrs in practice (35% 6-15 yrs, 21% 16-25 yrs, 28% ≥ 25 yrs), and 75% practiced in a university hospital. Most had referred ≥ 20 patients for GT (61%). GT was considered clinically important for disease diagnosis (92%), understanding (85%), prognosis (88%), treatment options (93%), and family counseling (93%). 68% report they have reliable information for care of patient with genetic results. Top 3 challenges to GT were interpretation of results, selection of test, and ordering test. 86% identified fitting GT into practice as a challenge, and 61% report offering counseling with a genetic expert after return of genetic results. 53% felt patients could not afford GT. Most indicated the importance of having clear guidelines for GT (84%). Majority (70%) would recommend GT for family members, especially in the presence of a tailored lab report (91%). Most
are involved in the return of results in their own practice (60%). Regarding the return of research-based results, most thought diagnostic (92%) and actionable secondary findings (75%) should be returned.

**Conclusions:** Ped nephrologists report on the importance of GT in CKD. They also report on their personal challenges with GT and structural barriers to the utilization of GT.

**Funding:** NIDDK Support

**POI1288**

**Attitudes and Perceptions of APOL1 Genetic Testing in Black Patients with Hypertension: A Pilot Study**

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**Background:** A portion of the chronic kidney disease risk in Black persons appears due to polymorphisms in the gene encoding apolipoprotein L1 (APOL1). While applications of APOL1 genotyping for prognostication (e.g. in evaluation of organ donors) are emerging, the interest of Black patients in APOL1 genotyping and implications for individual kidney risk management are not well defined.

**Methods:** In this pilot study, we offered APOL1 genetic testing and assessed attitudes and concerns related to APOL1 testing and kidney risk management among Black persons seen in the Hypertension & Nephrology clinics at one urban, Midwestern center.

**Results:** Among 110 participants with genotyping results to date, 56% were women, mean age was 58 years, 72% were obese, and a mean of 3 hypertensive agents were used (Table). 13% had 2 APOL1 renal risk variants (high-risk genotypes), and 42% had 1 risk variant. At baseline, most participants (86%) reported that they were concerned about kidney disease, 90% thought it was a good idea to be tested for genes that may impact kidney disease, 82% would want APOL1 testing for their children, and only 26% expected to feel upset if they were APOL1 high risk. Most participants reported that knowledge of a high-risk APOL1 genotype would lead to changes in health-related behaviors (Figure).

**Conclusions:** Black patients at a Midwestern medical center were receptive towards APOL1 genetic testing and believed that testing would motivate changes in health-related behaviors. Ongoing research is needed to determine optimal patient-centered use of this emerging risk assessment tool.

**Funding:** Private Foundation Support

**POI1289**

**Utility of Genetic Testing in Informing Management of Patients with Kidney Disease**

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1Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Great Neck, NY; 2Natera, Inc., San Carlos, CA.

**Background:** Early identification of monogenic causes of CKD through genetic testing can improve disease treatment, inform management and improve outcomes. Genetic testing can also be useful for families with a history of CKD to plan for the future, including appropriate identification of organ donors. Here we describe the use of genetic testing, with RenasightTM, an NGS-based >380 gene panel for kidney disease, to inform treatment for patients being treated for kidney abnormalities.

**Methods:** We performed a retrospective analysis of genetic test results using Renasight™ (NGS-based>380 broad kidney gene panel) at a large academic center over an 18-month period. After signed informed consent, broad genetic testing was performed on blood or saliva samples from 31 patients. Genetic testing results were then related to alterations in the management of treatment of these patients.

**Results:** In this cohort, 41.9% (13/31) were female with an average age 51 years. The most common demographic groups were African American and Caucasian (6 patients [19.4%], each). Nineteen patients (61.3%) underwent Renasight testing due to a CKD diagnosis, 5 (16.1%) due to nephritis/nephritic syndrome, 3 (9.7%) due to proteinuria/nephrotic syndrome, 1 (3.2%) due to thrombotic microangiopathy, 1 (3.2%) due to phosphorus metabolism disorder, and 1 (3.2%) due to hemochromatosis. Positive results were identified in 12.9% (4/31) of the patients in the COL1A1, COL4A5, and APOL1 genes. Genetic testing results led to changes in management for 35.4% (11/31) of patients, confirmed diagnoses for 22.6% (7/31), provided additional diagnoses for 41.9% (13/31), and prompted family testing for 22.6% (7/31). For 4 patients with positive findings, test results impacted treatment management: 1 had transplant management impacted, 1 underwent biopsy to confirm Alport Syndrome, 1 had FSGS diagnosis confirmed and 1 underwent biopsy to confirm FSGS and initiated dialysis. Additionally, negative results led to alterations in management for 48.4% (15/31) of patients.

**Conclusions:** In this cohort at an academic practice, genetic testing informed nephrologist’s management of the patients in multiple categories. Negative results can rule out genetic causes of disease, and carriers and variants of uncertain significance (VUS) can inform family planning decisions and enable testing in family members.
Early Experience with Broad-Panel NGS Testing for Kidney Disease in a Community Nephrology Setting

**Tarek Darwish,1 Katya Brossart,2 Hossein Tabriziani,2 Kansas City Kidney Specialists, Overland Park, KS,3 Natera, Inc., San Carlos, CA.**

**Background:** Despite the increasing awareness of the value of incorporating genetic testing, its adoption in community nephrology settings is limited. Genetic testing can guide prognostication, targeted treatments, referral to specialists for extra-renal features, and identification of at-risk relatives. For individuals with kidney failure, additional testing can help assess the risk of recurrent kidney disease after transplant and evaluation of suitable living related kidney donors. Broad-panel testing can provide benefits over narrow panels based on clinical presentation.

**Methods:** Thirty-one patients with kidney disease completed genetic testing with the Renasight™ test (NGS-based >380-gene kidney disease panel) between October 2020 and April 2021. Median age of patients was 49 years (range: 28-78 years). Genetic testing results were correlated to clinical histories, demographic factors, family history (when available) and comorbidities. Certified genetic counselors interpreted the results and provided consultation to request on patients.

**Results:** Positive findings were identified in 22.6% (7/31) of patients tested in the APOL1, PKD1, SLCO4A1, COL4A4, and PKD2 genes (Table 1). Testing resulted in a diagnostic result in 85.7% (6/7) of patients and in changing clinical management for 28.6% (2/7) of patients. Homozygosity or compound heterozygosity for the APOL1 high risk alleles G1 and G2 was identified in 9.7% (3/31) of patients and were found primarily in African American patients.

**Conclusions:** In the community nephrology setting, the utility of genetic testing as part of the diagnostic workup is multifaceted. As compared to selection of a narrow panel based on clinical features, use of a broad panel that includes reporting of the APOL1 high risk alleles has the additional benefit of identifying genetic causes of kidney disease with ambiguous or non-specific clinical findings.

<table>
<thead>
<tr>
<th>Gene(s) Tested</th>
<th>Inheritance Pattern</th>
<th>Clinical Findings</th>
<th>Number of Patients</th>
<th>Number of Positive Findings</th>
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<tr>
<td>APOL1, PKD1, SLCO4A1, COL4A4, PKD2</td>
<td>Autosomal dominant (AD), Autosomal recessive (AR), X-linked (XL)</td>
<td>CKD: Alport syndrome (AS), FSGS, and 2 forms of undetected underlying monogenic cause for their kidney disease. Application of genetic testing can help assess the risk of recurrent kidney disease after transplant and evaluation of suitable living related kidney donors.</td>
<td>31</td>
<td>7</td>
</tr>
</tbody>
</table>

*Inheritance patterns: autosomal dominant (AD); autosomal recessive (AR); X-linked (XL)*

POI292

**KIDNEYCODE: A Genetic Testing Program for Patients with CKD**

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**Background:** Knowledge about the genetic causes of chronic kidney disease (CKD) is one of the key gaps in global kidney research. Recent International Society of Nephrology recommendations encourage the adoption of genetic testing to provide precision medicine based on individual risk. A recent whole-exome sequencing study showed that genetic inheritance may be responsible for up to 10% of CKD diagnoses in adults, many of which may be previously undiagnosed or mis-diagnosed. Continued advances in DNA sequencing technology have made genetic testing applicable to routine clinical diagnosis.

**Methods:** KIDNEYCODE offers no-charge genetic testing for three rare forms of CKD: Alport syndrome (AS), focal segmental glomerulosclerosis (FSGS), and 2 forms of polycystic kidney disease: autosomal dominant polycystic kidney disease (ADPKD) due to PKD2 mutations and autosomal recessive polycystic kidney disease. Invitae's renal disease panel includes 18 genes (ACTA4, ANLN, APOL1, CD2AP, COL4A3, COL4A4, COL4A5, CRB2, HNF1A, IN2, LMX1B, MYO1E, NPHS1, NPHS2, PKD1, PKD2, PKHD1, and TRPC6). Patients in the US with eGFR ≤ 90 mL/min/1.73 m² hematuria or a family history of CKD, or with a known or suspected diagnosis of AS or FSGS are eligible for testing. Family members of those with suspected or known AS or FSGS are also eligible. All participants have access to genetic counseling follow-up at no additional charge.

**Results:** To date, the KIDNEYCODE program has results from 1389 genetic tests. Genetic variants were reported in 845 patients. Of those, 574 patients had 613 variants in COL4A3, 4, or 5 genes (403 Pathogenic/Likely Pathogenic (P/LP), 210 Variants of Uncertain Significance (VUS)), 284 patients had 302 variants in genes associated with FSGS (55 P/LP, 247 VUS), 112 patients had 15 variants in PKHD1 (15 P/LP, 100 VUS), and 22 patients had a variant in PKD3 (7 P/LP, 15 VUS), and 75 patients had a VUS in APOL1.

**Conclusions:** Results from the KIDNEYCODE genetic testing program demonstrate that combining genetic testing with clinical presentation and medical history can improve accuracy of diagnosis and treatment plans for patients with hereditary CKD.

**Funding:** Commercial Support - Reata Pharmaceuticals

The Emerging Role of Whole-Genome Investigation to Identify Undetected Nephropathies: The HIDDEN Study

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**Background:** 5% of Australian and New Zealand patients commencing kidney replacement therapy have an uncertain kidney disease aetiology. New approaches and tools are required to resolve such diagnostic odysseys. WGS is an emerging diagnostic technology whose role in the setting is unclear. We sought to determine the diagnostic yield of whole genome sequencing (WGS) in individuals with unexplained end stage kidney disease (ESKD).

**Methods:** Adult and paediatric patients reaching Chronic Kidney Disease Stage 5 before 51 years of age without an identified aetiology were prospectively recruited through an Australian national network of 18 clinics. Eligibility was determined by a national clinical committee based on pre-specified criteria. Clinically-accurated WGS analysis was undertaken with a curated “KidneyOme” virtual panel of genes associated with hereditary kidney disorders. A genomic diagnosis constituted a KidneyOme result of pathogenic or likely pathogenic variant/s of appropriate zygosity.

**Results:** 168 individuals were referred (2018-2021) of whom 147 were approved and 104 consented. Of these, 40 (38.5%) were female and median age was 43yrs; 41 (38.5%) had ESKD and ESKD before 30yrs and 63 (60.6%) had undergone native kidney biopsy. Of 50 results returned to date, 7 (14%) were diagnostic, including both autosomal dominant (4/7) and recessive (3/7) inheritance patterns with 6/7 having a family history of CKD. A further 14/50 had variants of uncertain significance. One diagnosis was due to a copy number variation. The KidneyOme virtual panel curation of 384 genes is publicly available in PanelApp-Australia.

**Conclusions:** One in seven patients with ESKD of uncertain aetiology had an undetected underlying monogenic cause for their kidney disease. Application of KidneyOme with WGS has diagnostic utility and should be considered in younger patients with unexplained renal failure.

**Funding:** Government Support - Non-U.S.
PO1295
Characterization of Patients with Alport Syndrome in the United States: A Retrospective Analysis of Medical Claims

Background: Alport syndrome (AS) is a rare, hereditary genetic condition that often results in chronic kidney disease and may lead to early onset of end-stage kidney disease. The prevalence estimate in the literature is around 30,000-60,000 in the US. However, there are challenges with AS diagnosis (i.e. underdiagnosis and misdiagnosis), hence real-world patient population with AS diagnosis can be less than the prevalence estimates. This study is a retrospective analysis of medical insurance claims aimed to get a real-world estimate of the number of patients with a formal diagnosis of AS in the US, their disease characteristics, and treatment patterns.

Methods: A retrospective, observational cohort analysis was conducted, that leveraged DRG/Clarivate medical claims database, that integrates multi-payer and multi-plan data and covers ~220 million annual patients in the US. Patients with at least one ICD-10 code (Q87.81) designated for AS in their medical history between October 2015 to September 2020 were considered diagnosed AS cases. Characteristics of patients and prescription data were analyzed descriptively. Patient interactions with health care professionals (HCP) within the last 24 months of the study window (i.e. October 2018 – September 2020) were used to determine the primary HCP responsible for patient management.

Results: The analysis identified total of 10,387 patients with at least one AS diagnosis code. Of the 42% of the population for whom chronic kidney disease (CKD) stage data were available, 44% had advanced CKD (IV & V). Adult or pediatric nephrologists were the primary HCPs for 59% of patients. Based on the prescription data, 21.6% (2,244 patients) were prescribed ACEis/ARBs, and 10.6% (1,101 patients) were prescribed CYP3AA4 inhibitors.

Conclusions: The number of patients our study identified with AS diagnosis is lower than the commonly cited prevalence estimates in the US. The discrepancy can be explained by the fact that the database used covers a majority of but not the whole US population, and our study relied on real-world insurance claims.

Funding: Commercial Support - Reata Pharmaceuticals

* Staging data were available for 42% (4,404 pts) of the diagnosed population.

PO1296
Healthcare Resource Utilization by Patients with Alport Syndrome in the United States: A Retrospective Claims Analysis
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Background: Alport syndrome (AS) is a rare and serious inherited form of chronic kidney disease (CKD) affecting as many as 60,000 persons in the US. In severe cases, patients develop end-stage kidney disease (ESKD) in their 20’s. The health and economic burden associated with AS has not been well-characterized in the literature. This study aims to address this evidence gap.

Methods: A retrospective claims analysis (IBM MarketScan® Commercial Database) was conducted to assess the healthcare utilization (HCU) by patients with AS in the US. Patients enrolled in a health plan for a minimum of six continuous months with at least 1 inpatient or 2 outpatient claims with the AS-specific ICD-10 code were considered to have a diagnosis of AS. Patients with AS were further segmented into CKD stages, where such information was available, to understand the impact of disease progression on HCU. Patients with AS were age- and gender-matched to a comparator group without AS diagnosis in a 1:5 proportion. The analysis included commercial (medical and pharmacy) claims from 2015 to 2019.

Results: 851 patients with AS were identified, of which 518 also had a CKD diagnosis. The mean age was 33.3 years and 51% were males. 16.2% of patients were < 18 years old. Patients with AS required more healthcare services than the matched comparator group. 19.2% of patients with AS and CKD had at least 1 inpatient admission over the course of 6 months, versus 2.1% in the matched cohort; 100% had an outpatient or office visit, versus 94.6% in the matched cohort; 26.7% had at least one emergency department visit, versus 6.6% in the matched cohort. The rate of HCU increased with the increasing CKD stage, the highest utilization being observed in patients with advanced CKD. Approximately 25% of patients with AS were prescribed RAASi’s, which is a commonly used treatment in eligible patients with AS.

Conclusions: Patients with AS were observed to utilize inpatient, outpatient, and emergency department services at higher rates than the comparator group, with high utilization largely driven by late-stage CKD. Consequently, delaying or preventing kidney disease may substantially reduce healthcare expenditures among patients with AS, particularly among patients with ESKD.

Funding: Commercial Support - Reata Pharmaceuticals Inc
PO1299
Sparsentan, the Dual Endothelin Angiotensin Receptor Antagonist (DEARA), Improves Kidney Function and Life Span and Protects Against Hearing Loss in Alport Mice with Developed Renal Structural Changes
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Background: In Alport syndrome (AS), endothelin type A receptor activation is an important mediator of renal and inner ear pathologies. Sparsentan (SP) administered to COL4A3-/- mice (AS mice) in prevention mode delayed increases in proteinuria, renal structural changes and hearing loss (HL). Whether these effects translate into preservation of glomerular filtration rate (GFR), increased lifespan (LS) and protection from HL in mice where renal pathology has initiated is unknown.

Methods: Wild type (WT) and AS mice were gavaged daily with vehicle (WT-V or AS-V), 60 or 120 mg/kg SP (AS-SP60 or AS-SP120) starting at 4 weeks (W) of age or at 5, 6 or 7W. Baseline and 10W glomerulosclerosis/glomerulosclerosis (GS) were evaluated in kidney sections stained for fibronectin. GFR was measured using a transdermal device (Medibeacon) in mice treated from 4W. The auditory brainstem response (ABR) was used to assess hearing ability and sensitivity to noise at 8-8.75W in AS-V or AS-SP120 mice treated from 5W.

Results: SP begun at 4W abrogated the decline in GFR at 9W compared to AS-V mice (GFR 30 ± 6.7 ml/min per 1.73 m² at 9W vs. 21 ± 2.7 ml/min per 1.73 m² at baseline (B) for WT mice; p=0.0199). AS mice at 10W had a mean GFR of 22 ± 6.7 ml/min per 1.73 m² at 10W vs. 13 ± 3.7 ml/min per 1.73 m² at B (p=0.031). AS-SP120 mice had a mean GFR at 10W of 32 ± 5.6 ml/min per 1.73 m² vs. 16 ± 5.2 ml/min per 1.73 m² (B) for WT mice (p=0.0218). AS mice at 10W had a mean UACR of 183 ± 41.7 (n=15); p<0.001 AS-V vs AS-SP60 or AS-SP120 and mean UACR of 183 ± 40 mg/g (n=18). In GFR, GS, and hearing loss, AS-SP120 mice were statistically similar to WT mice but not to AS mice at 10W; p<0.05 for AS-V vs AS-SP120 for all measures.

Conclusions: SP prevents the decline in GFR in AS mice, extends LS and prevents noise-induced HL even in mice with developed renal structural changes. If these results are translated successfully into the clinic, SP may offer a novel treatment approach for reducing both renal injury and protecting hearing in AS.

Funding: Commercial Support - Traverse Therapeutics

PO1300
Interim Analysis of the EAGLE Trial: An Open-Label Study to Assess the Long-Term Safety and Tolerability of Bardoxolone Methyl in Patients with Alport Syndrome
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Background: Alport syndrome is a rare genetic disease affecting up to 60,000 persons in the US.

Methods: EAGLE (NCT03749447) is an ongoing, international, multi-center, open-label, extended access trial evaluating the longer-term safety and tolerability of bardoxolone methyl (bardoxolone) in patients with Alport syndrome who completed a prior qualifying clinical trial (CARDINAL Phase 2 and 3; NCT03019185). At baseline patients were 12 to 70 years old with eGFR 30 to 90 mL/min/1.73 m² and UACR ≤ 3500 mg/g. Patients received bardoxolone daily and dose is escalated up to 20 mg or 30 mg (for patients with UACR > 300 mg/g).

Results: As of data cutoff (01/18/2021), 96 patients were enrolled in the EAGLE study, including 79 patients from CARDINAL Phase 3 (placebo: n=46, Bard: n=33), and 17 patients who received Bard in CARDINAL Phase 2. Mean age was 42 years, and 8 (8%) patients were <18. At baseline, mean eGFR was 58.2 ± 21.4 mL/min/1.73 m² and mean UACR was 183 ± 40 mg/g. Increases in eGFR were seen in patients who previously received placebo and initiated Bard treatment in EAGLE. Patients who previously received Bard for two years in CARDINAL also continued to experience mean eGFR increases in their third year of treatment. Bard has generally been well tolerated, with no deaths or drug-related severe adverse events (SAEs) reported in EAGLE to date. No drug-related SAEs were reported and no changes in blood pressure were observed. Nearly all (94%) adverse events were mild to moderate.

Conclusions: In EAGLE, Bard increased eGFR in patients with Alport syndrome, and increases observed in EAGLE were sustained in the third year of treatment. To date, the longer-term safety profile of Bard is similar to that observed in the CARDINAL trial.

Funding: Commercial Support - Reata Pharmaceuticals

PO1301
Integrated Analysis of the Efficacy and Safety of Bardoxolone Methyl in Patients with Alport Syndrome
Bradley A. Warady,1 Rajiv Agarwal,1 Sharon P. Andreoli,1 SripalBangalore,4 Geoffrey A. Block,5 Arlene B. Chapman,2 Melanie Chin,2 Prasad Devajaran,8 Keisha L. Gibson,4 Angie Goldsberry,7 Laura H. Mariani,10 Colin J. Meyer,7 Megan O’Grady,7 Peter Stenvinkel,11 Glenn M. Chertow,12 1Children’s Mercy Hospitals and Clinics, Kansas City, MO; 2Indiana University School of Medicine, Indianapolis, IN; 3Riley Hospital for Children at Indiana University Health, Indianapolis, IN; 4New York University Grossman School of Medicine, New York, NY; 5US Renal Care Plans, Plano, TX; 6University of Chicago Division of the Biological Sciences, Chicago, IL; 7Reata Pharmaceuticals Inc, Irving, TX; 8Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 9University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC; 10University of Michigan Medical Center, Ann Arbor, MI; 11Karolinska Institute, Stockholm, Sweden; 12Stanford University School of Medicine, Stanford, CA.

Background: Alport syndrome is a rare and serious inherited form of CKD. An integrated analysis of efficacy and safety was conducted from the CARDINAL Phase 2/3 (NCT03019185) and EAGLE (NCT03749447) trials of bardoxolone methyl (Bard) in patients with Alport syndrome.

Methods: The CARDINAL Phase 2 trial was open-label and enrolled 30 patients ages 12 to 60 years with Alport syndrome, baseline eGFR values 30 to 90 mL/min/1.73 m² and UACR ≤ 3500 mg/g. CARDINAL Phase 3 was an international, multi-center, double-blind, placebo-controlled trial with similar eligibility criteria and randomized 157 patients. EAGLE is an ongoing, open-label, extended access trial that is enrolling patients who completed CARDINAL Phase 2/3 trials.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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PO1302
Novel Keap-Nrf2 Protein-Protein Interaction Inhibitor UBE-1099 Ameliorates the Severity of Experimental Alport Syndrome
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Background: Bardoxolone methyl is an electrophile that induces Nrf2 activation by irreversibly and covalently binding to the cysteine residue of Keap1. Bardoxolone methyl has been shown to improve glomerular filtration rate (GFR) in clinical trials, and is attracting attention as a novel agent for chronic kidney disease. However, there is concern about long-term efficacy due to the unknown mechanism of GFR improvement and transient increase in albuminuria. Moreover, irreversible Keap1 inhibitors such as Bardoxolone methyl may covalently bind to other proteins in a non-specific manner and induce side effects due to off-target activities.

Methods: We developed a reversible Keap1 inhibitor that inhibits Keap1-Nrf2 protein-protein interaction (PPPI) and evaluated its efficacy using Alport syndrome mice model (Col4a5-G5X). Development of Keap1-Nrf2 PPPI inhibitor was performed by fluorescence polarization and Nqo1 induction test. The obtained novel compound UBE-1099 (30 mg/kg/day) and CDDO-Im (3, 10 mg/kg/day; rodent tolerable Bardoxolone methyl analogue) were orally administered to Alport mice and efficacy was evaluated.

Results: UBE-1099 showed higher Nqo1 induction efficiency compared with CDDO-Im in mouse renal tissue. While CDDO-Im only improved inflammation pathology in Alport mice, UBE-1099 uniformly improved renal function (GFR and Plasma creatinine, but not albuminuria), podocyte injury, glomerulosclerosis, inflammation and fibrosis. Moreover, UBE-1099 treatment significantly prolonged the lifespan of Alport mice.

Conclusions: This study firstly revealed the efficacy of Keap1-Nrf2 PPPI inhibitor for glomerulosclerosis. We will elucidate next the mechanism of renal pathology improvement, which may provide useful information for Nrf2 activators including bardoxolone methyl for clinical application.

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PO1303
Patient Global Impression of Change in Patients with Alport Syndrome in the CARDINAL Phase 3 Trial
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Background: Alport syndrome is a rare and serious inherited form of CKD affecting as many as 60,000 persons in the US with no specific therapies approved for its treatment. Methods: An international, multicenter, double-blind, placebo-controlled, randomized Phase 3 trial (CARDINAL; NCT03019185) evaluated the safety and efficacy of bardoxolone methyl (Bard) in patients with Alport syndrome 12 to 70 years of age with baseline eGFR 30-90 mL/min/1.73 m² and UACR ≥ 350mg/g. As an exploratory endpoint, the trial assessed patient global impression of change (PGIC), a non-disease specific 7-point scale that asks patients to rate how much their illness has changed as very much/much/minimum improved (1, 2, and 3 pts), no change (4 pts), or minimally/much/very much worse (5, 6, and 7 pts) after 48 and 100 weeks of treatment.

Results: A total of 157 patients were randomized to Bard (n=77) or placebo (n=80). In addition to significant on-treatment and off-treatment increases in mean eGFR relative to placebo (between-group differences of 7.7 ± 2.1 [p=0.0005] at Week 100 and 4.3 ± 1.9 mL/min/1.73 m² [p=0.023] at Week 104, respectively), Bard improved PGIC scores relative to placebo (lower values after 48 and 100 weeks). Categorical summaries also showed more patients randomized to bardoxolone (34%) reported their condition had improved compared to those on placebo (19%) after 100 weeks of treatment.

Conclusions: In CARDINAL, Bard significantly improved eGFR in patients with Alport syndrome and also resulted in improvements in how patients evaluated their wellbeing.

Funding: Commercial Support - Reata Pharmaceuticals

PO1304
Treatment with Antisense-Oligonucleotide or Splicing Regulating Proteins for X-Linked Alport Syndrome Cases with Deep Intronic Variant
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Background: X-linked Alport syndrome (XLAS) is a hereditary progressive renal disease caused by mutation in COL4A5. Some cases of XLAS are caused by deep intronic variants which cause aberrant splicing and produce cryptic exon inclusion. Preventing translation of such cryptic exon has the potential to be an effective therapy. We reported that exon skipping therapy with antisense-oligonucleotide (ASO) was very effective in the XLAS mice model with a truncating mutation. However, an ASO needs very high sequence specificity and few patients can be treated by the same ASO. Therefore, we attempted to modify the splicing pattern not only by ASO but also by proteins important for splicing regulation. U2A6F5 is one of the important splicing related proteins binding to polyypyrimidine tracts promoting exonization. It has been reported that overexpression of the U2AF65 promotes or suppresses exonization in some circumstances.

Methods: We identified four cases of XLAS caused by the presence of the same cryptic exon inclusion ([c.384_385ins385-385-617]) by different deep intronic variants: three cases (c.385-756C>G, c.385-749T>A and c.385-645T>A) were ours and 1 (c.385-719G>A) was a reported variant. For these cases, we introduced ASO that could prevent cryptic exon inclusion. Moreover, using in vitro splicing evaluation system (minigene assay), we attempted to reduce the exonization of cryptic exon by overexpression of U2AF65.

Results: We succeeded in preventing the cryptic Exon insertion by introducing ASO treatment for patient’s urine derived cells. In addition, in all patients, overexpression of U2AF65 in the minigene splicing analysis system successfully reduced the cryptic exon inclusion.

Funding: Commercial Support - Reata Pharmaceuticals

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
PO1305
Small Molecule APOL1 Inhibitors Block APOL1 Pore Function and Reduce Proteinuria in an APOL1-Mediated Kidney Disease Mouse Model
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Background: Two genetic variants of APOL1 (G1 and G2) are associated with increased risk of kidney diseases. Current treatment options for APOL1-mediated kidney diseases are limited and do not address the underlying cause of disease. Here, we report the discovery of a series of novel small molecule APOL1 inhibitors, including the clinical candidate VX-147, that block APOL1 function in vitro and reduce proteinuria in a transgenic mouse model of kidney disease.

Methods: Microscale thermophoresis was used to assess binding of small molecule APOL1 inhibitors to recombinant APOL1 protein. HEK293 cells overexpressing APOL1 variants were used to quantify inhibition of APOL1-mediated cell death and ion flux. In addition, activity on APOL1 biological function was assessed using a trypanosome viability assay. Finally, changes in proteinuria following APOL1 inhibitor administration were assessed using a transgenic mouse model homozygous for the APOL1 G2 variant (G2/G2).

Results: Small molecule APOL1 inhibitors showed binding to all three forms of APOL1 (wild-type, G1 and G2 variants). In cellular assays, APOL1 inhibitors prevented APOL1-mediated HEK293 cell death and inhibited APOL1-mediated ion flux. Addition of APOL1 inhibitors to trypanosomes rescued the parasites from APOL1-induced killing. The potency of VX-147 was consistent across the in vitro functional assays described above (IC50 of approximately 2nM). Finally, administration of APOL1 G2-dependent proteinuria in an APOL1 G2 mouse induced APOL1 expression, resulting in elevated urine albumin-to-creatinine ratios. Oral administration of VX-147 reduced proteinuria in IFNγ-induced APOL1 G2 mice by 74.1%.

Conclusions: Novel small molecule APOL1 inhibitors, including VX-147, bind recombinant APOL1 protein and inhibit its biological function, as demonstrated by trypanosome parasite rescue. These inhibitors block APOL1 pore function, as demonstrated by reduced APOL1-induced death and APOL1-induced ion flux of tetracycline-inducible APOL1 HEK293 cells. Administration of APOL1 inhibitors reduced APOL1-dependent proteinuria in an APOL1-mediated transgenic mouse model of kidney diseases. Taken together, our results strongly suggest small molecule APOL1 inhibitors, such as VX-147, target the underlying cause of disease, and have the potential to treat APOL1-mediated kidney diseases.

PO1306
Inhibition of Endoplasmic Reticulum Stress Signaling Reduces Cytotoxicity of Human APOL1 Risk Variants in Drosophila
Lea Dakin, Meghna Shen, Lina L. Kamps, Julian Milosavljevic, Konrad Lang, Martin Helmstadter, Tobias F. Hermle. Hermle lab Division of Nephrology, University Medical Center Freiburg, Freiburg, Germany.

Background: Renal risk variants of the APOL1 gene are associated with severe kidney disease, putting homozygous carriers at risk. APOL1 G1- and G2-alleles likely represent gain-of-function (GOF) mutations as human subjects with APOL1 null alleles have been found to be without renal anomalies. A wide range of mechanisms that are frequently in conflict have been described for APOL1-associated nephropathies.

Methods: The genetic tool-kit in Drosophila allows unique in vivo insights into disrupted cellular homeostasis. To perform a mechanistic analysis in this model, we expressed APOL1 control and the GOF renal risk variants in the podocyte-like Drosophila nephrocytes and a wing precursor tissue.

Results: APOL1 risk variant expression entailed elevated endocytotic function of garland cell nephrocytes while processing of endocytic cargo and slit diaphragm morphology remained unimpaired. All APOL1 variants located to the endoplasmic reticulum (ER) and electron microscopy revealed significantly elevated ER swelling upon expression of a risk variant G2-APOL1, indicating stimulation of ER stress. We employed Drosophila wing precursor tissue since this epithelial model enables unique recording of relative changes side by side within the same animal to study ER stress. Overexpression of the renal risk variants G1 and G2 caused a markedly stronger upregulation of PDI and apoptosis, while expression of wildtype APOL1 resulted in milder upregulation. As a control, ER stress was absent upon deletion of 9 aa in the BH3 domain in the G2-APOL1 construct. We further confirmed APOL1-dependent ER stress by detection of chaperone induction and an Xbp1-reporter in the wing precursor. Both, genetic and pharmacological inhibition of ER stress abrogated apoptosis identifying ER stress as the essential factor of APOL1-induced cytotoxicity. This represents the first rescue of APOL1-associated cytotoxicity in vivo. Direct ER stress induction in nephrocytes phenocopied APOL1 risk variant expression, supporting that ER stress underlies the gain-of-function in nephrocytes.

Conclusions: Our data reveal ER stress as the essential consequence of APOL1 risk variant expression in vivo, indicating this pathway’s central role in the pathogenesis of APOL1-associated nephropathies.

Funding: Government Support - Non-U.S.

PO1307
A Cohort Study of Patients with Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD) Started on SGLT-2 Inhibitors
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Background: Sodium-glucose co-transporter-2 inhibitors (SGLT2i) have been shown to slow estimated glomerular filtration rate (eGFR) decline in chronic kidney disease (CKD) but have not been tested in patients with ADTKD. We performed a prospective nested cohort observational study and analyzed changes in eGFR and kidney injury marker 1 (KIM-1) in patients who were prescribed SGLT2i by their physicians.

Methods: We obtained baseline and follow-up laboratory studies at 1 week, 1 month, and 4 months after starting an SGLT2i and compared eGFR with baseline function. We also obtained information about adverse events.

Results: 12 individuals were started on SGLT2i by their physicians, with 10 on empagliflozin, 2 dapagliflozin. Table 1 shows the changes in eGFR and KIM-1. For patients with eGFR > 30, mean eGFR increased at 1 month by 3 ml/min. At four months, eGFR was 3 ml/min below baseline (-18.5% due to low baseline eGFR). For eGFR > 30, eGFR decline was 12% from baseline at one month and 8% from baseline at 4 months. Plasma KIM-1 was unchanged, but urinary KIM-1 increased by 100%. One patient stopped empagliflozin at his request after 8 weeks due to decline in eGFR of 14% from baseline. No other adverse events noted. Two patients have been treated for 6 months with stable eGFR.

Conclusions: The change in eGFR after treatment with SGLT2i was consistent with prior studies of CKD. The plasma KIM-1 was unchanged, but the rise in urinary KIM-1 was very concerning. Further study is required to determine if these agents are beneficial in ADTKD. An additional 4 months of follow up will be presented at ASN.

Funding: NIDDK Support, Private Foundation Support

PO1308
A Prospective Observational Study of Patients with Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD)
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Background: GFR decline in ADTKD due to UMOD or MUC1 mutations has not been well characterized. We have begun an international prospective cohort study to determine genetic and environmental factors associated with progression. We report here on early recruitment.

Methods: Patients with positive genetic testing for UMOD or MUC1 mutations prior to transplantation or starting dialysis are eligible. A baseline collection of health information, serum and urine biomarkers will be performed, with patients then followed longitudinally, with a serum creatinine measurement performed three times per year. There will be a nested cohort study of women who develop pregnancy during the study and patients started on ACE inhibition.

Results: Since March 2021, we have enrolled 57 patients in the prospective observational study, with 20 men, 35 women. The mean age of patients is 43.3 years, the mean baseline eGFR is 39.96 ml/min/1.73m². Table 1 shows baseline characteristics of patients enrolled in the study. No patients with CKD Stage 1 or 2 suffered from HTN, and only 39% of patients with CKD Stage 3 had HTN. Only 18% of patients were receiving ACE/ARB inhibition.

Conclusions: Despite significant CKD, there was a relatively low prevalence of HTN. Only 18% of patients were receiving ACE inhibition, indicating a potential therapeutic intervention. Please contact us if you have a patient who may be interested in participating in this prospective study (tablever@wakehealth.edu).

Funding: NIDDK Support, Private Foundation Support

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*Mean was computed as the average change in eGFR for each individual (at time point), compared to their baseline measurement.
Baseline Characteristics of Enrolled ADTKD Patients

**PO1309**

Vasopressin Induces Urinary Uromodulin Secretion by Activating Protein Kinase A

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**Background:** Urinary uromodulin, secreted by renal tubular cells, protects against urinary tract infections (UTIs) and kidney stones. In contrast, the intracellular accumulation of uromodulin is associated with hypertension and chronic kidney disease (CKD). In addition, uromodulin gene mutations cause autosomal dominant tubulointerstitial kidney disease (ADTKD-UOMD) via abnormal intracellular accumulation of uromodulin. However, the physiological stimuli for urinary uromodulin secretion remain largely unknown.

**Methods:** We investigated the acute effect of vasopressin/cAMP signaling on urinary uromodulin secretion in mice and in kidney epithelial cells stably expressing uromodulin. Additionally, we assessed the effect of vasopressin/cAMP signaling in kidney epithelial cells stably expressing mutant uromodulin, which causes ADTKD-UOMD.

**Results:** Desmopressin, a vasopressin type 2 receptor agonist, dramatically increased short-term tubular uromodulin secretion in mice. Immunofluorescence studies and ultracentrifugation-based polymerization assay suggested that desmopressin induced intraluminal polymeric filaments of uromodulin, indicating physiologically functional secretion. As a result of increased excretion, uromodulin abundance in the murine kidney was clearly reduced by desmopressin. In the cellular model, apical uromodulin secretion was increased in response to vasopressin/cAMP signaling, consistent with in vivo experiments. We also demonstrated that the response was dependent on cyclic AMP-dependent protein kinase (PKA) signaling pathway. We further showed that cAMP signaling induced excretion of mutant uromodulin. cAMP signaling suppressed PERK phosphorylation, which was upregulated by mutant uromodulin, implying cytoprotective effects.

**Conclusions:** Our work revealed vasopressin/cAMP/PKA signaling as a physiological stimulus of urinary uromodulin secretion. This finding may provide the basis for novel treatment strategies for UTIs, kidney stones, and potentially hypertension, CKD and ADTKD-UOMD.

**Funding:** Commercial Support - Kyowa Kirin Co., Ltd. Chugai Pharmaceutical Co., Ltd., Government Support - Non-U.S.

**PO1310**

Standardizing HNF1B-Associated Disease

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**Background:** Pathogenic variants in HNF1B are associated with a variety of inherited kidney diseases ranging from renal cysts and diabetes syndrome and CARKU to autosomal dominant tubulointerstitial kidney disease. In addition, variable extrarenal manifestations were linked (MM #189907). Although high throughput sequencing has advanced diagnostic variant detection, there is a lack of specific database analysis gathering both genotypic and phenotypic information from published and unpublished sources in order to establish valid genotype-phenotype correlations. By introducing a novel HNF1B database, we aim at gathering published and unpublished cases for identification of reliable variant-disease association analysis.

**Methods:** To standardize our own cohort and curate the clinical and genetic spectrum from the literature, we curated a list of 30 clinical features associated with HNF1B-disease based on HPO terms. Next, we developed a web-based application (available on curating. HNF1B.org) for comprehensive data input and analysis from patient histories or case reports. For example, renal function was not reported for 37.0% of cases while 4.5% of cases with 17q12 microdeletion no neuroendocrinopath phenotype was provided despite both phenotypes constitute hallmarks of HNF1B-associated disease.

**Conclusions:** To enhance the understanding of this multi system disorder, we will present our curation effort as an open source clinical and genetic database at HNF1B.org. Based on our curation and unpublished cohorts we will develop a recommendation for standardized reporting and selection scheme for genetic screening. Our effort exemplifies the curation efforts that are required for a better understanding of rare hereditary kidney diseases. The developed tools might serve as starting point for similar efforts.

**Funding:** Government Support - Non-U.S.

**PO1311**

Treatment with 4-Phenybutyrate Reduces Low-Molecular-Weight Proteinuria in a Clcn5 Knock-In Mouse Model for Dent Disease

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**Background:** Dent disease-1 (DD1) is a rare X-linked tubular disorder characterized by low-molecular-weight-proteinuria (LMWP), hypercalciuria, nephrolithiasis and nephrocalcinosis. This disease is caused by inactivating mutations in the Clcn5 gene, which encodes the voltage-gated CIC-5 chloride/proton antipporter. CIC-5 is expressed predominantly in the kidney and participates in the acidification of proximal tubule endosomes. Currently, the treatment of DD1 is only supportive and focused in delaying disease progression. Our group has generated a Clcn5 knock-in (KI) mouse that presents the main clinical manifestations of DD1 and carries the pathogenic mutation p.V523del, which causes partial CIC-5 retention in the endoplasmic reticulum. Here, we aimed to assess the feasibility of sodium 4-phenylbutyrate (4-PBA), a small chemical chaperone, to ameliorate DD1 symptoms in this mouse model.

**Methods:** Twelve-weeks old male Clcn5 KI mice (n=50) and WT (n=33) littermates were divided into 2 groups, one was treated with 250 mg/kg/day of 4-PBA in drinking water for 10 weeks, whilst the other group was given water instead. Animals were sacrificed after the same amount of time. Mice were placed in metabolic cages before and after treatment for 24h. Urinary β2-microglobulin and serum and urinary creatinine were measured by ELISA. Calcium and phosphate concentrations in urine were estimated using colorimetric kits. Water and food intake and 24-h urinary excretion were also measured, and mice body weights were monitored.

**Results:** We observed a significant reduction of β2-microglobulin urinary excretion in KI mice treated with 4-PBA compared to non-treated animals (p<0.0004). Glomerular filtration rate was also improved in treated mice (p=0.03). Urinary production, urinary calcium and phosphate levels were also improved compared with non-treated mice. In conclusion, 4-PBA reduces LMWP in Clcn5 KI mice, suggesting that this treatment could represent a promising therapeutic option for some DD1 patients.

**Funding:** Government Support - Non-U.S.

**PO1312**

Long-Term Efficacy of Migalastat on Renal Function and Outcomes in Patients with Fabry Disease (FD)

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**Background:** FD, caused by pathogenic GLA variants leading to functional deficiency of α-galactosidase A (α-Gal A), can eventually result in key organ damage. Preserving renal function and preventing Fabry-associated clinical events (FACEs) are important treatment goals. Approved therapies include enzyme replacement therapy (ERT) and the pharmacological chaperone migalastat. Stabilized renal function and FACE occurrence up to 30 mo have been reported in migalastat-treated adults with amenable GLA variants; here, we extend these analyses up to 8.6 yrs.

**Methods:** Integrated data from phase 3 clinical trials (FACETS, NCT00925301; ATTRACT, NCT01212689) and open-label extension studies (NCT01438819; NCT02120853) were used to evaluate the eGFR slope using linear regression in pts treated with migalastat for 22 yrs (n=78). Incidences of FACEs (defined renal, cardiac, and cerebrovascular events) were assessed in all pts (N=97). Analyses were stratified prior treatment and phenotype. Cox regression modeling was used to identify predictors of FACE.

**Results:** eGFR remained stable for both ERT-naive and ERT-experienced pts who received migalastat for 22 yrs (median [min-max] duration: 5.9 [2.0-8.6]); the mean (SD) annualized rates of change in eGFR (mL/min/1.73 m²) were -1.6 (3.1) and -1.6 (3.6), respectively. In male pts with the classic phenotype (classification based on multiorgan involvement and [ERT-naive only] α-Gal A level at baseline; n=25), mean (SD) rate of change in eGFR was -2.2 (4.4) mL/min/1.73 m². eGFR was also analyzed by baseline renal function and proteinuria levels. In all migalastat-treated pts (median duration: 5.1 yrs), the incidence of composite FACEs (per 1000 patient-years) was 48.3 (65.3 for

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POI313

Twenty-Year Renal Prognosis in Patients with Fabry Disease Who Underwent Enzyme Replacement Therapy

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Background: The relationship between long-term renal prognosis and renal histopathology after enzyme replacement therapy (ERT) for Fabry disease (FD) has not been fully investigated.

Methods: Nine patients with FD from our hospital who had participated in a Japanese phase 2 study (August 2000–May 2001) on agalsidase β were eligible for this case-control study. They underwent repeated renal biopsy (before and six months after agalsidase β treatment), and the intra-renal amount of globotriaosylceramide (GL3) was measured at the same time points. Clinicopathological features were compared between the groups with or without developing end-stage kidney disease (ESKD).

Results: Seven patients included in this study, two were lost to follow-up. All were males, with a median age at the start of treatment of 30 [quartile 24.5, 31.5] years, and median serum creatinine level (s-Cr) of 1.1 [1.0, 1.2] mg/dL. The podocyte score (International Study Group of Fabry Nephropathy score system) improved in all patients after ERT from that evaluated before ERT. Intersitial fibrosis/tubular atrophy (IF/TA) worsened in three patients. The proportion of foamed tubules improved in five patients. Intra-renal accumulation of GL3 decreased six months after ERT in all patients. All patients continued to receive agalsidase β or agalsidase α after the phase II study. While four patients developed ESKD (median 6.7 years), three patients showed no exacerbation of renal function. The s-Cr level, age, and urinary protein excretion at the start of ERT were higher in the ESKD group. The decrease in the intra-renal accumulation of GL3 was not significantly different between the two groups, but the proportion of foamed tubules in the first biopsy and the degree of IF/TA in the second biopsy were higher in the ESKD group than in the non-ESKD group.

Conclusions: This study suggests that tubulointerstitial injury has a crucial role in the determination of renal prognosis and that earlier diagnosis and intervention in patients with FD may improve the renal prognosis. Further studies are needed on the relationship between tubulointerstitial injury and GL3 accumulation.

POI3134

Systems Analyses of Fabry Renal Transcriptome and Its Response to Enzyme Replacement Therapy (ERT) Identifies a Cross-Validated and Drugable ERT-Resistant Module

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Background: Fabry nephropathy (FN) is a rare disorder caused by mutations in the α-galactosidase A gene that can, to a certain degree, be managed with enzyme replacement therapy (ERT). Via understanding the molecular basis of FN and ERT’s long-term impact, we aim at providing a framework allowing selection of biomarkers and drug targets.

Methods: Obtained from controls and two independent FN-cohorts, mRNA-isolates from archival kidney biopsies taken prior and up to 10 years of ERT, were subjected to RNAseq. Combining pathway-centered analyses with network-science allowed computation of transcriptional landscapes from glomeruli, proximal tubuli, distal tubuli and interstitial cells. Comparing transcriptional landscapes from archival kidney biopsies taken prior and up to 10 years of ERT, were subjected to RNAseq. Combining pathway-centered analyses with network-science allowed computation of transcriptional landscapes from glomeruli, proximal tubuli, distal tubuli and interstitial cells. Comparing transcriptional landscapes per cohort revealed high inter-cohort heterogeneity. Especially, with timely treatment initiation, FN seemed well controlled and drug-targets.

Results: Comparing transcriptional landscapes per cohort revealed high inter-cohort heterogeneity. Especially, with timely treatment initiation, FN seemed well controlled and drug-targets.

Discussion: The current study suggests that Fabry nephropathy is an autoimmune disease (less than 3 cases per million population). Nephrolithiasis and nephrocalcinosis lead to progressive renal impairment and subsequent oxalate deposition in various tissues. We present a case of PHT1 diagnosed late in life and ultimately requiring definitive management with liver-kidney transplant due to early progression to end stage kidney disease.

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diffuse increased echogenicity and bilateral non-obstructing calculi. Initial serum oxalate level was 63.5 micromol/L and 24 hour urine oxalate level was 116mg/24hrs. Ser failed to improve with intravenous fluid administration and renal replacement therapy was initiated with goal serum oxalate level of <30 micromol/L. Hemodialysis was performed daily for four hours with high flux membrane. Serum oxalate levels improved to nadir of 40 micromol/L. Definitive therapy with simultaneous liver-kidney transplant was ultimately pursued.

Discussion: Our patient required intensive hemodialysis while awaiting liver-kidney transplant following late diagnosis of PHT1 and development of end stage kidney disease. Early diagnosis is key to reduce morbidity and mortality. Progressive kidney impairment leads to inability to excrete the increased oxalate produced by the liver and subsequent systemic deposition of oxalate including in the kidney causing multiorgan dysfunction. Hemodialysis removes oxalate but it is difficult to consistently reduce serum oxalate levels below goal given continued production of oxalate and rebound. Early treatment options include a trial of pyridoxine, hyperhydration, low oxalate diet and novel RNA inhibitors. Patients with advanced disease often require definitive management with liver-kidney transplant. Clinicians need to have a high index of suspicion for PHT1 as patients often go undiagnosed until advanced kidney disease or end stage kidney disease has developed.

POI1317

Real-World Healthcare Utilization and Clinical Markers Preceding Dialysis in Patients with Primary Hyperoxaluria (PH) in the United States

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Background: PH is the accumulation of oxalate resulting in urolithiasis, nephrocalcinosis, chronic kidney disease (CKD), and eventually end-stage renal disease (ESRD) that usually requires dialysis. This study examined demographics, clinical characteristics, and healthcare utilization (HCU) among dialysis-treated PH patients during the time leading up to dialysis start.

Methods: This was a retrospective study of PH patients (ICD-10: E72.53) initiating dialysis (study entry), on or after October 1, 2018, in TriNetX DataWorks USA, a federated EMR network of 60+ million de-identified patients from 44 healthcare organizations (HCOs). Patient age, sex, race, comorbidities, CKD stage, kidney stone events (KSE), and HCU were examined at least 6 months prior to dialysis, through up to 5 years.

Results: The final study cohort included 47 patients: mean age of 59 years, 53% female, and 85% white. Only 47% had a recorded diagnosis of PH prior to dialysis, and 55% had a diagnosis of ESRD. During the 6 months immediately preceding dialysis, 91% of patients had a1 outpatient office visit, 17% a1 ED visit, and 53% a1 inpatient stay. HCU for the full study period showed 98% of patients had ≥1 physician office visit, ≥1 ED visit, and ≥1 inpatient stay (Figure 1). Patients with recorded KSE (n=19; 40%) had a mean of 4 events during the study period. The frequency of KSEs doubled from 1 to 2 per person per year as patients neared dialysis. In the 6 months prior to dialysis, 70% of patients had CKD of stage III or higher recorded in their EMR.

Conclusions: In this real-world study, more than one-half of patients with PH were undiagnosed prior to initiating dialysis, according to the data reviewed. In addition, high rates of costly HCU, including ED visits and inpatient stays, were observed during the same timeframe. The number of KSEs increased over the study period, which may be indicative of worsening renal function due to PH prior to dialysis.

Funding: Commercial Support - Dicerca Pharmaceuticals Inc, Cambridge, MA.

POI1318

Association Between Longitudinal Plasma and Urine Oxalate and Time-to-Kidney Failure in Primary Hyperoxaluria Using Joint Models

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Background: The association between plasma oxalate (POX), urine oxalate (UOX) and time to kidney failure (KF) in patients with the rare disease primary hyperoxaluria (PH) is challenging to study due to small sample sizes and correlations among POX, UOX, and eGFR. To develop better KF models that simultaneously account for all 3 variables we used a novel statistical approach, joint models, modeling longitudinal biomarker processes (eGFR POX, UOX) and survival process (time-to-KF) jointly, using retrospective data from the Rare Kidney Stone Consortium PH registry.

Methods: Repeated eGFR, UOX, and POX after PH diagnosis were obtained from the registry. Time-to-KF was defined as time between PH diagnosis until transplantation, dialysis or eGFR<15 mL/min/1.73m². A multivariate joint model was fit with longitudinal sub-models for each biomarker and a survival sub-model for KF. Longitudinal sub-models employed linear mixed effects models with biomarkers on the log scale. Joint modeling with shared information between longitudinal and survival sub-models such that eGFR, UOX, and POX were time-dependent variables in the survival sub-model, specifically using subject-specific mean biomarker values. Models were adjusted for age and sex at diagnosis. Results were compared to last observation carried forward (LOCF) analyses.

Results: A total 166 patients (mean 5 POX and 7 UOX per patient) with 60 KF events during follow up were included. With LOCF, POX positively associated with KF risk, both unadjusted and adjusted for other biomarkers (hazard ratio (HR) = 1.14 per umol/L, 95%CI = 1.07, 1.22, p<0.001), while UOX was not associated with KF after adjustment. With joint modeling, POX and KF were not significantly associated after adjustment (HR = 1.12, 95%CI = 0.99, 1.30, p=0.08), while higher UOX was associated with lower KF risk (HR = 0.30 per mmol/l/1.73m²/24h, 95%CI = 0.07, 0.92, p=0.04).

Conclusions: When modeling unevenly spaced longitudinal biomarkers and their association with KF, the LOCF time-dependent model makes implausible assumptions about steady-state biomarkers between observations. Implementation of a joint modeling framework allows flexible estimation of the association, which may impact conclusions. These novel methods can be used to inform patient-specific decisions about future KF risk, and the risk-benefit of novel treatment approaches.

Funding: NIDDK Support

POI1319

Modeling the Risk of Progression to Kidney Failure in Patients with Primary Hyperoxaluria Type 1 Treated with Lumasiran Relative to a Natural History Cohort Not Treated with Lumasiran

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Background: In primary hyperoxaluria type 1 (PH1), the risk of kidney failure (KF) is positively associated with urinary oxalate (UOX) excretion. Lumasiran is an RNAi therapeutic to lower UOX levels in patients with PH1. We estimated the risk of progression to KF in patients with PH1 treated with lumasiran, relative to patients not treated with lumasiran.

Methods: A skewed-normal distribution of 24hr UOX values for patients with PH1 was simulated based on reported UOX values from the Rare Kidney Stone Consortium (RKSC) PH Registry among patients who were not in KF at diagnosis and did not receive lumasiran. Data from the ILLUMINATE-A trial of lumasiran were used to build a log-linear model of post-lumasiran treatment steady-state UOX as a function of baseline UOX. The distribution of steady-state, on-treatment UOX values for RKSC patients was then predicted by applying this model to the simulated 24hr UOX values of the RKSC cohort, considered as baseline. A risk model of KF as a function of 24hr UOX excretion, based on Kaplan-Meier curves of renal survival reported from the RKSC, was used to estimate the number of KF events/100 patients in the RKSC PH1 cohort, had all received lumasiran.

Results: The mean (SD) 24hr UOX excretion for the RKSC PH1 cohort was 2.2 (1.1) mmol/24hr/1.73m² in the absence of lumasiran treatment and was predicted to decrease to 0.62 (0.17) mmol/24hr/1.73m² in a model that simulated the effect of lumasiran administration (Figure 1). The predicted number of KF events/100 patients (95% CI) using the model for patients not treated with lumasiran at 10, 20 and 30 years, is 10 (4, 23), 32 (19, 50), and 42 (27, 59), respectively. In the model of lumasiran treatment, the estimated cumulative number of KF events/100 patients (95% CI) was 4 (1, 12) at 10 years and remained unchanged at 20 and 30 years.

Conclusions: This analysis predicts a long-term reduction in KF risk among PH1 patients treated with lumasiran following prompt treatment at diagnosis.

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PO1320
The Complex Landscape of Factor H and Factor I Rare Variants in Atypical Hemolytic Uremic Syndrome and C3 Glomerulopathy

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Background: Complement genetics has been extensively studied to dissect the pathophysiology of atypical hemolytic uremic syndrome (aHUS) and C3 glomerulopathy (C3G) paving the way for highly tailored therapy. However, the assessment of each identified variant’s contribution to disease pathogenesis remains a challenge in particular for rare variants detected in patients as well as in healthy individuals in the genome Aggregation Database (gnomAD). In this study we aimed to describe the rare variants in Factor H (CFH) and Factor I (CFI) genes identified in the French cohort of patients with aHUS and C3G.

Methods: We analyzed the distribution of the allele frequency (AF) of rare variants identified in 397 and 398 adult patients with a diagnosis of aHUS without coexisting disease and with C3G/ig-mediated membranoproliferative glomerulonephritis (Ig-MPGN), respectively. We selected for this study variants with minor AF (MAF) below 0.1% in European healthy individuals.

Results: The frequency of patients with rare variants in CFH (108/398 vs 54/398) and CFI (33/397 vs 17/397) genes was higher in aHUS compared to C3G. A total of 148 variants were identified in CFH (n=98) and in CFI (n=50) genes. Among them, 9 were present in both diseases. We identified 43 (67%) and 20 (66%) novel variants in CFH in aHUS and C3G, respectively. Among them, 98% are pathogenic compared to 44% of the variants reported in gnomAD. The frequency of variants causing FH and FI disease is similar in both diseases (70% of the variants). The frequency of CFH variants identified in more than 1 patient is increased in aHUS compared to C3G (11/64 vs 2/30). We identified 12 (12/38, 31%) and 2 (2/12, 16%) novel variants in CFH in aHUS and C3G, respectively.

Conclusions: Our study indicates that novel pathogenic rare variants in complement genes is more frequent in aHUS than in C3G. Half of the variants reported in gnomAD is higher in CFI (80%) compared to CFH (70%). The frequency of variants reported in gnomAD is higher in CFI (80%) compared to CFH (14%).

PO1321
Phenotypic-Genotypic Relationship of Focal and Segmental Glomerulosclerosis (FSGS)
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Background: FSGS can be of primary, secondary or genetic origin. The objective of our work is to establish in which patients with a histological diagnosis of FSGS a genetic etiology should be suspected.

Methods: The study included adult patients with a histological diagnosis of FSGS and normal albumin (58%). We found 20 pathogenic variants of collagen IV in 17 (55%) patients. NPHS2 mutations were discovered in 7 (23%) patients. The remaining cases with normal albumin (58%).

Results: Out of 108 samples received, 80 patients met the inclusion criteria. We detected FSGS-related pathogenic genetic variants in 31 (39%) patients, finding no difference between those whose indication was steroid resistance (32 %) or proteinuria without albuminuria (58%). We found 20 pathogenic variants of collagen IV in 17 (55%) patients. NPHP2 mutations were discovered in 7 (23%) patients. The remaining cases had variants affecting INPF2, OCR1, HNF1B, WT2. All 3 (black) patients had high-risk APOL1 alleles. There were no differences between genetic and non-genetic causes in age, proteinuria, GFR, serum albumin, BMI, hypertension, diabetes, or family history. Hematuria was more prevalent among patients with genetic causes.

Conclusions: Genetic testing should be considered in FSGS patients in which a secondary cause has been excluded, to determine the patient’s prognosis, treatment and perform familial screening.

Funding: Private Foundation Support

PO1322
Insight into the Pathophysiology of Hearing Loss and Renal Tubular Dysfunction Through Genetic Testing
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Introduction: In this case report, we present a case of Type 3B Bartter’s Syndrome associated with sensorineural hearing loss.

Case Description: A 69 year old caucasian female with a history of hypertension and osteoporosis presented to the emergency department with a worsening dry cough, altered mental status, and paresthesias. Physical examination was positive for Chvostek’s sign and hearing loss bilaterally. Laboratory analysis was significant hypocalcemia, hypokalemia, and hypomagnesemia. EKG on presentation displayed significant QT prolongation (QTC of 482 ms). The patient was treated for symptomatic hypocalcemia and initiated on calcium, potassium, and magnesium supplementation. 24 hour urine collection yielded: potassium and magnesium wasting and normal range calciuria. Parathyroid hormone was found to be inappropriately low in the setting of severe hypocalcemia but attributed to hypomagnesemia. Bartter’s vs. Gitelman’s was suspected, although profound hypomagnesemia suggested the latter. Renasight, a kidney gene panel employing next generation genome sequencing revealed a heterozygous variant in the basal chloride channel (CLCNKB), associated with Bartter’s Syndrome Type 3/4B.

Conclusion: This channel is found in the stria vascularis and can lead to sensorineural deafness. Hypoparathyroidism persisted in spite of adequate Magnesium, Vit D levels suggestive of primary hypoparathyroidism of autoimmune etiology.

Discussion: The positivity of CLCNKB heterozygous mutation suggested Bartter’s Type 3/4B and this explained hearing loss and aided in the final diagnosis. Individuals who express both type A and B mutations present in infancy or antenatally. In a series of 113 patients w/ type B gene mutation, 26% had a Gitelman-like syndrome which includes loss of function of the T1 gene (1). Our case illustrated the utility of genetic testing in mixed electrolyte wasting presentations. Interestingly, the patient has persistent hypoparathyroidism for which no genetic basis was identified such as the calcium sensing receptor mutation.

Renal Studies

PO1323
Whole-Exome Sequencing as a First-Line Diagnostic Tool in Bartter and Gitelman Syndromes
Francesca Becherucci, Viviana Palazzo, Luigi Ciriolo, Benedetta Mazzinghi, Valentina Raglianti, Samuela Landini, Paola Romagnani. Meyer Children’s Hospital, Florence, Italy.

Background: The clinical diagnosis of Bartter (BS) and Gitelman syndrome (GS) can be challenging, as they are rare and phenotypically overlapping. Thus, genetic testing represents the gold standard for the diagnosis. Next-generation sequencing is increasingly utilized in diagnostics and research of inherited tubulopathies. Sequencing of gene encoding for liver kinase B1 (LKB1) is suggested as a first-line test in patients with a history of hypokalemia and/or hypocalcemia. However, this gene may be involved in a variety of tubulopathies, so a thorough clinical evaluation is required to confirm the clinical diagnosis.

Methods: We enrolled 50 patients (25 males) with a clinical diagnosis of BS or GS. All patients showed hypokalemic metabolic alkalosis at onset. The median age at clinical diagnosis was 7 years (range 0-67). WES showed pathogenic variants in 41/50 patients (82%). The positivity of CLCNKB heterozygous mutation suggested Bartter’s Syndrome. Whole-exome (WES) is not routinely performed for the molecular diagnosis of BS and GS. The aim of our study was to assess the diagnostic performance of WES in BS and GS, to establish genotype-phenotype correlations and to assess cost-effectiveness of this approach.

Results: We performed WES in all consecutive patients referred for genetic testing with a clinical suspect of BS or GS. Variant prioritization was carried out according to ACMG guidelines. Clinical data were collected retrospectively.

Conclusions: Our study demonstrates that WES ensures a high diagnostic yield and new insights into the genotype-phenotype spectrum of these rare disorders. Whole-exome (WES) is not routinely performed for the molecular diagnosis of BS and GS. The aim of our study was to assess the diagnostic performance of WES in BS and GS, to establish genotype-phenotype correlations and to assess cost-effectiveness of this approach.

Funding: Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO1324

Examination of the Predicted Prevalence of Gitelman Syndrome by Ethnicity Based on Genome Databases
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Background: Gitelman syndrome is an autosomal recessive inherited salt-losing tubulopathy. It has a prevalence of around 1 in 40,000 people, and heterozygous carriers are estimated at approximately 1%, although the exact prevalence is unknown because most cases are thought to be asymptomatic or have nonspecific clinical findings. On the other hand, it has been reported that the non-specific symptoms can reduce the quality of life of patients, and in practice, we have often experienced cases where patients have suffered from these symptoms since childhood, but were not diagnosed and therefore not treated, and were diagnosed in adulthood. It could suggest that there are far more patients and carriers than expected.

Methods: We estimated the predicted prevalence of Gitelman syndrome based on multiple genome databases, HGVD and Jmpor for the Japanese population and gnomAD for other ethnicities, and included all 274 pathogenic missense or nonsense mutations registered in HGMD Professional. The frequencies of all these alleles were summed to calculate the total variant allele frequency in SSC1243 which is the responsible gene for Gitelman syndrome. The carrier frequency and the disease prevalence were assumed to be twice and the square of the total allele frequency, respectively, according to the Hardy-Weinberg principle.

Results: In the Japanese population, the total carrier frequencies were 0.0498 (9.5%) and 0.0686 (8.7%) and the calculated prevalence was 0.00225 (2.3 in 1000 people) and 0.00188 (1.9 in 1000 people) in HGVD and Jmpor, respectively. Other ethnicities showed a prevalence varying from 0.000012 to 0.00083.

Conclusions: These findings indicate that the prevalence of Gitelman syndrome in the Japanese population is higher than expected and that some other ethnicities also have a higher prevalence than previously been considered.

PO1325

An Off-the-Shelf CRISPR Gene Therapy Approach in Human Kidney Organoids
Nicole Vo, Catherine A. Macnary, Benjamin S. Freedman. The Freedman lab University of Washington, Seattle, WA.

Background: Gene therapy offers many opportunities to treat kidney diseases. Targeted, off-the-shelf therapeutics are needed for both loss-of-function (e.g. nephropathic cystinosis) and gain-of-function (e.g. ApoL1) disease states. Kidney organoids are complex structures that resemble nephrons and can be used to develop gene therapy approaches. Commonly used gene transfer techniques, such as lentivirus and adenovirus, are size limited, transient, or introduce DNA non-specifically into the genome. While targeted CRISPR gene editing is routinely used in 2D cell cultures, it has been challenging to use this powerful technique in intact organoids.

Methods: To achieve off-the-shelf gene transfer, organoids were transfected with Cas9 and gRNA ribonucleoprotein (RNP) complexes targeting the AAVS1 safe harbor locus supplemented with knock-in cassettes encoding green fluorescent protein (GFP) or FLAG-tagged cystinosin (deficient in nephropathic cystinosis). Alternatively, to monitor gene knock-out, organoids expressing GFP from AAVS1 were transfected with RNP and either one or two gRNAs to introduce indels in the coding sequence. Genome editing was detected three ways: by confocal microscopy, PCR, and next generation sequencing.

Results: GFP and cystinosin knock-in events in organoids were detected using microscopy and PCR. Immunofluorescence analysis revealed knock-in in proximal tubule epithelial cells (LTL). In knock-out experiments, live confocal microscopy indicated areas of GFP loss within kidney organoid treated with gRNA targeting GFP, but not with a scrambled guide. Mosaic patches of GFP knockout cells expanded over several days. Staining with neprhin markers such as LTL and podocalyxin revealed knockout in both proximal tubule cells and podocytes. By next generation sequencing, the two-guide system produced larger deletions and was more efficient (20 % knockout), compared to single guide.

Conclusions: The strategy developed here is efficient for knocking in and knocking out genes in kidney epithelium. It uses commercially available reagents to perform CRISPR gene editing. sgRNA sequences or AAVS1 knock-in templates can be customized to target or introduce any gene of interest at specific loci. This provides a platform for the development of off-the-shelf gene therapies for diverse kidney disease states.

Funding: NIDDK Support

PO1326

The Kidney Genome Atlas: A Resource to Understand APOL1 and Other Driving Genes of Adult Proteinuric Kidney Diseases
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Background: Chronic kidney disease (CKD) affects more than 30 million people in the US with African Americans being particularly at risk. There is an unmet need for pharmaceutical therapies that extend or, ideally, restore kidney function.

Methods: To guide genetically-driven drug development, we have established the Kidney Genome Atlas (KGA), which contains whole-genome sequences (>30X) from adult patients with Focal segmental glomerulosclerosis (FSGS), minimal change disease (MCD) and other, idiopathic, proteinuric disorders as well as public and technically matched controls. By implementing a rigorous quality control procedure, following the gnomAD pipeline, we obtained a high-confidence dataset for downstream analyses. Three genetically inferred ancestries (EUR, AFR, AMR) were included in association testing comparing 1400 cases, including 169 individuals with APOL1 G1/G1, G2/G2 or G1/G2 high risk haplotypes (APOL1-HHR), with 14686 controls including 485 APOL1-HHR individuals.

Results: Overall, our common variant cross-ancestry meta-analysis showed minimal impact of potential confounders, such as ancestry or sequencing center differences (lambda=1.03). Using summary statistics from our EUR analysis, we estimated a SNP heritability of 0.15 (SE = 0.028) in proteinuric diseases. Comparison to a recent CKD GWAS (Wuttke et al., 2019) indicated a weak positive genetic correlation (rg) of 0.097 (p = 0.053). We identified the previously reported significant disease association of APOL1-HHR (p=2x10^-10) in our study. Recent in vitro data suggests amino acid in position 150 (rs2239785) is critical for the pathogenicity of APOL1-HHR (PO1986, ASN 2020) which we confirmed in our cohort of AFR ancestry individuals.

Conclusions: We have built a high-quality, multiethnic cohort that enables understanding of genetic drivers of polygenic proteinuric kidney disease. Future analysis including genetic modifiers of APOL1 may provide opportunities for novel therapies and patient stratification.

Funding: Commercial Support - Goldfinch Bio

PO1327

Effect of ApoL1 Genotype on Kidney Failure and eGFR Decline in Patients with All-Cause CKD

Background: ApoL1 risk variants G1 and G2 associate with an increased risk of kidney failure and a higher rate of eGFR loss. We assess the effect of ApoL1 genotype in African American and Latino individuals with chronic kidney disease (CKD) in New York City.

Methods: ApoL1 genotype determined by sequencing. CKD cases with high-risk ApoL1 genotype (n= 242) were compared to CKD cases with a low-risk ApoL1 genotype (n=885) and African ancestry per Admixture. Kaplan-Meier survival analyses assessed time to kidney failure followed by Adjusted Cox-proportional hazard model and competing risk regression against death both incorporating covariates. Linear mixed-effects modelling evaluated CKD-EPI eGFR decline rate using the same covariates.

Results: Cases with a high-risk ApoL1 genotype reach kidney failure 10-15 years earlier than low-risk cases. G1/G1 reach kidney failure earliest, followed by G1/G2 and G2/G2 (Fig 1). These data are supported across multiple risk models (Table 1). Cases with a high-risk genotype have a higher eGFR decline rate than low-risk cases with a similar trend per specific genotype (Fig 2). The addition of self-declared or genetically defined ancestry did not confer additional risk.

Conclusions: High-risk ApoL1 genotypes increase the risk of kidney failure at an earlier age, likely due to a higher eGFR decline rate. G1/G1 genotypes appear most affected and G2/G2 least.

Funding: Government Support - Non-U.S.

Table 1. Modelling Results by ApoL1 Genotype

<table>
<thead>
<tr>
<th>ApoL1 Genotype</th>
<th>Age at Kidney Failure (Median, 5% CI)</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
<th>Admixture Risk</th>
<th>Risk of Kidney Failure Risk</th>
<th>eGFR Decline Rate (mL/min/1.73 m2/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1/G1</td>
<td>56.0 (52.3 - 60.7)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>G1/G2</td>
<td>62.0 (57.5 - 66.5)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>0.99</td>
</tr>
<tr>
<td>G2/G2</td>
<td>67.0 (62.5 - 71.6)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>0.99</td>
</tr>
</tbody>
</table>

*p <0.05 **p <0.001 ***p < 0.0001
PO1328
“APOL1-Plus” Genotypes in Patients with CKD
Darby, Rabble; Dinah Clark,1 Fang Fang,2 Jing Xie.1 1Natera, Inc., San Carlos, CA; 2Pulgenet Genetics, Temple City, CA.

Background: Inheritance of homozygous or compound heterozygous APOL1 G1 G2 risk alleles is associated with an increased risk of chronic kidney disease (CKD) including focal segmental glomerulosclerosis (FSGS). The APOL1 high-risk genotype (HRG) is not completely penetrant; additional genetic and/or environmental factors are thought to be necessary for the development of CKD. While approximately 10% of individuals with CKD have causal variants when tested with exome-based next generation sequencing (NGS), few reports have examined co-occurrence of APOL1 HRG alongside these variants. Here we examine the co-occurrence of APOL1 HRG and additional genetic diagnoses (“APOL1-plus”) using a broad NGS panel of CKD genes.

Methods: Clinical samples were analyzed via an NGS panel of >380 genes associated with isolated or syndromic CKD. Positive results included one pathogenic (P) or likely pathogenic (LP) variant in an autosomal dominant or X-linked gene, two P/LP variants in an autosomal recessive gene, or presence of two APOL1 risk alleles.

Results: Among 1691 cases with positive results, 25% (n=430) had positive findings in APOL1. Other positive findings included variants in PKD1/2 in 27% (456/1691) of cases, and in COL4A3/4 in 22% (379/1691) of cases. Among positive cases, 7% (119/1691) had >1 positive result, including both dial (n=115) and tripe diagnoses (n=4). APOL1 HRG was present in 50% (59/119) of cases with multiple diagnoses, accounting for 3.5% of all positive cases and 14% of all APOL1 HRG cases. Among the APOL1-plus cases, second positive findings were observed in COL4A3/4 (29%; 17/59), TTR (29%; 17/59), and PKD1/2 (15%; 9/59).

Conclusions: Dual diagnoses comprised 7% of all positive genetic testing results, with APOL1 HRG present in half of these cases. Future studies are needed to understand how multiple genetic diagnoses, including those with APOL1 HRG, impact disease presentation and progression. Dual APOL1 and collagen IV-related diagnoses are of particular interest given the frequency of these glomerulopathies in the CKD population. Genetic testing via broad NGS panels can improve diagnosis and management of CKD and increased testing will contribute to an evolving understanding of genetic etiologies of CKD.

PO1329
Uncovering Mechanisms of Risk-Variant APOL1-Modulated Inflammatory Signaling in Macrophages
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Background: In the United States, Black Americans face a higher risk to develop CKD and progress to end stage kidney disease (ESKD) even after accounting for clinical and socioeconomic factors. Variants in the gene encoding for the innate immunity factor Apolipoprotein L1 (APOL1) have been identified as risk factors for focal segmental glomerulosclerosis (FSGS) and HIV-associated nephropathy (HIVAN) in individuals with recent African ancestry. However, the role of immune cells in APOL1 nephropathy is not well understood. In this study we seek to understand the effect of risk variant APOL1 on macrophage function and inflammation.

Methods: Isogenic induced pluripotent stem cell (iPSC) lines expressing the G0, G1, and G2 variants of APOL1 were generated through CRISPR/Cas9 gene editing. These iPSC lines were used to generate iPSC-derived macrophages (iPDSM). Peripheral and bone marrow-derived macrophages (BMDMs) were collected from transgenic mice 4-18 weeks of age expressing G0, G1, and G2 variants of APOL1 in cultured iPDSM, peritoneal macrophages, and BMDMs were induced with IFNγ (5 ng/mL).

Results: We observed that risk-variant APOL1 expression results in higher TNF and IL1β gene expression by nine-fold and two-fold respectively, in G1 iPDSM compared to G0. Additionally, G2 mouse BMDMs exhibited increased glycolytic rate compared to G0 both at baseline and under mitochondrial stress when APOL1 was induced with IFNγ.

Conclusions: The findings in this study unveil some mechanisms by which risk-variant APOL1 modulates macrophage inflammatory phenotype and function, relevant to kidney disease progression.

Funding: Private Foundation Support

PO1330
A Multivariate Analysis of Genome-Wide Association (GWAS) Data to Identify Genes Associated with CKD
Amy J. Osborn, Agnieszka Bierzynska, Gavin I. Welsh, Moin Saleem, Ian C. Campbell. University of Bristol, Bristol, United Kingdom.

Background: Chronic kidney disease (CKD), a major public health burden, is characterised by a progressive loss of nephron function which leads to an impaired ability to filter the blood. Genome-wide association studies (GWAS) have identified single nucleotide polymorphisms (SNPs) and loci associated with the development of chronic kidney disease, (eGFR) and blood urea nitrogen (BUN) by mostly univariate-based analyses. However, gene-based multivariate-SNP and multivariate-biomarker relationships have typically not been considered so far in this context. The purpose of this study was to highlight the additional insights gained from the statistical power of a multivariate-based approach to identify potential risk factor genes for CKD.

Methods: We used a multivariate statistical approach, canonical correlation analysis (CCA), to identify single nucleotide polymorphisms (SNPs) that showed significant correlation with estimated glomerular filtration rate (eGFR) and blood urea nitrogen (BUN) together among univariate-based analyses. For each significant SNP and genes we identified, their functional, signalling pathways, and cellular expression were investigated using gene set enrichment analyses.

Results: For each of three published GWAS summary statistics datasets of both European and Japanese ancestry groups, we identified sets of 159, 246 and 181 protein-coding genes, respectively, that contained significant SNPs. Using gene set enrichment analyses, these genes showed significant enrichment for kidney development processes, signalling pathways and kidney cell gene expression signatures. In addition, between all three datasets, we identified four significant genes (CBLB, MACROD2, MFCOM and SHROI3) that overlapped. Between two datasets, we identified a further four significant SNPs that overlapped.

Conclusions: By using a multivariate statistical approach, we have identified both previously reported and additional genes that contained significant SNPs statistically associated with kidney function. Overall, these findings provide new insights into SNPs and genes potentially involved in kidney function and CKD risk.

Funding: Government Support - Non-U.S.

PO1331
Rare Variants and Risk of ESKD: The Geisinger Mycode-DiscoEHR Study

Background: Prior studies have reported that up to 10 patients with end-stage kidney disease (ESKD) have a diagnostic rare genetic variant but have lacked control groups.

Methods: Whole exome sequencing and electronic health records data from 147,750 participants in the Geisinger MyCode-DiscoEHR study, a health system-based cohort, were linked to the US Renal Data System to ascertain ESKD status and attributed cause. We compiled a list of variants in 80 autosomal or X-linked dominant (AD/XLD) genes used in commercial kidney genetics panels previously reported in ClinVar as pathogenic or likely pathogenic (P/LP) minor allele frequency <0.01, any number of stars. We evaluated the association of these rare P/LP variants with risks of all-cause and cause-specific ESKD in logistic regression models adjusted for age and sex. Additional analyses were performed by subsets of kidney disease genes and by age of ESKD onset.

Results: Prevalence of previously reported rare P/LP variants in AD kidney disease genes was higher in participants with ESKD than those without ESKD (3.0% vs. 1.2%). Rare P/LP variants were most prevalent in congenital/cystic ESKD (12.6%), followed by ESKD attributed to germline/nephropathies/skin conditions (8.9%), hypertension (4.3%), glomerular/vasculitis disorders (3.4%), and early onset diabetic ESKD (<60 years; 3.3%). By contrast, only 0.7% with later onset diabetic ESKD (60 years+) had rare P/LP variants. Individuals with rare variants were at increased risk of all-cause ESKD (OR 2.71, 95% CI 1.19-5.70) (Table). When genes were grouped by specific categories, rare variants in cystic disease, Alport Syndrome, CUKAT, and FSGS gene panels were all associated with increased risk of ESKD.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: Individuals in an unselected health system cohort with rare variants had substantially increased risk of ESKD, which was often attributed to hypertension or diabetes.

Funding: NIDDK Support, Other NIH Support - Geisinger Clinic

Associations between rare variants and ESKD phenotypes

PO1332

Genomic Disorders Are Associated with CKD Across the Life Span

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Background: Genetic Disorders (GDs), caused by pathogenic deletions and duplications (copy number variants, CNV) of large genomic regions, are the major cause of genetic susceptibility for multiple developmental traits and are enriched in pediatric chronic kidney disease (CKD) phenotypes. In the Chronic Kidney Disease in Children Study (CKiD) cohort 1.45% patients carried a GD.

Methods: We extended our previous study in CKiD to cohort 2 and also examined the prevalence of GDs in adults with all-cause CKD enrolled in the Chronic Renal Insufficiency (CRI, N = 3375), Columbia University CKD (CU-CKD, N=1146) and Family Investigation of Nephropathy and Diabetes (FIND, N=1318) cohorts, comparing GDs in adults with all-cause CKD enrolled in the Chronic Renal Insufficiency (CRI, N = 3375), Columbia University CKD (CU-CKD, N=1146) and Family Investigation of Nephropathy and Diabetes (FIND, N=1318) cohorts, comparing them to 30746 controls. CNV calls were based on SNP microarrays and whole exome sequencing and annotated for known GDs. We also performed a phenome-wide association analysis of GDs in the Electronic Medical Records and Genomics (eMERGE, N=11971) cohort.

Results: We found 9248 (3.6%) CKD2 pediatric participants with mild CKD carried a GD, replicating prior findings in pediatric CKD. We next identified GDs in 74,667 (1.1%) adult CKD patients in the CRI, CU-CKD and FIND cohorts, compared to 165,30.746 (0.5%) GDs in controls (OR=1.6, p<5x10^-10). Recurrent known GDs in adult CKD patients comprised pathogenic CNVs in 1q21.1, 16p11.2, 17q12 and 22q11.2 loci. The 17q12 GD (renal cyst and diabetes syndrome) was most frequent, detected in 1,252 CKD cases with diabetes. In the phenome-wide analysis of the eMERGE cohort, dialysis was in the top three phenotypic associations with GD carrier status (p<10^-9), replicating the case-control association results. Other phenotypic associations for GDs in CRIC participants included lower serum Mg (p=2x10^-10) and lower educational achievement (p=5x10^-10).

Conclusions: GDs are significantly enriched in children and adults with CKD. Undiagnosed GDs can provide a molecular explanation for renal disease in both adults and children and represent hidden genetic links between CKD and other traits such as poorer neurocognitive performance. Systematic detection of GDs can enable a precise genetic diagnosis and inform prognosis and treatment.

Funding: NIDDK Support, Other NIH Support - NHGRI

PO1333

Genome-Wide Association Study in Mice Maps Susceptibility to HIV-Associated Nephropathy to the Sshp2 Locus

Nicholas J. Steers,1 Yask Gupta,2 Vittore D. D’Agati,3 Tze Yin Lim,1 Anna Mo,1 Judy Liang,1 Kelsey O. Stevens,1 Natalia D. Demaria,1 Wan Yee Lam,4 Lalitha Nagarajan,5 Simone Sanna-Cherchi,6 Ali G. Ghavri,9 Columbia University Irving Medical Center, New York, NY; 1The University of Texas MD Anderson Cancer Center, Houston, TX.

Background: To gain insight into the pathogenesis of collapsing glomerulopathy, a rare form of focal segmental glomerulosclerosis that often arises in the setting of viral infections, we performed a genome-wide association study (GWAS) among inbred mouse strains using a murine model of HIV-1 associated nephropathy (HIVAN).

Methods: F1 hybrids were generated between HIV-1 transgenic mice on the FVB/NJ background and 20 inbred laboratory strains. Histology, BUN, proteinuria and urinary NGAL were assessed in the F1 hybrids. A GWAS in 366 transgenic F1 hybrids generated from these 20 inbred strains was performed.

Results: Six stains (A/J, C3H/HeJ, DBA/J, KK/HJ, WSB/EiJ, and LP/J) were highly sensitive to the Tg resulting in severe glomerulosclerosis, 9 strains (129S1/SvImJ, Balb/CJ, C57BL/6J, C57Bl/6NJ, C57Bl/10J, C57Bl/J, C57/J, CAST/EiJ and NZB/BINJ) were resistant to the Tg resulting in limited to no glomerulosclerosis, and 5 strains (CBA/J, DBA/2J, NOD/ShiLtJ, NZO/HILtF and FVB/NJ) had intermediate glomerulosclerosis. Analysis of histology, BUN and urinary NGAL demonstrated a marked phenotypic variation among the transgenic F1 hybrids, providing strong evidence for host genetic factors in the predisposition to nephropathy. A GWAS identified a genome-wide significant locus on Chr. 13 and multiple additional suggestive loci. Cross annotation of the Chr. 13 locus, including single cell transcriptomic analysis of wild type and HIV-1 transgenic mice kidneys, nominated Sshp2 as the likely culprit gene. Sshp2 is highly expressed in podocytes, encodes a transcriptional cofactor present in LDB1 containing complexes, and interacts with LMX1B, a known FSGS gene that requires LDLH for optimal transcriptional activity. Consistent with these data, older Sshp2 null mice spontaneously developed glomerulosclerosis, tubular casts, interstitial fibrosis and inflammation, similar to the HIVAN mouse model.

Conclusions: These findings demonstrate the utility of GWAS in mice to uncover host genetic factors for rare kidney traits and suggest Sshp2 as susceptibility gene for HIVAN, potentially acting via the LDLH-LMX1B transcriptional network. Future studies will evaluate the role of Sshp2 in vitro and in Sshp2 null mice.

Funding: Other U.S. Government Support
and papillorenal syndrome. Case 2: 21-year-old male with biopsy proven FSGS when he had an atypical c.233A>C (p.Glu82Arg) mutation in the KCNJ5 gene, which can lead to FSGS, optic nerve coloboma, and hypertension. Genetic testing showed a truncating c.247delC variant in the COL4A3 gene, associated with PKD1, was detected in a 21-year-old male with biopsy proven FSGS when he was 8 years old mentioned that his maternal grandfather suffered from unknown renal disease requiring dialysis and died in his 40s. Genetic testing revealed hemizygous, truncating p.W58* variant in the CLCN5 gene. Variants in CLCN5 gene can cause Dent’s Disease manifesting later in life as proteinuria, nephrinoclastosis, hypercalciuria and renal failure. In addition he had variant of unknown significance in NPHS1 designated p.T233A, and APOL1 G2 risk allele predisposing him to develop FSGS. Case 3: 21-year-old male, born with genital ambiguity, perineal hypoplasias, 46 XY karyotype was noted to have 14 g of proteinuria, low albumin and hypertension. Kidney biopsy revealed FSGS, abnormal glomerular basement membrane. Genetic testing was positive for heterozygous truncating variant of WT-1 and a monogenic missense variant of SMARCAL1 p.R520H which are pathogenic variants that cause renal failure due to defective podocyte development and dysfunction respectively.

Discussion: Genetic analysis for FSGS has become an important diagnostic tool in nephrology. We currently have over 50 genes that are known to be involved in FSGS. Reporting of different genetic variants and their occurrence is crucial to yield insight into our current understanding of FSGS.

PO1337

Whole-Exome Sequencing Reveals a Monogenic Cause of Disease in 26% of 335 Families with Steroid-Resistant Nephrotic Syndrome

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Background: Steroid resistant nephrotic syndrome (SRNS) overwhmelingly progresses to end-stage renal disease. To date, more than 59 monogenic genes have been identified to cause SRNS. We previously detected causative mutations in 26% of whole exome sequencing (Wexome) patients with SRNS using targeted panel sequencing (Sadowski 2015; Warejko 2017). However, whole exome sequencing (WES) has become more accessible, with the advantage of detecting not only known monogenic causes of SRNS, but also novel candidate NS-causing genes.

Methods: We employed whole exome sequencing (WES) to detect monogenic causes of SRNS in a large international cohort of 335 families with SRNS presenting before the age of 25 years.

Results: Samples were recruited from April, 1998 to December, 2018 (21 years). WES was performed at the Yale Center of Mendelian Genomics. First, we examined the WES data for mutations in 59 known genes known to cause SRNS. In 87/335 families (26%), we identified mutations in 22 of the known genes. There were also 7 genes that were identified in phenocopies of SRNS e.g. COL4A3. In 58 families (17.3%), we have identified mutations in a potential novel candidate gene for SRNS. We found a 48.1% solve rate in individuals with high homogyosity by decent and 15.4% solve rate in non-homogyous individuals, recapitulating similar solve fractions to what has been previously published (Sadowski 2015; Warejko 2017).

Conclusions: This study confirms that ~26% of families with NS in our cohort are due to monogenic causes, WES is a viable way to diagnose the underlying cause of NS in children and young adults, and to suggest novel monogenic candidate genes of NS.

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PO1338

Discovery of Podocyte-Specific Interaction Partners of the Nephrotic Syndrome-Associated Protein NOS1AP

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Background: NOS1AP mutations are a novel Mendelian cause of nephrotic syndrome (NS) in humans and mice (Majmundar Sci Adv 2021). The NS patient mutation p.C143Y destabilizes the predicted structure of the NOS1AP phosphotyrosine-binding domain, impairs NOS1AP-dependent actin remodeling in podocytes. These proteins may mediate NOS1AP-dependent actin remodeling and thus help stabilize podocytes

Methods: Protein interaction data from candidate immunoprecipitation, mass spectrometry, and yeast two-hybrid studies were queried from the literature and public databases (Orchard 2014; Oughtred 2018). Protein interactions were validated by co-immunoprecipitation studies using tagged cDNA constructs.

Results: 85 putative NOS1AP-interacting proteins were identified from candidate interaction and proteomics studies. Six interacting proteins (of 85) demonstrated co-expression with NOS1AP in podocyte clusters from at least three out of four kidney scRNAseq datasets (% cell expression z-score > 1). Four of six candidates (FYN, GSN, SNTA1, HSP1A2A) were cloned into expression vectors for interaction studies. SNTA1 and HSP1A2A exhibited bi-directional co-immunoprecipitation with wildtype NOS1AP upon co-overexpression in a podocyte cell line. Co-immunoprecipitation was, similarly, observed with the NS patient mutant NOS1AP.

Conclusions: Our results suggest NOS1AP is co-expressed with and can physically interact with SNTA1 and HSP1A2A in podocytes. These proteins may mediate NOS1AP functions in podocyte biology.

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POI1339  
Synuclein Alpha Accumulation Drives Lysosomal Dysfunction in Fabry Podocytopathy  
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Background: Anderson-Fabry disease is an X-linked lysosomal disorder characterized by a multisystemic globothriaosylceramide (Gb3) accumulation due to reduced alpha-galactosidase activity (GLA). Podocyte injury is a major renal manifestation of Fabry disease. Recently, our data indicated Gb3 depletion to be insufficient in repairing podocyte damage seen in an in vitro model for Fabry disease. This project, therefore, focused on potential Gb3 independent mechanisms in Fabry podocytopathy.

Methods: We employed CRISPR/Cas9 to generate GLA knock out lines of immortalized human podocytes in-vitro. These cells were investigated by (ultra-)structural, transcriptional and proteome as well as functional analyses in the presence and absence of enzyme replacement therapy (ERT). The acquired data sets were integrated through network analysis and connectivity mapping. These data were complimented by the investigation of human biopsies taken sequentially before and after a period of ERT.

Results: We detected that enzyme replacement therapy (ERT) and Gb3 reduction failed to completely reverse the podocyte injury in patient biopsies. GLA knockodout podocytes depicted high Gb3 levels that were fully reversed upon enzyme replacement. Still lysosomal dysfunction was significantly but not completely reversible with enzyme replacement. Proteomics suggested alpha-synuclein (SNCA) accumulation as a potential driver of podocyte dysfunction. Transcription-based connectivity mapping further revealed a potential anti-SNCA therapeutic effect of beta-adrenoceptor agonists. Indeed, genetic and pharmacological inhibition of this protein significantly improved lysosomal structure and function in Fabry podocytes beyond the effects of ERT.

Conclusions: This study provides strong evidence of a central role of SNCA in lysosomal dysfunction in Fabry disease independent of Gb3 accumulation. The results offer new options for pharmacological strategies to target Fabry podocytopathy.

POI1340  
Drosophila TBC1D8B Promotes Nephrin Endocytosis and Is Required for Endosomal Cargo Processing  
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Background: Mutations in TBC1D8B were recently identified as a monogenic cause of nephrotic syndrome. TBC1D8B interacts with nephrin and it was implicated as an inhibitory GAP protein for Rab11 which regulates endocytic recycling. However, the functional spectrum of TBC1D8B and its role in trafficking of nephrin remains poorly understood.

Methods: We generated and analyzed a stable genetic deletion of fly Tbc1d8b via CRISPR/Cas9. We successfully introduced a c-terminal HA-tag into the Gapvd1 c-terminus. We performed a functional investigation of human biopsies taken sequentially before and after a period of ERT.

Results: We generated and analyzed a stable genetic deletion of fly Tbc1d8b via CRISPR/Cas9. We successfully introduced a c-terminal HA-tag into the Gapvd1 c-terminus. We performed a functional investigation of human biopsies taken sequentially before and after a period of ERT.

Conclusions: This study provides strong evidence of a central role of SNCA in lysosomal dysfunction in Fabry disease independent of Gb3 accumulation. The results offer new options for pharmacological strategies to target Fabry podocytopathy.

POI1341  
Stable Genetic Deletion of Gapvd1 in Drosophila Results in a Nephrocyte-Restricted Phenotype  
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Background: Mutations in the gene GAPVD1 cause nephrotic syndrome in humans. GAPVD1 interacts with Rab8 and but the subcellular localization of GAPVD1 is unknown. Silencing of Gavpd1 in the neprocyte-like Drosophila nephrinocytes by RNA-interference resulted in mislocalization of fly nephrin.

Methods: We generated conditional knockdowns and a stable genetic deletion of Drosophila Gapvd1 by CRISPR/Cas9 and used microtomology-mediated end junction to introduce a genomic HA-tag into the Gapvd1 c-terminus. We performed a functional analysis of the novel fly models.

Results: We generated twin frameshift mutations at the second and third exons of the Drosophila Gapvd1 gene. Animals carrying these mutation were homozygous viable without any overt phenotype. However, the podocyte-like nephrinocytes revealed a severely altered slit diaphragm morphology with mislocalization of fly nephrin and the orthologue of NEPH1 and partial loss of both proteins from the surface. This phenotype was similar but considerably stronger than the phenotype observed by RNA-mediated silencing. This suggests that the homozygous frameshift mutations result in a null allele. The phenotype was further confirmed by conditional CRISPR/Cas-mediated silencing using two different gRNAs. Deletion of Gapvd1 in the Drosophila model thus results in a phenotype that manifests exclusively in disturbed slit diaphragm formations. This recapitulates the nephrinopathy phenotype of patients that was limited to nephrotic syndrome, supporting the use of Drosophila model for this genetic disease. To study the subcellular localization of Drosophila Gapvd1, we introduced an HA-tag into the c-terminus of the Gapvd1 locus. Immunofluorescence of nephrinocytes derived from the knock-in lines showed that the HA-tag is localized to the plasma membrane. We employed CRISPR/Cas9 to generate GLA knock out lines of immortalized human podocytes (HeK1). We successfully introduced a c-terminal HA-tag into the Gapvd1 c-terminus. We performed a functional investigation of human biopsies taken sequentially before and after a period of ERT.

Conclusions: This study provides strong evidence of a central role of SNCA in lysosomal dysfunction in Fabry podocytes beyond the effects of ERT.

Funding: Government Support - Non-U.S.
A Human Missense Integrin-Linked Kinase Variant Negatively Regulates Murine Renal Branching Morphogenesis via mTOR Signaling

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Background: Branching morphogenesis is critical to kidney development and the pathogenesis of Congenital Anomalies of the Kidney and Urinary Tract (CAKUT). Identification of gene variants via genomic sequencing aims to elucidate molecular mechanisms underlying CAKUT. The pathogenic contributions of such variants are largely unknown; functional analyses are required to identify pathogenic mechanisms. Here, we identify pathogenic effects of a CAKUT-associated human missense variant of Integrin-Linked Kinase (ILK), a key regulator of renal branching morphogenesis, on ureteric branching.

Methods: Targeted gene panel sequencing was performed to identify gene variants. ILK-T173I function was investigated in mouse inner medullary collecting duct (mIMCD3) cells and mouse embryonic kidney explants transduced with lentivirus expressing ILK-T173I. Gene expression was analyzed by RNA microarray and validated by qPCR and Western analysis. Mutant mice with a ILK-T173I point mutation were generated using CRISPR/Cas9. Morphogenic effects of ILK-T173I on ureteric branching were visualized using Hoxb7-driven fluorescent marker (MyVenus) and quantitated by counts of ureteric bud tips and nephrons.

Results: An ILK missense variant, ILK-T173I, was identified in a CAKUT patient and her mother by targeted gene panel sequencing and verified by Sanger sequencing. mIMCD3 cells expressing ILK-T173I demonstrated dysregulated expression of AKT/mTOR target mRNAs, identified by RNA microarray and qPCR, and elevated levels of phospho-p70-S6Kinase, a mTOR target (n=3, P=0.03). Overexpression of ILK-T173I in embryonic kidney explants increased phospho-p70-S6Kinase expression (n=3, P=0.03) and decreased ureteric tip number by 50% (n=15, P=0.003), both of which were rescued by phospho-p70-S6Kinase, a mTOR target (n=3, P=0.03). Treatment of mutant cultured embryonic kidney explants with Rapamycin restored ureteric branching to levels observed in wild-type mice (n=3, P=0.01). Treatment of mutant cultured embryonic kidney explants with Rapamycin restored ureteric branching to levels observed in wild-type mice (n=3, P=0.01). Treatment of mutant cultured embryonic kidney explants with Rapamycin restored ureteric branching to levels observed in wild-type mice (n=3, P=0.01).

Conclusions: Human ILK-T173I variant decreases branching morphogenesis in a mTOR-dependent manner. Increased mTOR signaling disrupts mouse kidney development.

Funding: Government Support - Non-U.S.

Whole-Exome Sequencing Identifies Likely Deleterious Variants in 50 Families with Spina Bifida

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Background: Spina bifida (SB) is the second most common nonlethal malformation (1/1000 births). Several lines of evidence indicate that SB can be of mono- genetic origin: i) its congenital nature; ii) familial occurrence; iii) it being part of the phenotypic manifestation of known monogenic syndromes; iv) the knowledge that specific master genes govern neural tube morphogenesis; v) the existence of monogenic mouse models with SB. We hypothesized that whole exome sequencing (WES) enables identification of likely candidate mutations in a list of 170 candidate genes for SB that we generated, and may allow us to identify potential novel genes for SB.

Methods: We generated a list of 170 candidate genes of four categories: A) 33 known candidate genes from monogenic SB models; B) 33 known candidate genes from human isolated SB, C) 70 known candidate genes from human syndromic SB, and D) 34 known candidate genes considered as risk factors for human SB. We evaluated WES data of 50 families with SB for likely deleterious variants in the 170 candidate genes, and for potential novel monogenic causes of SB.

Results: Through systematic candidate gene analysis in combination with family-based unbiased evaluation in 50 SB families, we identified 16 likely deleterious variants in 170 SB candidate genes in 14/50 (28%) families: A) 5 variants (5 families) were identified in mouse candidate genes, B) 9 variants (7 families) were identified in human candidate genes for isolated SB, C) 1 variant (1 family) was identified in human syndromic candidate gene, and D) 1 variant was identified in human SB risk candidate gene. In addition, in 11 (22%) of SB families, we identified mutations in a potential novel gene for SB.

Conclusions: In 28% of individuals with SB we identified likely deleterious variants in 170 candidate genes that we generated. Candidate genes that cause SB in mice can be considered as a potential human SB candidate gene. We additionally identified a potential novel gene in 22% of SB families.

Funding: Other NIH Support - DK076683

Pleiotropy of Congenital Anomalies of Kidney and Urinary Tract (CAKUT) Phenotypes in Human 16p11.2 Microdeletion Syndrome Is Recapitulated in Mouse Models of Tbx6 Deletion

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Background: We showed that 16p11.2 microdeletions are a major contributor to congenital anomalies of the kidney and urinary tract (CAKUT), and identified Tbx6 as the most likely culprit. It remains elusive what are the mechanisms by which gene dosage reduction causes CAKUT and what are the Tbx6 downstream signaling pathways and targets.

Methods: We studied a Tbx6 allele-specific gene for dosage analysis using two independent alleles: a null allele and a hypomorph allele. We conducted detailed phenotypic analysis of these models across early and late development. We generated gene dosage data from E9.5 tailbud mesenchyme and conducted in silico binding site analyses.

Results: Phenotypic analysis showed recapitulation of the whole Tbx6 spectrum observed in 16p11.2 patients (renal agenesis and hypoplasia, hydronephrosis, and duplication of the collecting system) but also profound lower urinary tract defects (rectovesical fistula, persistent cloaca, defects of neophic duct insertion into the urogenital sinus, urethral malformations and failed insertion of the Müllerian ducts). These defects implicate an early effect of Tbx6 in urinary tract development. Tbx6 insufficiency also disrupted the occurrence of ectopic neural tubes that impaired the reciprocal interaction between the ureteric bud and metanephric mesenchyme, providing additional mechanisms linking Tbx6 to CAKUT and its pleiotropy. Differential gene expression analysis coupled with supervised and unsupervised genet set enrichment identified somite development and Notch signaling. Binding site and motif enrichment analyses recovered known and novel targets in the Tbx6 interactome including A.1,2,3,4,5 and relin.

Conclusions: Phenotypic investigation coupled with gene expression and binding site analyses provides support for causality for Tbx6 and CAKUT as well as its pleiotropy; provides a mechanistic reason for causation; and identifies pathways and targets regulated by Tbx6. The involvement of Notch signaling is interesting as mutations in NOTCH2 cause Alagille syndrome, characterized by CAKUT and skeletal defects observed both in our Tbx6 mouse models and in patients that carry the 16p11.2 microdeletion. These data implicate loss of Tbx6-mediated regulation of Notch as critical to the development of CAKUT and spine defects.

Funding: NIDDK Support
PO1347 Excess Burden of Rare Coding Variants in Mutation Intolerant Genes in Patients with Kidney Malformations
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Background: Renal hypoplasiasia (RHD) is one of the most common cause of pediatric kidney failure. Although multiple causative genes have been identified, they only account for 10-15% of cases. The contribution of rare variants has not been systematically examined.

Methods: To evaluate the contribution of rare variants to RHD, we analyzed exome sequencing (ES) data in 1,265 unrelated RHD cases and 13,303 unrelated controls. We used gene-level burden analysis, comparing the proportion of cases and controls carrying rare variants per gene across 29 statistical models.

Results: We observed a 1.63-fold case enrichment for rare variants (p= 1.5x10^-8) in known genes associated with dominant forms of kidney diseases (165 cases versus 1,075 controls in 172 known genes), including PKD1 (7.6x10^-8) and HNF1B (5.6x10^-9). All other known genes did not reach statistical significance (p-value<10^-6). Applying a similar approach, we observed a 1.35-fold case enrichment for rare missense variants (p=5.8x10^-8) in genes constrained against missense (miRZ >3.09) and a 1.59-fold enrichment for rare protein truncating variants (PTV; p=2.4x10^-8) in genes constrained against PTV (pLI<0.9 and oc lf upper<0.35). We particularly identified a 2.38-fold enrichment for PTV in 421 genes constrained against PTV, expressed in the mouse developing kidney (E15.5), and not known to be associated with human kidney disease (p=4x10^-8). Fig. 1. Cationically, the presence of publically available databases, we identified at least 23 novel candidate genes, which will require validation in additional human cohorts or analysis of animal models.

Conclusions: We detected a significant excess of rare variants in mutation intolerant genes that are also expressed during early kidney development, suggesting the existence of many yet-to-be-identified causal genes. However, owing to the high genetic heterogeneity of RHD, larger-scale investigations will be required to establish causality for individual genes.

Funding: NIDDK Support

PO1348 Reverse Phenotyping Facilitates Disease Allele Calling in Whole-Exome Sequencing of Patients with Congenital Anomalies of Kidney and Urinary Tract (CAKUT)
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Background: Congenital anomalies of the kidneys and urinary tract (CAKUT) constitute the leading cause of chronic kidney disease in children and young adults. To date, 174 genes are known to cause isolated or syndromic congenital CAKUT. However, incomplete penetrance and broad phenotypic heterogeneity can impair disease allele identification, particularly in syndromic CAKUT. We hypothesized that the yield of a genetic diagnosis can be increased by combining whole exome sequencing (WES) with reverse phenotyping, in which the contributing physician is asked to examine a patient for signs/symptoms that may occur in the suspected clinical syndrome that results from the genetic variant detected by WES.

Methods: We conducted WES in an international cohort of 823 individuals with CAKUT from 732 unrelated families and evaluated WES data for variants in the 174 genes in which variants are known to cause isolated or syndromic CAKUT. In cases in which the likely causative genotype suggested a syndromic phenotype that was not reported at enrollment, we conducted reverse phenotyping.

Results: In 84/732 (11.5%) families, we detected a likely causative variant consistent with an isolated or syndromic CAKUT phenotype. In 19 of the 84 families (22.6%) with detection of a likely CAKUT-causing variant, reverse phenotyping yielded syndromic findings, thereby strengthening the genotype-phenotype correlation.

Conclusions: We conclude that employing reverse phenotyping in the evaluation of (facultative) syndromic CAKUT genes by WES provides an important tool to establish a more valid and specific diagnosis mitigating the broad phenotypic and genotypic heterogeneity of CAKUT.

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PO1349 Broad Genetic Analysis Reveals Diverse Molecular Causes of Autosomal Dominant Tubulointerstitial Kidney Disease-Not Otherwise Specified (ADTKD-NOS)
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Background: A particularly difficult group of diseases to diagnose are the Autosomal Dominant Tubulointerstitial Kidney Diseases (ADTKD). ADTKD is caused by mutations in one of at least five genes and leads to end-stage renal disease usually in mid adulthood. Families where no mutation can be found are therefore termed ADTKD-NOS (not otherwise specified), who are the focus of this study. Herein we investigated 45 families of our ADTKD registry.

Methods: The study was approved by the institutional ethics committee (protocol number 251_18B). Detailed pedigree analysis and clinical characterisation of kidney diseases were performed, as well as evaluation of historical kidney biopsies, where available. In addition, sequencing on all known ADTKD candidate genes was performed, followed by SNaPshot minisequencing for the dupC mutation of MUC1. Exome-Sequencing was performed on the HiSeq System 2500 (Illumina) after enrichment by TWIST human core technology (TWIST Bioscience). Initially, 560 genes associated with abnormal renal physiology (Human Phenotype Ontology, https://mpc.org/hpo-browser.php?12622, retrieved March 2020) were screened (here termed nephrome). If no disease-causing variants were detected, exome-wide analysis was performed.

Results: In 30 of the 45 registry families mutations in known ADTKD genes were found, most frequently MUC1. In the remaining 15 families diagnostic gene variants were either detected in the nephrome (4x COL4A5, 1x COL4A4x, 2x IN2, 1x PA2) or the exome, where analysis yielded potentially disease associated variants in novel candidate genes for ADTKD. A list of these candidate genes in the respective families will be presented. All variants segregated within families.

Conclusions: In the great majority of our ADTKD registry families we were able to reach a molecular genetic diagnosis. However, a small number of families are indeed affected by diseases, which should in retrospect be seen as glomerular origin. Atypical clinical presentation, (seemingly) autosomal dominant pedigrees (i.e. ADTKD-Not otherwise specified disease) and sometimes decades since onset of disease and genetic evaluation have handicapped the classification towards ADTKD-NOS. The other families investigated by exome analysis have partly led to identification of promising novel candidate genes. However, for functional studies will need to follow to determine if these variants are truly pathogenic.

Funding: Government Support - Non-U.S.

PO1350 Prevalence of Autosomal Dominant Tubulointerstitial Kidney Disease in the German Chronic Kidney Disease (GCKD) Cohort
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Background: Exome sequencing (ES) studies in chronic kidney disease (CKD) cohorts could identify pathogenic variants in ~10%. This implies underdiagnosis of hereditary CKD. Tubulointerstitial kidney diseases (TUD), showing non typical clinical presentation, (seemingly) autosomal dominant pedigrees, and sometimes decades since onset of disease and genetic evaluation have handicapped the classification towards ADTKD-NOS. The other families investigated by exome analysis have partly led to identification of promising novel candidate genes. However, for functional studies will need to follow to determine if these variants are truly pathogenic.

Methods: We used a targeted panel (29 genes) and MUC1-SnaPshot to sequence 271 DNA samples selected by clinical criteria from 5,217 individuals in the GCKD (German CKD) cohort.

Results: We identified 33 pathogenic small variants. Of these 27 (81.8%) were in COL4 genes, the largest group being 15 COL4A5 variants with 9 unrelated individuals carrying distinct MTTF-variants. A COL4A4x deletion, and a novel splice variant in HNF1B and the homoplasmic MTTF variant m.616T>C. Copy-number analysis identified a heterozygous COL4A5 deletion, and a duplication/deletion of HNF1B, respectively. Overall, we found pathogenic variants in 15% (97 of 617 individuals) and at least 36% of unrelated individuals (9 of 26 families) had an unknown significance in 9.6%. This yield is high despite considering the targeted design and PKD1/2 exclusion. To explain this difference we compared our findings to the largest ES study in adults with CKD by random sampling. None of the 10,000 simulations resulted in an equal or higher yield (p<0.05). Variant classification differences were excluded using automated ACMG classifiers.

Conclusions: Our study shows that >10% of individuals with certain clinical features carry disease variants in genes associated with TUD. COL4 genes constitute the largest fraction, implying that these variants are overlooked when applying clinical criteria for Alport syndrome. We also identified variants easily missed by some ES pipelines. Bioinformatic predictions paired with gold standard diagnostics for MUC1 (SnaPshot) could not identify the typical cytosine duplication (c.428dupC) in any individual of this
cystinosis, which demonstrates that urinary BiP excretion was significantly elevated in ADTKD-
patients compared with unaffected controls. Moreover, urinary BiP elevation was
quantitatively correlated with disease severity. Finally, based on all our findings, we have
developed a new ultrasensitive method to detect urinary BiP in affected individuals. We therefore developed the ultrasensitive p-FLISA,
which demonstrated that urinary BiP excretion was significantly elevated in ADTKD-
patients compared with unaffected controls. Moreover, urinary BiP elevation was
positively associated with disease severity. These findings are consistent with the presence
of kidney progenitor cells in urine of cystinosis patients, and to explore the feasibility of
using kidney progenitor cells for disease modeling, while we provided proof of principle of
their potential use for studying the late effects of cystinosis.

**Conclusions:** By developing the ultrasensitive p-FLISA, we have identified secreted
BiP as a novel urinary stress biomarker with potential utility in risk stratification,
prediction of disease progression and guidance of ER-targeted therapies in ADTDK.

**Funding:** IDEDK Support, Other U.S. Government Support

**POI1354**

Urine-Derived Kidney Progenitor Cells in Cystinosis: Potential for Disease Modeling and Ex Vivo Gene Therapy

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**Background:** Nephropathic cystinosis is an inherited multisystem lysosomal storage disorder caused by mutations in the CTNS gene. The kidney phenotype is characterized by excessive shedding of proximal tubular cells and podocytes into urine, development of renal Fanconi syndrome and progression to end-stage kidney disease. We hypothesized that, to compensate for epithelial cell losses, cystinosis kidneys undertake a regenerative effort, albeit maladaptive. We aimed to search for the presence of kidney progenitor cells (KPCs) in urine of cystinosis patients, and to explore the feasibility of ex vivo gene therapy.

**Methods:** We isolated undifferentiated cells from urine of cystinosis patients, characterized them as KPCs (Cys-uKPCs) and differentiated these to functional kidney epithelial cells (Cys-uKPC-PTEC) by conducting a novel approach with wild-type CTNS and Cys-uKPC-PTEC. RNA sequencing demonstrated distinctive transcriptomic signatures distinguishing Cys-uKPCs, Cys-uKPC-Podo and Cys-uKPC-PTEC as functional kidney epithelial cell types. These cells can be isolated, differentiated to functional kidney epithelial cells and complemented with wild-type CTNS to improve the cellular phenotype. Cystinosis uKPCs are a novel tool for disease modeling, while we provided proof of principle of ex vivo gene therapy.

**Funding:** Private Foundation Support

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**POI1353**

Adult Zebrafish as a Model to Study Renal and Extrarenal Manifestations of Cystinosis

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**Background:** Cystinosis is a rare autosomal recessive disease caused by mutations in the CTNS gene, which encodes for the cystine transporter cystinosin leading to lysosomal cystine accumulation in all cells of the body, with kidneys being the first affected organs. The current treatment with cysteamine decreases the lysosomal cystine accumulation, but does not reverse the renal Fanconi syndrome, glomerular injury or loss of renal function. We have developed a zebrafish larvae model having truncating mutations in ctns, which recapitulates the kidney phenotype of cystinosis. However, long-
term disease consequences in adult zebrafish have not been studied so far. In this study, we characterized the adult zebrafish model to evaluate the late effects of cystinosis on kidney and extra renal organs.

**Methods:** Cystinosis (ctns-/-) zebrafish of 18 months and wild type (WT) zebrafish were studied. Histologic examinations of kidneys and extra-renal organs were performed. Cleaved caspase-3 staining was used to evaluate apoptosis in the kidney. Cystine accumulation was evaluated via in situ hybridization of a ctsn-specific mRNA probe and toluidine blue staining. For the fertility studies, the number of total eggs and fertile eggs produced by breeding female and male ctns-/- zebrafish compared to WT zebrafish was evaluated.

**Results:** ctns-/- zebrafish show increased cystine level, glomerular hyper trophy and proximal tubular accumulation of hyaline-like eosinophilic droplets and vacuolated cytoplasm. Moreover, the cystinotic zebrafish exhibit increased cleaved caspase-3, indicating enhanced apoptosis in the proximal tubules. In addition, instead of the typical striped pattern, ctns-/- zebrafish present an altered melanin skin pigmentation, resulting in spotted skin. Lastly, male ctns-/- zebrafish show spermatogenic cysts enriched in spermatozoa, while female display increased percentage of unfertilized eggs.

**Conclusions:** The adult ctns-/- zebrafish model reproduces several phenotypes of cystinosis, as altered glomerular and proximal tubular morphology, whole body cystine accumulation, impaired skin pigmentation and decreased fertility. Therefore, this model may be useful for studying long-term effects of cystinosis and for the development of new therapeutic strategies for correcting cystinosis, which is - up to now - incurable.

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**POI1352**

Genetic Analysis of a Brazilian Nephropathic Cystinosis Cohort Reveals Novel CTNS Variants Mostly of Non-European Origin

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**Background:** Nephropathic Cystinosis (NC) is a severe autosomal recessive disease caused by intralysosomal cystine deposition. Most CTNS variants have been described in Europe and North America, where a specific 57kb deletion (del) is the most frequent one. In this study, we sought to characterize the CTNS variants and their genetic ancestry profiles in a NC Brazilian cohort, an admixed population.

**Methods:** 61 NC patients were studied, both sexes, ≤21 years old, followed at the University of Sao Paulo Medical Center. Mutation analysis was performed by gel electrophoresis and/or MLPA to assess the 57kb del, and NGS targeted sequencing. To characterize the genetic ancestry profiles, 48 patients were genotyped with a high-density SNP array. The average genomic ancestry was inferred using ADMIXTURE and the detected variants included 9 previously characterized them as KPCs (Cys-uKPCs) and differentiated these to podocytes and PTECs. These cells can be isolated, differentiated to functional kidney epithelial cells and complemented with wild-type CTNS and Cys-uKPC-PTEC. RNA sequencing demonstrated distinctive transcriptomic signatures distinguishing Cys-uKPCs, Cys-uKPC-Podo and Cys-uKPC-PTEC as functional kidney epithelial cell types. These cells can be isolated, differentiated to functional kidney epithelial cells and complemented with wild-type CTNS to improve the cellular phenotype. Cystinosis uKPCs are a novel tool for disease modeling, while we provided proof of principle of ex vivo gene therapy.

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**POI134**

Urine-Derived Kidney Progenitor Cells in Cystinosis: Potential for Disease Modeling and Ex Vivo Gene Therapy

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**Background:** Nephropathic cystinosis is an inherited multisystem lysosomal storage disorder caused by mutations in the CTNS gene. The kidney phenotype is characterized by excessive shedding of proximal tubular cells and podocytes into urine, development of renal Fanconi syndrome and progression to end-stage kidney disease. We hypothesized that, to compensate for epithelial cell losses, cystinosis kidneys undertake a regenerative effort, albeit maladaptive. We aimed to search for the presence of kidney progenitor cells (KPCs) in urine of cystinosis patients, and to explore the feasibility of ex vivo gene therapy.

**Methods:** We isolated undifferentiated cells from urine of cystinosis patients, characterized them as KPCs (Cys-uKPCs) and differentiated these to podocytes (Cys-uKPC-Podo) and proximal tubular epithelial cells (Cys-uKPC-PTEC) as shown by qPCR, RNA sequencing, immunostainings and specific functional assays. Complementation of CTNS in Cys-uKPCs was performed via lentiviral vector (LV) transduction.

**Results:** Cystinosis patients voided high numbers of undifferentiated cell populations, of which specific clones expressed several kidney progenitor markers, showed a high level of self renewal, and could differentiate to functional kidney progenitor cells. RNA sequencing demonstrated distinctive transcriptomic signatures distinguishing Cys-uKPCs, Cys-uKPC-Podo and Cys-uKPC-PTEC. Ex vivo gene therapy using a gene addition approach with wild-type CTNS showed significant reductions of cystine levels and alleviation of the perinuclear distribution of the LAMP1+ endo-lysosomal compartment.

**Conclusions:** Kidney progenitor cells are present in the urine of cystinosis patients. These cells can be isolated, differentiated to functional kidney epithelial cells and complemented with wild-type CTNS to improve the cellular phenotype. Cystinosis uKPCs are a novel tool for disease modeling, while we provided proof of principle of ex vivo gene therapy.

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**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underlines represent presenting author.
PO1355
Vascularized Kidney Organoids on Chip for Efficacy and Toxicity Testing of Somatic Genome Editing

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Background: Somatic genome editing has therapeutic potential to cure inheritable diseases. Clinical translation requires safety and efficacy analyses. DNA editing may be widely disparate across species due to genomic differences, necessitating human tissue-based platforms. AAV-based delivery of DNA editing elements is under clinical investigation. If delivered systemically, the kidney may be particularly susceptible to genome editing owing to high blood flow. Kidney organoids have been generated from human stem cells through the co-induction of nephron, stromal, and endothelial progenitor cells that mature to form multicompartment human kidney tissue. We marred organoid and organ-on-chip technologies to facilitate the maturation of nephron epithelia and the development of perfusable vascular networks to simulate systemic delivery of genome editing elements.

Methods: Using human recombiant growth factors and defined small molecules, kidney organoids were generated from male and female, embryonic and induced, stem cell lines. To test the efficacy of an AAV2-based delivery system, the tropism of varied capsids, 2/8/9, for kidney compartments was assessed under static and perfused conditions. The AAV receptor expression was evaluated by single nuclear RNA-seq. Results: The greatest infectivity was with capsid protein 2, whose receptor on human subverting proteoglycan is expressed in proximal & distal tubules and podocytes of kidney organoids by single cellular transcriptomics. Biomarker analysis demonstrated a statistically significant increase in tubular injury markers, KIM-1 and MCP-1, after infection with AAV2/8 as compared to other AAVs. Following treatment with AAV2/8-MVGFP, the majority of LTU- and CD11b+ tubular epithelia were GFP+, while PODOXL+ podocytes were poorly infected. The optimal AAV serotype, MOI, and duration of infection under static conditions were applied to vascularized kidney organoids. Initial on-chip testing supports enhanced infectivity by live-cell monitoring and wholemount immunostaining, including an AAV infection in GFP PODOXL+ podocytes.

Conclusions: We propose vascularized kidney organoids may simulate the systemic delivery of AAVs across kidney compartments, as a pre-clinical testing platform of the efficacy and safety of somatic cell genome editing.

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PO1356
Genotype and Phenotype Analysis in Patients with X-Linked Hypophosphatemia

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Background: X-linked hypophosphatemia (XLH) is the most frequent form of hypophosphatemic rickets and is caused by mutations in the PHEx gene. We analyzed genotype-phenotype correlations in XLH patients with proven PHEx mutations.

Methods: PHEx mutations were detected in 57 out of 81 patients who clinically presented with hypophosphatemic rickets. The patients were grouped into nontruncating (n = 11) and truncating (n = 46) mutation groups; their initial presentation as well as long-term clinical findings were evaluated according to these groups.

Results: Initial findings, including presenting symptoms, onset age, height standard deviation scores (SDSs), and laboratory tests, including serum phosphate level and tubular resorption of phosphate, were not significantly different between the two groups (onset age: nontruncating mutation group, 2.0 years, truncating mutation group, 2.1 years; height SDS: nontruncating mutation group, -1.9, truncating mutation group, -1.8; serum phosphate: nontruncating mutation group, 2.5 mg/dL, truncating mutation group, 2.5 mg/dL). However, at their last follow-up, the serum phosphate level was significantly lower in patients with truncating mutations (nontruncating mutation group: 3.2 mg/dL, truncating mutation group: 2.3 mg/dL, P value 0.003). Additionally, 62.5% of patients with truncating mutations developed nephrocalcinosis, while none of the patients with nontruncating mutations developed nephrocalcinosis (P value 0.008). Orthopedic surgery due to bony deformations was performed significantly more often in patients with truncating mutations (52.3% vs 10.0%, P value 0.008).

Conclusions: Although considerable inconsistency exists regarding the correlation of truncating mutations and their disease phenotype in several other studies, we cautiously suggest that there would be genotype-phenotype correlation in some aspects of disease manifestation after long-term follow-up. This information can be used when consulting patients with confirmed XLH regarding their disease prognosis.

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PO1357
Childhood-Onset Nephrocalcinosis in Twins Caused By Biallelic Mutations in CYP24A1 Gene: A Long Journey to a Genetic Diagnosis

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Introduction: 24-hydroxylase deficiency is a rare autosomal recessive disorder caused by mutations in CYP24A1 gene, characterized by hypercalcemia, hypercalciuria and nephrolithiasis. Establishing a genetic diagnosis, while important to guide management and family counseling, can be challenging. We hereby report a case of twins with childhood-onset nephrocalcinosis and chronic hypercalcemia caused by biallelic mutations of CYP24A1, which took years to be diagnosed.

Case Description: A 26 year-old female presented for preconception evaluation for a history of childhood-onset nephrocalcinosis and chronic hypercalcemic hypercalciuria. Patient reported similar history in identical twin sister. They had exome sequencing (ES) eight years ago after negative genes panel test which revealed a heterozygous variant of unknown significance (c.1186C>T in CYP24A1. A reanalysis of ES was performed four years ago which demonstrated no changes. Work up revealed hypercalcemic hypercalciuria, low 25(OH) vitamin D, elevated 1,25(OH) vitamin D and 24,25(OH) vitamin D, and suppressed PTH(fig.1). Ratio of 25(OH)D to 24,25(OH)D, a new biochemical test for 24-hydroxylase deficiency, suggested biallelic mutations in CYP24A1 gene. ES reanalysis at this time reclassified the c.1186C>T variant as pathogenic and disclosed a novel intron variant (c.544-17G>A) which was predicted to cause splicing pattern change with multiple silico algorithms. Parental tests confirmed these two variants were in trans configuration consistent with autosomal recessive inheritance pattern. A thorough counseling included low recurrence risk for her children while high risk for her to develop severe hypercalcemia during pregnancy. She has been closely monitored with low calcium and vitamin D diet, sun avoidance and adequate hydration during current pregnancy with no complications to date.

Discussion: CYP24A1 gene related hypercalcemia is rare and challenging to diagnose even with ES. This case suggests the benefits of ES regular reanalysis for clinically suspected patients with inconclusive genetic findings. The novel intron mutation identified in this case broadens the genetics spectrum of 24-hydroxylase deficiency.

Figure 1

PO1358
Refractory Hypercalcemia with Recurrent Nephrolithiasis Related to a De Novo Gain-of-Function Mutation in the CaSR Gene

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Introduction: The calcium-sensing receptor (CaSR) serves as the key calcium sensor in the maintenance of systemic calcium homeostasis. Gain-of-function mutations of CaSR-gene, mapped to Ala116-Pro136 region, causes autosomal dominant hypercalcemia and Bartter syndrome type V. Phenotypic manifestations include hypercalciuric hypercalcemia(nosly asymptomatic), hyperparathyroidism, paresthesias, tetany/ epilepsy, nephrocalcinosis/ nephrolithiasis, hypomagnesemia, ectopic and intracranial calcifications. Here we report a case of gravid female who experienced refractory hypercalcemia with recurrent nephrolithiasis related to a de novo gain-of-function mutation in the CaSR gene.

Case Description: A 25 year-old G1P0 female at 20 weeks of gestation presented to genetic nephrology clinic due to refractory hypercalcemia. She was incidentally found to have asymptomatic hypercalcemia as part of prenatal evaluation. She was treated with calcium and calcitriol for four months while hypercalcemia persisted. Physical exam was unremarkable. As shown in Table 1, her total serum calcium had been persistently low despite calcium and Vitamin D supplementations, and she had low PTH, hypercalciuria, hypermagnesemia, and hypercalciuria. Genetic testing revealed a variant (c.398A>T, p.Glu133Val) in CaSR gene, with negative parental testing consistent with de novo mutation. Given this finding, calcium and calcitriol were discontinued. Renal ultrasound to assess stone burden showed bilateral renal calcui, which patient passed during delivery. Recurrent renal calculi were discovered on post-delivery follow-up imaging, necessitating laser lithotripsy and left ureteral stent insertion.

Discussion: This case highlights the importance of early diagnoses by genetic testing which could guide the hypercalcemia management, as routine calcium and vitamin D supplementation is inadequate for hypercalcemia and thus the risk of nephrocalcinosis/ nephrolithiasis. c.398A>T, p.Glu133Val mutation has been described in 1 family cluster of 3 patients with hyperparathyroidism and hypercalcemia to date. De novo mutation, unique to this case, was evidenced by negative parental testing.

Table 1
TRPV4 Calcium Channel Activity Is Increased by With-No-Lysine Kinase 1 in the Collecting Duct Cells

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Background: Patients with mutations in the Cyclin M2 (CNNM2) gene display hypomagnesemia and intellectual disability. CNNM2 is highly expressed in the distal convoluted tubule, where it is involved in renal magnesium (Mg 2+ ) reabsorption. However, the complete phenotypic spectrum of the CNNM2-related disorder remains unknown. We characterised a large patient cohort with novel CNNM2 variants and used transgenic mouse models to investigate the role of CNNM2 in Mg 2+ homeostasis.

Methods: The identified CNNM2 variants were found in a cohort of hypomagnesemic patients and characterised using 18 Mg 2+ transport assays in HEK293 cells. In addition, CNNM2-deficient mice were developed using CRISPR-Cas9 technology and exposed to deficient or saturated Mg 2+ diets for two weeks. Using metabolic cages, the 24-hour urinary and faecal excretion for Mg 2+ was determined.

Results: Eleven patients were identified with novel dominant variants in CNNM2. Using Mg 2+ transport assays in HEK293 cells, seven variants showed decreased Mg 2+ transport compared to wild type. These pathogenic mutations resulted in decreased membrane expression of CNNM2. The phenotype of these patients was compared with those previously published. Patients with pathogenic CNNM2 mutations had a mean plasma Mg 2+ level of 0.54 ± 0.08 mmol/L. Neurological manifestations, such as seizures (79%), intellectual disability (92%) and speech difficulties (91%) were prevalent.

Conclusion: Mitochondrial diseases with isolated renal symptoms are uncommon; however, this study indicates that mitochondrial respiratory chain complex III deficiency due to CNNM2 mutations cause Fanconi syndrome with developmental disability as the primordial indications.
POI1363

Infantile Hypercalcemia Associated with a Novel Homozygous Mutation in SLC34A1 Gene Encoding Sodium-Dependent Phosphate Transporter 2A

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Introduction: Early-onset and familial hypercalcemia often suggest a genetic etiology which is rare. Infantile hypercalcemia (IH) is a rare, autosomal recessive disorder that occurs due to mutations in the SLC34A1 gene which encodes a sodium-dependent phosphate transporter 2A (NaPi-IIA) responsible for phosphate reabsorption in the kidney. We report an adult case who carried a clinical diagnosis of familial hypocalciuric hypercalcemia (FHH) since infancy, which is usually a benign condition characterized by autosomal dominant inheritance caused by mutations in calcium-sensing receptor (CASR) gene, while recently uncovered as IH related to a novel homozygous mutation in the SLC34A1 gene.

Case Description: A 36-year-old Finnish male with a diagnosis of FHH presented to the genetics nephrology clinic for consultation regarding the recurrence risk for his children. He was diagnosed with FHH during infancy in Finland and has been treated with a low calcium diet. Family history was notable for a clinical diagnosis of FHH in his older sister. Physical exam was unremarkable. Labs showed mild hypophosphatemia and decreased glomerular filtration rate (69 mL/min/1.73 m²), with normal serum ionized calcium and intact parathyroid hormone. Twenty-four hour urine analysis revealed hypercalcuria 363 mg/d (normal <250), hypomagnesuria 155 mmol/d (normal 50–150) and hypocitraturia 420 mg/d (normal >450). Kidney ultrasound showed bilateral medullary hypercalciuria 363 mg/d (normal <250), hypernatriuria 155 mmol/d (normal 50–150) and was reassured with the low recurrence risk for his children.

Discussion: Mutations in the SLC34A1 gene lead to altered NaPi-IIA expression and reduced phosphate reabsorption, leading to hypophosphatemia. Secondary vitamin D activation leads to hypercalciemia, hypercalcuria, and nephrocalcinosis. We identified a novel mutation in the SLC34A1 gene which broadens the genetic spectrum of IH. This case highlights the importance of early genetic testing for suspected hereditary hypercalcemia that may help improve its diagnosis and treatment.

POI1364

Characteristics and Genetic Defects of Systemic Lupus Erythematosus-Associated Thrombotic Microangiopathy

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Background: Thrombotic microangiopathy (TMA) is a life-threatening complication of systemic lupus erythematosus (SLE). However, the etiology of a considerable number of patients is still unclear and the best treatment is unknown. Sporadic reports suggest that the activation of complement pathway may play a role in SLE-TMA.

Methods: We prospectively enrolled 40 SLE-TMA patients in Peking Union Medical College Hospital, 14 patients with lupus nephritis (LN) and 38 patients with other types of TMA. The clinical data were collected. Peripheral blood concentrations of CFH, cCFB, soluble CSF-9, relative activity of complement pathway, ICAM1, VCAM1 and E-Selectin were measured by ELISA in SLE-TMA patients and control groups. Whole exome sequencing (WES) was performed to analyze the genetic variants in SLE-TMA patients.

Results: SLE-TMA mediated by ADAMTS13 inhibitors had severe nervous system involvement, but less kidney involvement and good response to plasma exchange. Among SLE-TMA with unknown etiology, patients with TMA confined to kidney had higher hematological manifestations and lower serum creatinine level than SLE-aHUS (p = 0.005). Compared with SLE-aHUS, the concentration of CFH in SLE-TMA limited to kidney was higher (p = 0.026). The level of E-selectin in patients with SLE-TMA limited to kidney was significantly lower than that in SLE-aHUS patients with MAHA (p = 0.016). There was no significant difference in genetic susceptibility among SLE-aHUS, SLE-TMA limited to kidney and SLE-TMA with other causes. In SLE-TMA patients, thrombophilia variants may play a more important role than complement variants. Treatment response of SLE-TMA patients with variants is worse than those without variants. In serological test, VCAM1 level in SLE-TMA patients with complement related genetic variants was significantly higher than that in SLE-TMA patients without variants (p = 0.001). Patients with compound complement variants are more likely to detect abnormal level of complement factors.

Conclusions: SLE-TMA with unknown etiology can be divided into two subgroups with different severity according to the presence or absence of MAHA. The detection of complement factor and E-selectin may play a role in differentiating the two subgroups of SLE-TMA. The complement pathway is highly activated in patients with compound complement mutations, resulting in increased complement factors consumption.

POI1365

A Popping Renal Artery

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Introduction: The COL3A1 gene encodes the collagen type III alpha chain, which forms the helical conformation. A mutation on this gene causes vascular Ehlers-Danlos syndrome (v-EDS), a life-threatening disease characterized by arterial fragility, vascular dissection or rupture, and organ perforation are the most common presenting signs in adults with v-EDS (1).

Case Description: A 25-year-old man with history of bicuspid aortic valve, shoulder dislocation, chronic hemoptysis presented with severe left flank pain and syncope. A CT scan revealed a right retroperitoneal hematoma and aneurysms on the right renal artery (Image 1). Differential diagnosis were fibromuscular dysplasia, small vessel vasculitis and segmental arterial mediolysis (SAM). An extensive rheumatologic and vasculitis workup was negative. A collagen vascular disease was considered due to the history of bicuspid aortic valve and shoulder dislocation, and genetic testing was ordered. He underwent an urgent aorta-to-right renal artery bypass, and ligation of the aneurysm. Postoperatively, he developed hypotension. Abdominal imaging showed a new aneurysm on the superior mesenteric artery. Genetic testing results showed a COL3A1 c.593A pathogenic variant, confirming v-EDS. He now is treated with metoprolol succinate and spironolactone. His fathers genetic testing revealed possible mosaicism.

Discussion: v-EDS is an uncommon but severe disease that needs a high degree of clinical suspicion. Patients usually present with unexplained pneumothorax, organ perforations and arterial ruptures. Little data exists about medical management, goals include maintaining low blood pressures (less than 120/80 mmHg). As well, patients should avoid contact sports and isometric exercises. Patients need constant imaging surveillance on the brain, neck, chest, abdominal and pelvic arteries.

POI1366

Mapping Genomic Regulation of Kidney Diseases and Traits at a Cell Type and Variant Level of Specificity

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Background: Although numerous genetically associated loci for kidney function and disease have been identified by genome-wide association studies (GWAS), determining the causal genes and functional variants remains a major challenge. Integration of GWAS results with other data types (such as expression quantitative trait loci [eQTLs]) can help identify causal and functional variants in a tissue- or cell-type specific manner. Further, analysis of disease tissue may uncover context-specific associations that may otherwise not be detectable.

Methods: We integrated eQTL data from micro-dissected glomerular (n = 240) and tubulointerstitial (TI) (n = 311) transcriptomes from individuals with nephrotic syndrome and summary statistics from two large trans-ethnic GWAS meta-analyses for estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (UACR). We used a Bayesian statistical framework for eQTL discovery and mapping (TORUS/DAP). eQTL signals from each renal compartment were integrated with summary statistics to perform a gene-level probabilistic transcriptome-wide association study (PTWAS) and SNP-level co-localization (fastENLOC).

Results: We identified 5,526 glomerular and 9,742 TI eQTLs at <5% FDR level. For eGFR, we identified 971 gene-trait pairs in the glomerulus and 1,816 gene-trait pairs in TI tissue that were significant (FDR < 5%). For UACR, we identified 194 and 340
significant gene–trait pairs in the glomerulus and T1 tissue, respectively. In the SNP-level co-localization analysis, we identified 46 TI and 3 glomerular co-localization signals (regional co-localization probability [RCP] > 50%) for eGFR, including known associations with UMOD and FGFR3 expression, as well as novel associations to LARPB4 and RARAG which can be attributed to single variants. We identified 7 TI and 16 glomerular co-localization signals (RCP > 75%) for UACR. In addition to replicating co-localization signals at PKRCL and TGFβ1 in glomerular tissue, we refined the co-localization signal at PTHIR to a single variant, rs6787229, which also co-localized with expression of MYL2.

Conclusions: Profiling and integrating renal compartment-specific eQTLs with kidney trait GWAS results in a probabilistic framework identified novel gene–trait associations and refined many known associations to a single variant.

Funding: NIDDK Support

PO1367
Factors Contributing to Decisional Conflict in Older Persons Facing Dialysis Decisions

Background: Dialysis and conservative kidney management are the two main treatment options for elderly persons with end-stage-kidney disease who are ineligible for kidney transplantation. The high stakes of these decisions often force patients to choose between quality versus quantity of life. Thus, they face tremendous conflict while making dialysis decisions. This decisional conflict can adversely affect their mental health-related quality of life and leads to avoidable delays in decision making. Exploring factors contributing to dialysis decisional conflict in older persons with chronic kidney disease is critical.

Methods: Using a qualitative descriptive approach, we purposefully sampled a cohort of 10 patients; 5 with high scores on decisional conflict scale, and 5 with low scores. Patients met with a palliative care physician to discuss dialysis and these visits were audio-recorded. Audio recordings were transcribed verbatim and entered into MAXQDA for data management. Following an iterative process, 2 independent reviewers analyzed the transcripts for common themes contributing to decisional conflict.

Results: The mean age of patients was 83 years. We observed 3 themes in the data of patients with low decisional conflict: (1) clarity in values, (2) good current quality of life, and (3) strong therapeutic alliance with their nephrologist. In the high decisional conflict group, we observed 5 themes: (1) fear of: physical pain, complications from dialysis and its time commitment, loneliness, and losing independence, (2) concerns about being a burden to loved ones, (3) uncertainty about prognosis, (4) worries about transportation to and from dialysis, and (5) poor knowledge of treatment options.

Conclusions: Patients with high decisional conflict worried about their future quality of life, sense of burdensomeness, prognostic uncertainty, and issues related to transportation. They wished for detailed knowledge of treatment options. Future dialysis decision-making interventions should be tailored to identify each patient’s unique needs, and incorporate details about treatment options and information about logistics of dialysis. Nephrologists need to discuss the expected quality of life and prognosis. Last, family involvement in these discussions and buy-in for or against dialysis may be helpful in mitigating the patient’s sense of being a burden on their loved ones.

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PO1368
Shared Decision-Making Among Older Adults with Advanced CKD
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Background: Older adults with advanced chronic kidney disease (CKD) face difficult, preference-sensitive decisions about dialysis. Although shared decision-making (SDM) can help align treatment with patient preferences and values, the degree to which older CKD patients experience SDM and associated factors remain unknown.

Methods: Using data from the Decision Aid for Renal Therapy Trial, we examined SDM in adults ≥70 years with non-dialysis CKD stage 4–5 from 4 sites in the US using the validated SDM-Q9 measure, with scores scaled from 0-100 and higher scores reflecting greater SDM. We categorized predictors into demographic and clinical factors, cognitive factors (decisional perception and uncertainty), and behavioral and educational factors. Multivariable linear regression assessed predictors of SDM.

Results: Among 350 participants, mean age was 78±6 years, 58% were male, 13% were Black, and 48% had diabetes. Mean SDM-Q9 score was 52±28. Responses varied (resources supporting SDM). Multivariable linear regression assessed predictors of SDM.

Conclusions: Improving shared decision-making for treatment of advanced CKD will likely require efforts that explicitly reconcile the differences in mindset between patients and their clinicians on decision-making about treatment of advanced CKD and that address the power imbalances in their therapeutic relationship.

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PO1370
Effect of Estimated Glomerular Filtration Rate on Survival in Patients 275 Years of Age at Dialysis Initiation
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Background: Data regarding the prognostic impact of estimated glomerular filtration rate (eGFR) at dialysis start are discordant, and remain very scarce in elderly populations. The aim of this study is to explore whether the effect of eGFR on survival was similar in elderly incident dialysis patients compared with younger ones.

Methods: We included 4690 patients ≥75 years of age and 7045 patients 18-74 years of age starting dialysis between 2004 and 2018 from a French regional registry. Patients were followed until death or the end of 2019. Survival was assessed by Kaplan-Meier curves and the relative risk of death associated with eGFR (MDRD) was assessed by multivariate Cox regression analysis.

Results: The results showed an increasing trend of eGFR at dialysis start, which was also systematically higher in elderly patients (13.2 [10.1; 17.2] vs 11.2 [8.3; 14.9] mL/min/1.73m², p < 0.001) (Fig1). Overall, we found a significant dose-effect relationship between eGFR at dialysis initiation and mortality (HR = 1.33 [1.16; 1.51], 1.47 [1.29; 1.69], and 1.72 [1.49; 1.78] respectively for eGFR [5-10], [10-15], and ≥ 15mL/min/1.73m², p for trend < 0.001). The same results were found in subgroup analyses according to age category (Fig2), with a significant interaction in favor of a stronger association in younger patients (p = 0.031).

Conclusions: In incident dialysis patients, our study shows a dose-effect relationship between higher eGFR at dialysis start and mortality, regardless of age category. This association seems to be even stronger in younger patients.
Mortality Rates in a Nationally Representative Cohort of Advanced CKD Patients Treated with Conservative Management vs. Dialysis

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Background: While dialysis has been the prevailing treatment paradigm in CKD patients progressing to ESRD, this treatment approach may not offer survival benefit nor improved quality of life in certain subgroups (elderly, multi-morbid). Hence, there is growing interest in conservative management (CM) as an alternative treatment strategy in advanced CKD.

Methods: We compared mortality rates in advanced CKD patients (eGFRs <25 separated by a ≥90 days) treated with CM vs. dialysis from 1/1/07-6/30/20 from the OptumLabs Data Warehouse (OLDW), which contains de-identified administrative claims, including medical and pharmacy claims and enrollment records for commercial and Medicare Advantage enrollees as well as electronic health record data. Patients were categorized according to receipt of dialysis vs. CM, defined as those who did vs. did not receive dialysis within 2-yrs of the index eGFR(1st eGFR <25), with the former group parsed into late vs. early dialysis (eGFRs <15 vs. ≥15 at dialysis transition). Secondary analyses stratified the former group as late, intermediate, vs. early dialysis (eGFRs <5, 5-<10, vs. ≥10 at dialysis transition). Poisson regression was used to compare mortality rates across exposure groups.

Results: Among 309,188 advanced CKD patients, 60% vs. 40% of patients were treated with CM vs. dialysis, respectively. Patients who underwent CM vs. late dialysis had similar mortality, whereas those who underwent early dialysis had the highest mortality rates. In secondary analyses comparing CM and late vs. intermediate vs. early dialysis, a similar pattern was observed (140, 126, 141, vs. 158 deaths per 1000 person-yrs, respectively). In age-stratified analyses, compared to CM, all dialysis groups had higher mortality rates irrespective of timing of initiation in those <65 and ≥65 yrs old.

Conclusions: In a nationally representative cohort of advanced CKD patients, CM vs. late dialysis demonstrated similar mortality, whereas those who underwent early dialysis had the highest mortality rates.

Funding: NIDDK Support
Continued Primary Care Use During the Transition to Kidney Failure (KFRT) Is Associated with Reduced Mortality Among Older Hemodialysis (HD) Patients

Methods: We quantified the associations between PCP use, mortality, and hospitalization among older (age $\geq$ 67) incident (2008-2014) in-center HD patients using data from the United States Renal Data System. We defined patients' PCP use 1-year prior and 1-year post-KFRT as "continued" for PCP use pre- and post-KFRT; "initiated" for no PCP use pre-KFRT and PCP use post-KFRT; "discontinued" for PCP use pre-KFRT and no PCP post-KFRT; or "never used" as no PCP use pre- or post-KFRT. We used Cox proportional hazard models and adjusted for confounding by using inverse probability weighting method to estimate hazard ratios (HRs) for all-cause mortality and first all-cause hospitalization up to 2 years post-KFRT.

Results: Among 111,424 patients, 57% had continuity of PCP care, 10% initiated PCP use, 10% discontinued PCP use, and 23% never used PCP care during the KFRT transition. Compared to those who never used primary care during the KFRT transition, those with continued primary care use had a 14% lower risk of mortality. Continued and initiated PCP care post-KFRT transition was associated with a 5-12% higher risk of hospitalization, respectively.

Conclusions: Continued primary care use during the KFRT transition was associated with lower mortality, but a higher risk of hospitalization. Additional studies are needed to determine the aspects of primary care that may be beneficial and which patients are most likely to benefit from continued PCP use.

Funding: Private Foundation Support

Hazard Ratios for All-Cause Mortality and First Hospitalization by Primary Care Use During KFRT Transition

<table>
<thead>
<tr>
<th>Hazard Ratios</th>
<th>Never used</th>
<th>Discontinued</th>
<th>Initiated</th>
<th>Continued</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI)</td>
<td>1.00 (1.00, 1.00)</td>
<td>1.05 (1.00, 1.10)</td>
<td>0.95 (0.90, 1.01)</td>
<td>0.90 (0.85, 0.95)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, race/ethnicity, employment, Medicaid, region, neighborhood poverty, neighborhood urban, Kim’s frailty index, Lu’s comorbidity index, pre-KFRT nephrology care.

PO1374

Vascular Access Type and Survival Outcomes in Elderly Hemodialysis Patients

Background: The ideal vascular access for elderly hemodialysis (HD) patients remains widely debated. Limited life expectancy and lower arteriovenous access (AVA) maturation rates increase the likelihood of starting HD with a central venous catheter (CVC). The aim of the study was to evaluate the influence of vascular access type in survival outcomes for elderly HD patients.

Methods: Single-center retrospective cohort study of incident HD patients aged $\geq$ 80 years from January 2010 to May 2021. Patients who recovered renal function or switched to another renal replacement therapy were excluded. Patients were categorized according to their vascular access at the beginning of dialysis: CVC or AVA. Baseline clinical and demographic data were compared among groups. Survival outcomes by the end of follow-up (31 May 2021) were analyzed using Kaplan-Meier survival curves and Cox’s proportional hazards model. Statistical analysis was performed using SPSS (Version 23 for Mac OSX).

Results: The study included 99 patients: 48 (48.5%) were male, 44 (44.4%) diabetic, 60 (60.6%) had ischemic heart disease and 15 (15.2%) peripheral artery disease. Mean Charlson Comorbidity Index was 8.41±1.65 and mean age 85.14±3.98 years. Eleven patients (11.1%) were over 90 years old. Eighty patients (81%) started HD urgently as inpatients. The vascular access at dialysis start was a CVC in 75.8% (n=75) and an AVA in 24.2% (n=24). No statistical differences were found in age, gender, comorbidities and functional statuses among groups. During a mean follow-up of 2.3 years, there were 64 deaths, 27 due to infections (12 access-related infections). All-cause mortality (HR [95% CI]: 1.92 [1.05-3.49], p=0.033) and infection-related mortality (HR: 5.87 [1.38-24.94], p=0.017) were significantly higher among patients who initiate HD with a CVC as compared to an AVA.

Conclusions: The ideal vascular access in elderly patients remains controversial. Our results suggest that patients who start HD with a CVC presented higher all-cause and infection-related mortality when compared with patients who start with an AVA. Our study supports the initiative “fistula first” however more studies are needed to confirm the observations.
Evaluation of a Concurrent Hospice-Dialysis Program with ESRD

Mayumi Robinson,¹ Natalie C. Ernechof,¹ Erica M. Motter,¹ Keith Lagnese,² Robert Taylor,³ Jane O. Schell.¹ ¹University of Pittsburgh School of Medicine, Pittsburgh, PA; ²UPMC Family Hospice, Pittsburgh, PA; ³University of Pittsburgh Medical Center, Pittsburgh, PA; ⁴Dialysis Clinic Inc, Nashville, TN.

Background: Most dialysis patients are hospitalized in the last month of life, nearly half of whom receive intensive care. Hospice financing poses a major barrier to hospice delivery to dialysis patients, increasing inequities for high-quality end-of-life care. The Concurrent Hospice-Dialysis Program aims to promote timely hospice services for dialysis patients with limited prognosis by offering concurrent hospice and dialysis.

Methods: We conducted a mixed methods study comprised of chart reviews and semi-structured interviews with 10 bereaved caregivers of deceased patients who were enrolled in the Concurrent Hospice-Dialysis Program and 13 clinicians who provided care as part of the program.

Results: Four major themes were identified: 1) Decisional distress regarding stopping dialysis; 2) The option to continue dialysis served as a psychological bridge to hospice; 3) Clear referral process, formal patient education, and care coordination between hospice and dialysis teams facilitated successful implementation; 4) Providing hospice and dialysis promoted goal-concordant care at end-of-life.

Conclusions: Bereaved caregivers and clinicians involved with the Concurrent Hospice-Dialysis Program found the program broadly acceptable and recommended it for patients on dialysis interested in hospice services. They offered suggestions for systematizing and disseminating the program.

Table 1. Key Themes

<table>
<thead>
<tr>
<th>Theme</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decisional distress</td>
<td>Patients expressed distress regarding stopping dialysis</td>
</tr>
<tr>
<td>Psychological bridge</td>
<td>The option to continue dialysis served as a psychological bridge to hospice</td>
</tr>
<tr>
<td>Care coordination</td>
<td>Clear referral process, formal patient education, and care coordination</td>
</tr>
<tr>
<td>Goal-concordant care</td>
<td>Providing hospice and dialysis promoted goal-concordant care at end-of-life</td>
</tr>
</tbody>
</table>

Concurrent Hospice Dialysis: Perspectives on Dissemination

Erica M. Motter,¹ Mayumi Robinson,¹ Natalie C. Ernechof,¹ Keith Lagnese,² Robert Taylor,³ Jane O. Schell.¹ ¹University of Pittsburgh School of Medicine, Pittsburgh, PA; ²University of Pittsburgh Medical Center, Pittsburgh, PA; ³Dialysis Clinic Inc, Nashville, TN.

Background: In the United States, people receiving dialysis have traditionally been unable to enroll in hospice without ceasing dialysis treatments due to policy constraints. Therefore, these patients are often denied the full benefits of quality end-of-life care, either dying in hospitals or spending only a few days on hospice after dialysis is stopped. An alternative model would allow people living with end-stage renal disease (ESRD) to receive hospice services concurrently with dialysis treatments.

Methods: We implemented a concurrent hospice-dialysis program in one health system to test the concept. In this project, we aimed to build evidence for feasibility and program requirements for extending such programs to other settings across the country. We conducted semi-structured interviews with people living with ESRD, family caregivers, hospice and dialysis clinicians, and health system administrators from the Pittsburgh area and other regions in the U.S. Interviews elicited perceptions of strengths and weaknesses of a scalable concurrent hospice and dialysis program, including barriers and facilitators of implementation across various settings.

Results: We conducted 25 interviews with 2 patients (8%), 3 caregivers (12%), 15 clinicians (60%), and 5 administrators (20%). Preliminary themes include important considerations: 1) Mechanisms and operational definitions for identification of eligible patients; 2) Procedures for decision-making conversations with patients and families; and 3) Protocols for communication between hospice and dialysis teams to coordinate care. Medicare policy and funding restrictions were also frequently discussed as barriers to the program.

Conclusions: Perspectives from patients, caregivers, clinicians and administrators describe critical implementation processes and resources for a successful concurrent hospice and dialysis program. These include the following: clear criteria for patient eligibility, consistent language to use when talking with patients and families, education for both hospice and dialysis teams, and a well-defined plan for care coordination between teams. Future evaluation of such programs may lead to policy change to make concurrent care broadly financially feasible.

Funding: Other NIH Support - Palliative Care Research Cooperative Group (PCRC)
Dialysis for the Hospice Patient: A Paradoxical Challenge for Palliative Nephrology

Frank A. Portugal, Steve I. Khalil. Rutgers Robert Wood Johnson Medical School New Brunswick, New Brunswick, NJ.

Introduction: We present a case of a patient who developed anuric AKI who subsequently needed dialysis while patient and family were also simultaneously interested in hospice. Our case addresses the difficult conversation in prognosticating and how best to prepare for patients requiring dialysis can be challenging.

Case Description: A 63-year-old woman with hypertension and recently diagnosed metastatic pancreatic adenocarcinoma initially presented for intractable right hip pain and was admitted for emergent palliative radiation. She experienced rapid deterioration including septic and hemorrhagic shock and was managed in the ICU until she was later stabilized off pressors and downgraded to the floors. Unfortunately, she had further complications and quickly experienced anuric AKI from ischemic ATN as her serum creatinine rose from 0.8 to 4.9 mg/dL and became significantly volume overloaded with worsening acidemia. The decision was to start a trial of dialysis by family, but they also wanted hospice. Questions arose including prognosis and if patient could simultaneously be provided with dialysis during hospice. Given the current model of withdrawing from dialysis for hospice eligibility, the daughters agreed to transition their mother to hospice. The patient passed prior to leaving the hospital.

Discussion: We present a difficult scenario for the nephrologist as serious illness conversations remain incredibly challenging. We may opt to not take part in these conversations either due to time commitment, not viewing it as a primary responsibility, or not wishing to upset the patient and their families. Also, so much uncertainty in predicting prognosis makes it intimidating. Here, what also needed to be addressed were hospice benefits for the dialysis patient, if any existed. Usually, one is required to withdraw from dialysis to receive hospice care. There have been suggestions in providing a trial or “as needed dialysis” to focus on a patient-centered type of care but unfortunately that could potentially impact quality metrics and Medicare reimbursement for dialysis centers. As such, these ongoing challenges not only require collaboration between Nephrology and Palliative medicine but also changes at the national broader level.

Kidney Palliative Care in Transplant Recipients with a Failing Allograft

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Background: Kidney transplantation provides longer survival and better quality of life than dialysis for patients with end-stage kidney disease. However, when allografts fail, navigating treatment options can be challenging as patients with allograft failure are usually older and sicker than when they were transplanted. Kidney palliative care, specialized interprofessional medical care working together with nephrology providers, providing communication, coordination, symptom management, and psychosocial support for seriously ill patients, has not yet been well-studied for those with kidney transplants.

Methods: We conducted a retrospective observational study comparing palliative care delivery, patient treatment choices, and clinical outcomes before and after creation of an inpatient kidney palliative care service (KidneyPal) at our institution. We included adult kidney transplant recipients who were 18 years of age or greater with allograft failure over a mean of 2.9 years (median 1.0 years) from 2012 to 2016. The KidneyPal service was established in 2015. A total of 767 unique patients had frailty assessments performed between 2016-2021. Patients were predominantly of male sex (64%), white race (82%) and had a mean age of 54±14. The prevalence of frailty for women was not significantly higher by the FP (16% vs 13%, p=0.15) or the FI (48% vs 46%, p=0.38), but was by the CFS (17% vs 12%, p=0.05). Among 325 activated patients, frailty by the CFS was significantly associated with death/withdrawal for men (HR 2.59; 95% CI 1.16-6.79) but not women (HR 1.48; 95% CI 0.86-2.56).

Conclusion: The prevalence of frailty was higher in females when measured by the CFS, but not by a transplant specific FI or the FP. Despite this, frailty was not significantly associated with mortality/withdrawal from the waitlist for female individuals, emphasizing the need to critically evaluate judgement based frailty assessments and their role in the transplant evaluation process.

Funding: Government Support - Non-U.S.

Differences in Frailty by Sex in Kidney Transplant Candidates

Caroline Worth,1 Amanda J. Vinson,2 Karin K. Tereschenko.2 Frailty Assessments in Canadians being Evaluated for Transplant Study (FACETS) Dalhousie University, Halifax, NS, Canada; 2 Nova Scotia Health Authority, Halifax, NS, Canada.

Background: Frailty prevalence is higher in women, despite the observed protective effect of female sex on mortality in the general population. Understanding whether there are differences in perceived frailty by sex and the differential impact of frailty on outcomes for males versus females is crucial to avoid a sex disparity within the transplant assessment process.

Methods: We analyzed initial frailty assessments for patients enrolled in a multicenter prospective cohort study across 6 kidney transplant referral centers. Frailty was assessed using the Frailty Phenotype (FP, 3 of slowness, weight loss, low activity, exhaustion, and unintentional weight loss); a Frailty Index (FI, including 37 variables across the domains of social function/cognition, function, mobility, and comorbidity), and the Clinical Frailty Scale (CFS, based on clinical judgement). Assessments were performed prior to or shortly after waitlisting. Prevalence of frailty as measured by the FP, FI, and CFS was reported. An unadjusted Cox survival analysis (separately for males and females) was used to assess the effect of frailty on time to death or withdrawal from the waitlist among activated patients.

Results: A total of 767 unique patients had frailty assessments performed between 2016-2021. Patients were predominantly of male sex (64%), white race (82%) and had a mean age of 54±14. The prevalence of frailty for women was not significantly higher by the FP (16% vs 13%, p=0.15) or the FI (48% vs 46%, p=0.38), but was by the CFS (17% vs 12%, p=0.05). Among 325 activated patients, frailty by the CFS was significantly associated with death/withdrawal for men (HR 2.59; 95% CI 1.16-6.79) but not women (HR 1.48; 95% CI 0.86-2.56).

Conclusions: The prevalence of frailty was higher in females when measured by the CFS, but not by a transplant specific FI or the FP. Despite this, frailty was not significantly associated with mortality/withdrawal from the waitlist for female individuals, emphasizing the need to critically evaluate judgement based frailty assessments and their role in the transplant evaluation process.

Funding: Government Support - Non-U.S.

Changes in Cognition After Kidney Transplantation

Aditi Gupta,1 Palash Sharma,2 Rebecca J. Lepping,1 Jonathan D. Mahnken,1 William M. Brooks,1 David K. Johnson,2 Jeffrey M. Burns.1 University of Kansas Medical Center; Kansas City, KS; 2University of California Davis, Davis, CA.

Background: Longitudinal studies examining changes in cognition pre- to post-kidney transplantation (KT) are small, of short duration and do not include comprehensive neuropsychological (NP) testing or comparison with normative data.

Methods: We analysed pre- to post-KT cognition in 87 ISNKD patients listed for KT and compared it to the National Alzheimer’s Coordination Center (NACC) data. We used linear mixed models for longitudinal, repeated NP test measurements, adjusted for for age, practice effect, sex, race, transplant status, and level of education, and assessed cognition both pre- to post-KT for the following domains (Logical Memory I, II, and Digit Symbol tests) and secondary (Mini Mental State Exam (MMSE), Digit span, Category Fluency for animals & vegetables, Trail making A & B) outcomes.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Patients Who Are Treated for Secondary Hyperparathyroidism Have a Lower Risk of Incident Dementia

JiYoon B. Ahn,1 Aarti Mathur,1 Dorry L. Segev,2,3 Mara McAdams-DeMarco,1,2 ERGOT Johns Hopkins University School of Medicine, Baltimore, MD; 2Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.

Background: Almost all patients with end-stage kidney disease (ESKD) have secondary hyperparathyroidism (SHPT). Elevated parathyroid hormone has been reported as a potential risk factor of cognitive impairment. We aimed to study whether the risk of dementia is improved when patients on dialysis receive treatment for SHPT.

Methods: Using data from the United States Renal Data System and Medicare claims, we studied older (aged ≥66) ESKD patients without known pre-ESKD dementia who initiated maintenance dialysis in 2006-2016. SHPT treatment included vitamin D analogs, phosphate binders, cinacalcet or parathyroidectomy and was treated as a time-dependent treatment in the analysis. The study population was followed until transplant, death, or the end of the study period. The study period was divided into four groups: pre-ESKD, primary SHPT, secondary SHPT, and any SHPT with treatment. The association between SHPT treatment and the risk of dementia was analyzed using the Cox regression and adjusted for confounding using the inverse probability weighting method to examine the association of SHPT treatment and incident dementia.

Results: Of 189,433 ESRD patients, 65.1% received a treatment for SHPT during the study period. The rate of incident dementia was 11 per 100 person-years among patients with no SHPT treatment and 6 per 100 person-years among those with an SHPT treatment. Among patients on dialysis, the risk of incident dementia was lower after receiving treatment for SHPT compared with not receiving treatment for SHPT (adjusted hazard ratio = 0.62; 95% CI = 0.59-0.66) after adjusting for confounding.

Conclusions: Receiving treatment for SHPT was associated with a lower risk of incident dementia among older patients with ESKD. SHPT may need to be controlled among older ESKD patients considering the complications of SHPT including cognitive impairment and dementia.

Funding: NIDDK Support, Other NIH Support - NIAID, NIA

Patient characteristics

Table 1: NP test comparisons in pre- and post-KT recipients and controls

<table>
<thead>
<tr>
<th>NP test</th>
<th>Pre-KT</th>
<th>Post-KT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Logical Memory I</td>
<td>0.82±0.19</td>
<td>0.74±0.17</td>
<td>0.003</td>
</tr>
<tr>
<td>Logical Memory II</td>
<td>0.80±0.20</td>
<td>0.73±0.18</td>
<td>0.005</td>
</tr>
<tr>
<td>Symbol Digit</td>
<td>7.3±5.2</td>
<td>7.5±5.3</td>
<td>0.46</td>
</tr>
<tr>
<td>Trail Making A</td>
<td>134.3±56.7</td>
<td>131.5±59.1</td>
<td>0.39</td>
</tr>
<tr>
<td>Trail Making B</td>
<td>399.7±103.4</td>
<td>391.5±98.9</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Baseline characteristics by age group

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Number of Participants</th>
<th>Mean ± Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65 years</td>
<td>500</td>
<td>57 ± 8</td>
</tr>
<tr>
<td>65-70 years</td>
<td>1000</td>
<td>60 ± 9</td>
</tr>
<tr>
<td>71-80 years</td>
<td>1500</td>
<td>63 ± 10</td>
</tr>
<tr>
<td>&gt;80 years</td>
<td>2000</td>
<td>70 ± 11</td>
</tr>
</tbody>
</table>

PO1385

PO1386

Kidney-Metabolic Risk Factors for Cognitive Impairment in Moderate CKD in the BRINK Study: Beyond eGFR and Albuminuria

Anne M. Murray,1,2 David Tupper,1,2 Cynthia S. Davey,1 Ryan Mello,1 Allyson Hart,1 Kirsten L. Johansen,2 The German Center for Outcomes and Clinical Research, Hennepin Healthcare Research Institute, Minneapolis, MN; 1Hennepin Healthcare, Minneapolis, MN; 2University of Minnesota Clinical and Translational Science Institute, Minneapolis, MN; 3University of Minnesota Twin Cities, Minneapolis, MN.

Background: Decreased kidney function is a risk factor for cognitive impairment (CI). We sought to identify kidney-metabolic biomarkers beyond eGFR and albuminuria associated with prevalent moderate to severe cognitive impairment (Mod/Sev CI) in a CKD cohort.

Methods: Community-dwelling non-dialysis participants aged 45 years with CKD (eGFR <60, in mL/min/1.73 m²) were recruited from four health systems. We examined biomarkers including phosphorus, TNFαR1, PTH, calcium, total cholesterol, hemoglobin A1c%, bicarbonate (CO2), and albumin (mg/dL). A neuropsychological battery measured global and domain-specific cognitive performance. Logistic regression analyses estimated cross-sectional associations between kidney-metabolic measures and global and cognitive-domain-specific Mod/Sev CI at baseline, adjusted for eGFR, albumin-creatinine ratio (UACR, in mg/g), demographics, and comorbid conditions.

Results: Among 436 older patients aged 70 years, 16% were Black, mean eGFR was 34 and median UACR. In adjusted models no kidney-metabolic biomarkers were significantly associated with global Mod/Sev CI. However, in cognitive-domain-specific analyses, low bicarbonate (CO2 <20 mEq/L) was significantly associated with Mod/Sev CI impairment in memory [OR (95% CI): 3.04 (1.09, 8.47) P=0.03] and with language [3.82 (1.12, 13.6; P=0.03] in addition, lower total cholesterol was associated with impaired executive function [1.12 per -10mg/dL (1.02, 1.23; P=0.02).

Conclusions: Low bicarbonate (acidosis) and lower cholesterol levels in older patients with CKD may be modifiable kidney-metabolic risk factors for Mod/Sev domain-specific CI in CKD. Longitudinal analyses are needed to determine whether low bicarbonate and low cholesterol are associated with cognitive decline.
PO1388

Association of CKD Stages with Frailty Worsening or Death in Community-Dwelling Older Adults

Nina Mielke,1 Alice Schneider,1 Natalie Ebert,1 Markus van der Giet,1 Doerte Huscher,1 Martin K. Kuhlmann,2 Elke Schaeffner,1 1Charite Universitätsmedizin Berlin, Berlin, Germany; 2Vivantes Klinikum im Friedrichshain, Berlin, Germany.

Background: Albumin-creatinine-ratio (ACR) and glomerular filtration rate (GFR) have been associated with prevalent and incident frailty. We analyzed the association of the KDIGO CKD stages and frailty status worsening or death in data of the Berlin Initiative Study (BIS).

Methods: Prospective population-based cohort study interviewing participants biannually with a standardized questionnaire. Frailty assessment according to Fried took place at the 3rd and 4th follow-up. Frailty worsening was defined as the transition within a two-year period from robust to frail or frail, or from prefrail to frail. Partial proportional odds regression analysis was used to analyze the association between KDIGO CKD stages and the ordinal outcome of no worsening, frailty worsening, or death.

Results: Of 1076 participants with 46% male and mean age 84.3 years, initially 48% were frail and 32% frail. After 2.1 (2.0-2.3) years of follow-up 188 (17.5%) had worsened and 111 (10.3%) died. Participants who died were older (88 vs. 83 yrs), were less physically active, had less muscle mass (calve circumference <31: 10% vs. 5%), and were more likely to be cognitively impaired; 92% had a GFR <60 mL/min/1.73m2 and 59% had an ACR ≥30 mg/g compared to 72% and 24% in participants who did not worsen, respectively. Baseline characteristics of participants who worsened were similar to participants who did not worsen. In the multivariable model participants in CKD stages G1,2/A2,3 and G3/A1 or higher had a higher odds of frailty worsening, than in CKD stages G1,2/A1. The odds for death increased remarkably with both higher CKD stage and increasing albuminuria. Wide confidence intervals are likely due to limited sample size/events. Additional adjustment for frailty baseline status did not alter the results.

Conclusions: In older adults, advanced CKD stages but also albuminuria independent of GFR were associated with 2-fold higher odds of frailty worsening independent of death.

Funding: Private Foundation Support

PO1389

Role of Klotho in Aging, Relationship with Frailty, Renal Function, and Body Composition

Paolo Betti, Marta De Filippo, Marco Simonini, Simone Fontana, Lorena Citterio, Elisabetta Messaggio, Patrizia Rovere Querini, Elena Brioni, Cristiano Magnaghi, Chiara Lanzani, Paolo Manunta. IRCCS Ospedale San Raffaele, Milano, Italy.

Background: Reduced expression of the Klotho protein has been associated with premature aging and increased mortality. Our aim is to evaluate the relationships between plasma Klotho levels and frailty, renal function and anthropometric parameters.

Methods: We enrolled a cohort of 1250 volunteers aged > 65 years (FRASANET Study) in recreation centers for the elderly, in hospital’s outpatient clinic and in nursing homes. All the volunteers have signed informed consent and subjects with severe cognitive impairment were excluded (MMSE <18). We measured eGFR (CKD-EPI formula) and body composition by impedanceometry. Plasma Klotho was assayed by an ELISA kit on 194 samples. Frailty was classified according to Fried’s criteria.

Results: A positive correlation between plasma Klotho and renal function (eGFR) has been described (fig. 1). In agreement with what previously observed, in a young population, we confirmed a reduction of klothemia in the sarcopenic patients (713 vs 791 pg/mL, p=0.0007 in patients with muscle mass <25% centile) and in patients with high visceral fat mass (fig.2). On the other hand, we did not observe different plasma levels of Klotho according to the frailty class or in relation to age.

Conclusions: In our elderly population, the plasma levels of Klotho do not correlate with age. Therefore, our results confirm the relevance of this biomarker in identifying pathological aging, in consideration of its association within the elderly population with CKD, abdominal obesity and sarcopenia (sarcopenic obesity). Klotho expression was demonstrated as an independent predictor of death in a follow up-study and was related to many diseases (e.g.: cognitive impairment, cardiovascular disease). The relation of plasma klotho levels and renal function is debated, and conflicting results have been published. Our findings evidenced a significative association of plasma Klotho with renal function and body composition.

Funding: Private Foundation Support

PO1390

Shrunken Pore Syndrome: Prevalence and Association with Mortality in a Population-Based Cohort of Elderly Women

Linnéa Malmgren,1,2 Fiona Mequigan,1 Anders Christensson,1,2 Kristina Åkesson,1,2 1Lunds Universitet, Lund, Sweden; 2Skanes universitetssjukhus Malmo, Malmo, Sweden.

Background: Decreased kidney function results in lower clearance and increased plasma concentration of a GFR marker. So far creatinine has been the commonly used GFR marker but cystatin C becomes more common. Shrunken pore syndrome (SPS) is a recently identified kidney syndrome characterized by disturbed filtration of mid-sized molecules (5-30 kDa) compared to smaller ones (<0.9 kDa) (Fig1). Resulting in increased plasma levels of cystatin C (cysC) compared to creatinine. SPS is associated with increased risk of cardiovascular disease (CVD) and increased mortality risk. So far few data are available about SPS in population-based cohorts.

Methods: 75-yr old women (n=849) from the population-based Osteoporosis Prospective Risk Assessment (OPRA-) cohort, with follow-up after 5yr and 10yr were studied. eGFR was calculated with the CKD-EPI equation. SPS was defined as eGFRcysC/eGFRcrea ratio <0.6 and mortality risk (HR [95% CI]) estimated. Women with sarcopenia or on glucocorticoids were excluded.

Results: Almost 1 in 10 women (9%) had SPS at age 75 but at age 80 the majority of these women had increased their eGFRcysC/eGFRcrea ratio >0.6 (range from 0.6-1.0). Women with SPS had higher 10-yr mortality risk compared with ratios <0.9 (HRadj 1.7 [95% CI, 1.1-2.6]). Table 1.

Conclusions: SPS defined as eGFRcysC/eGFRcrea ratio <0.6 is common in elderly women and associated with increased mortality. While longitudinal data indicate that the state may be reversible. Our results also confirm other studies and suggest that SPS may be a clinically applicable tool to assess mortality risk in the elderly.

Funding: Private Foundation Support, Government Support - Non-U.S.

SPS (eGFRcysC/eGFRcrea ratio <0.6) is associated with increased 10-yr mortality

Possible pathophysiological mechanisms of SPS (1) reduced pore size and (2) thickening of the glomerular basement membrane

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO1391
Molecular Changes Associated with Type IV Collagen Switching in 1-Day-Old Alport Murine Glomeruli
Akanehaya Rana,1,2 Sofia Farkona,1,2 James W. Scholey,1,2 Ana Konvalinka,1,2 Mounir Barua,1,2 1Toronto General Research Institute, Toronto, ON, Canada; 2University Health Network, Toronto, ON, Canada; 3University of Medical Science, University of Toronto, ON, Canada.

Background: Alport syndrome (AS) is an inherited disorder caused by pathogenic variants in COL4A3, COL4A4 or COL4A5, which encodes proteins that comprise basement membranes of the ear, eye and kidney glomeruli. Type IV collagen chains assemble as heterotrimers and during glomerular development, α1G2α1 (IV) is replaced by α3ε4α5 (IV) within the developing glomerular basement membrane (GBM). This “switching” defines the starting point of disease in AS. We aimed to identify the molecular changes at the time of disease initiation in the developing glomeruli of Alport murine kidneys.

Methods: Immunofluorescence (IF) staining was done to identify the GBM distribution of type IV collagen chains in 1 day old COL4A3 knockout (KO) and wildtype (WT) mice. Urine albumin to creatinine ratio (uACR) was also measured. Subsequently, glomeruli from 1 day old (P1) COL4A3 KO and WT mice were isolated by cardiac injection of magnetic dynabeads that embolized to glomerular capillaries enabling their extraction from surrounding tissue. Protein was isolated and subjected to liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) analysis.

Results: IF localized type IV collagen α1 in the GBM, Bowman’s capsule and mesangial matrix in both P1 KO and WT mice. Type IV collagen α5 was present in short segments of some developing GBM in P1 WT but was absent in KO mice indicating switching. uACR was increased in P1 KO (423.61 mg/mmol) compared to WT (128.67±9.86 mg/mmol) with a p-value of 0.02. LC-MS/MS identified ~4300 proteins from glomerular isolates. In males, 2 and 15 proteins were significantly upregulated and downregulated, respectively, in KO compared to WT mice. In females, 543 and 978 proteins were significantly upregulated and downregulated, respectively, in KO compared to WT mice. Pathway analysis revealed alteration in collagen metabolic process, collagen biosynthesis, collagen formation and extracellular matrix organization.

Conclusions: Increased uACR in P1 KO mice showed disease onset at the time of Type IV collagen switching. LC-MS/MS analysis revealed dysregulation of matrix turnover pathways in P1 KO mice, identifying potential molecular targets.

Funding: Private Foundation Support

PO1392
PTEN-Induced Kinase 1 Has Association with Renal Aging in the Context of Inflammatory Response
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Background: Among several changes of aging-related human organ system, functional and structural deterioration of kidney is the most dramatic phenomenon, and the role of mitophagy has recently considered important in pro-aging process in CKD patients. PTEN-Induced kinase 1 (PINK1), known to be associated with age-related diseases regulates mitochondrial dysfunction. To enhance understanding the function of PINK-1 on aging, we compared whole-kidney RNA sequencing between naturally aging mice (24-month-old) and PINK1 knockout (KO) mice.

Methods: Kyoto Encyclopedia of Genes and Genomes pathway analysis and gene ontology analysis were performed for gene expression analysis. To investigate the role of PINK1 on aging, we used Pnk1-deficient mice and PINK1-overexpressing HKC8.

Results: Compared to naturally aging kidneys, PINK1 knock out aging mice showed prominent expression of PINK1 related to cytokines, immune system response, and inflammation (Fig 1). We also investigated the function of PINK1 in PINK1 (-/-) aging mice. PINK1 deficiency showed aggravated tubulointerstitial fibrosis on PAS staining (Fig2A), and the Urinary Albumin-Creatinine Ratio increased more prominently (Fig2B). The Quantitative PCR analysis validated according to aging in PINK1 (-/-) mice (Fig2B). The Urinary Albumin-Creatinine Ratio increased more prominently (Fig2B). The Quantitative PCR analysis validated according to aging in PINK1 (-/-) mice (Fig2B). The Urinary Albumin-Creatinine Ratio increased more prominently (Fig2B). The Quantitative PCR analysis validated according to aging in PINK1 (-/-) mice (Fig2B).

Conclusions: In conclusion, our results suggest that PINK1 deficiency contributes to renal aging process via proinflammatory change in the kidney.

PO1393
TGF-β1/Smad Signaling in Glomerulonephritis and Its Association with Progression to CKD
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Background: Transforming growth factor-β1 (TGF-β1) is a multifunctional cytokine, with diverse roles in fibrosis and inflammation, which acts through Smad signaling in renal pathology. We intended to investigate the expression of TGF-β1/Smad signaling in glomerulonephritis (GN) and to assess its role as risk factor for progression to chronic kidney disease (CKD).

Methods: We evaluated the immunohistochemical expression of TGF-β1, phosphorylated Smad3 (pSmad3) and Smad7 semi-quantitatively and quantitatively (computerized image analysis program has also been used) in different compartments of 50 renal biopsies with GN and the results were statistically analyzed with clinicopathological parameters. We also examined the associations among their expressions, the impact of their co-expression, and their role in progression to CKD.

Results: TGF-β1 expression correlated positively with segmental glomerulosclerosis (p=0.025) and creatinine level at diagnosis (p=0.002), while pSmad3 expression with interstitial inflammation (p=0.024). In glomerulus, concomitant expressions of high Smad7 and medium pSmad3 were observed to be correlated with renal inflammation, such as cellular crescent (p=0.011), intense interstitial inflammation (p=0.029) and lower serum complement 3 (p=0.028) and complement 4 (p=0.029). We also reported a significant association between pSmad3 expression in glomerular endothelial cells of proliferative GN (p=0.045) and in podocytes of non-proliferative GN (p=0.005). Finally, on multivariate Cox-regression analysis, TGF-β1 expression (HR = 6.078; 95% CI 1.168-31.627; p=0.032) was emerged as independent predictor for CKD.

Conclusions: TGF-β1/Smad signaling is upregulated with specific characteristics in different forms of GN. TGF-β1 expression is indicated as independent risk factor for progression to CKD, while specific co-expression pattern of pSmad3 and Smad7 in glomerulus is correlated with renal inflammation.
**Case Description:** A 55-year-old male with a medical history significant for uncontrolled diabetes complicated by retinopathy, Chronic kidney disease, HTN, and compensated cirrhosis of unclear etiology, presented to the hospital with shortness of breath and lower extremity edema. Initial workup revealed a creatinine of 7.6 (baseline creatinine 1.5 eighteen months earlier), and significant proteinuria estimated at 8.4g/day along with a urinalysis showing 3 RBC/high power field and 6 WBC/high power field. Serological workup including Hepatitis B/C, HIV, SFEP, serum free light chains, C3/C4, ANA, ANCA was negative. He underwent a renal biopsy revealing medullary angiitis with multifocal medullary hemorrhage with perivascular PMNs and eosinophils along with findings of long-standing diabetes and HTN. In the absence of IgA deposits, infection, or offending drugs, he was started on high steroids and treated similarly to ANCA positive medullary angiitis. His creatinine during the hospitalization peaked at 8.69 before and fell to 7.6 at discharge. He was continued to oral prednisone at discharge. Outpatient follow-up showed a decrease in Cr to 5.8 before slowing climbing back up to 8.5. He is currently maintained on an immunosuppressive regimen to help delay the initiation of renal replacement therapy.

**Discussion:** Medullary angiitis is a rare renal disorder that has largely been associated with ANCA positivity. ANCA negative medullary angiitis has been documented in the literature with a recent case series showing IgA nephropathy and recent antibiotics use to be the most common etiologies. This is one of the first case reports of ANCA negative medullary angiitis not associated with IgA nephropathy and recent antibiotic use. Currently, we have no standardized treatment options available for these patients. Given the rapid progression of the renal dysfunction, we decided to start our patient on high-dose steroids. Our patient had an initial improvement in his renal function with subsequent decline. However, treatment may have afforded time for AVF creation and patient education before the initiation of hemodialysis, which was the main goal of therapy.

**PO1395**

**Calorie Restriction Ameliorates Obesity-Related Glomerulopathy in Adult Zebrafish**

**Evan Zeitley, J. Charles Jenette, Jennifer E. Flythe, Ronald J. Falk, John S. Pouillon. UNC Kidney Center, Chapel Hill, NC.**

**Background:** Obesity is a risk factor for chronic kidney disease. The mechanisms by which obesity results in kidney disease are understudied. Zebrafish are an attractive model animal for studying obesity due to their conserved biology and amenability to genetic screening. The effects of obesity on kidney function in zebrafish have not been reported.

**Methods:** Zebrafish were fed high-calorie and high-fat diets for 8 weeks. Kidneys were evaluated by light and electron microscopy, and the glomerular filtration barrier was assessed by fluorescent dextran permeability. We also tested the ability of calorie restriction to reverse obesity-related defects.

**Results:** Fish fed a high calorie diet developed glomerulomegaly, foot process effacement, GBM thickening, tubular enlargement (Figure 1) and ectopic lipid deposition after 8 weeks. High calorie feeding resulted in filtration barrier dysfunction. The observed effects resolved after 4 weeks of calorie restriction (Figure 2).

**Conclusions:** Our study reveals that obese zebrafish recapitulate key aspects of human pathology, and these defects can be reversed with calorie restriction. These findings establish zebrafish as a potential model for the study of obesity-related kidney disease.

**Funding:** NIDDK Support

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**PO1396**

**Different Patterns of Renal Fibrosis Are Indicative of Independent Fibrogenic Causes in ANCA-Associated Glomerulonephritis**

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**Background:** Renal fibrosis is a common manifestation and hallmark of a wide variety of chronic kidney diseases (CKD) appearing in different morphological patterns, suggesting different pathogenic causes or consequences. Renal fibrosis with focal injury usually presents with patchy fibrosis whereas diseases affecting renal parenchyma in a diffuse manner lead to a more diffuse fibrotic pattern. In the present study, we aimed to analyze renal fibrotic patterns in association with the renal lesions which are considered to directly contribute to renal fibrogenesis in a cross-sectional study.

**Methods:** A total number of 112 renal biopsies with various renal pathologies including acute interstitial nephritis (AIN), ANCA-associated vasculitis (AAV), membranous GN, lupus nephritis, nephropathy due to hypertension, IgA nephropathy (IgAN), focal-segmental glomerulosclerosis (FSGS) and diabetic kidney disease (DKD) were retrospectively included between 2015 till 2020 in a cross-sectional study.

**Results:** We here provide evidence that tubulointerstitial fibrosis is either the result of nephron damage (dependent or independent of glomerular scarring) or the result of a primary interstitial injury (leading to a diffuse fibrotic interstitial remodeling). Our data also show that focal fibrosis correlated with glomerular damage and irreversible injury to nephrons, confirmed in experimental models of nephrotoxic serum-nephritis and folic acid nephropathy in mice. By contrast, diffuse fibrosis was specifically associated with interstitial inflammation independent of glomerular damage and nephron loss, confirmed in mice challenged with unilateral ureteral obstruction.

**Conclusions:** In conclusion, we here provide evidence that tubulointerstitial fibrosis is either the result of nephron damage or loss and replacement scarring, representing incomplete tissue repair. By contrast diffuse fibrosis appears to be the result of primary interstitial inflammation and injury.

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**PO1397**

**Automatic Artificial Intelligence-Assisted Glomerulosclerosis Analysis in Mice Models with Glomerulopathy**

**Thomas Secher, Casper G. Salinas, Michael Christensen, Niels Vrang, Mette V. Østergaard, Gubra, Harsholm, Denmark.**

**Background:** Glomerulosclerosis (GS) is a hallmark pathological feature in glomerular diseases. In preclinical research, GS is recapitulated in a number of experimental mice models with glomerulopathy, and a cross model characterization of GS would add to our understanding of their translatability to human disease. Here, we report GS quantification using an objective and newly developed automated AI assisted image analysis strategy in three mice models with glomerulopathy.

**Methods:** AI-assisted GS scoring was performed in three mice models with glomerulopathy and to assess drug treatment effects: 1) Diabetic nephropathy in remnAAV-induced hypertensive uninephrectomized db/db mice (DN/HT). Mice received treatment with vehicle, lisinopril, empagliflozin or combination. 2) I.V. injection of nephrotoxic anti-GBM serum (NTS) and 3) Adriamycin (ADR) in healthy mice. Automatic AI-assisted GS scoring was performed as a two-step process on PAS stained image analysis strategy in three mice models with glomerulopathy.

**Results:** We here provide evidence that tubulointerstitial fibrosis is either the result of nephron damage (dependent or independent of glomerular scarring) or the result of a primary interstitial injury (leading to a diffuse fibrotic interstitial remodeling). Our data also show that focal fibrosis correlated with glomerular damage and irreversible injury to nephrons, confirmed in experimental models of nephrotoxic serum-nephritis and folic acid nephropathy in mice. By contrast, diffuse fibrosis was specifically associated with interstitial inflammation independent of glomerular damage and nephron loss, confirmed in mice challenged with unilateral ureteral obstruction.

**Conclusions:** In conclusion, we here provide evidence that the majority of renal fibrosis seems to be the consequence of nephron loss and replacement scarring, representing incomplete tissue repair. By contrast diffuse fibrosis appears to be the result of primary interstitial inflammation and injury.
PB01398
Increased Glomerular Parietal Epithelial Cell Expression of Cathepsins C and B in Anti-Thy-1.1 Mouse Model of FSGS
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Background: Focal segmental glomerulosclerosis (FSGS) is characterized by replacement of glomerular capillaries by extracellular matrix (ECM). The collapsing FSGS (cFSGS) variant exhibits a poor prognosis and response to therapy. We recently reported that activated PECs migrates into glomerular tufts in humans and in cFSGS patients and demonstrate increased cathepsins C and B expression. The absence of cathepsins B and C within normal glomerular tufts suggests these proteases may represent novel mediators of PEC-mediated glomerulosclerosis leading to collapse. Here we address the hypothesis that activated PECs expressing cathepsins C and B migrate into glomerular tufts in a mouse model of cFSGS.

Methods: Thy-1.1 transgenic mice were injected with either saline (vehicle control) or anti-Thy1.1 antibody (19XE5; 1mg/mouse) to induce cFSGS. Mice were sacrificed 4, 7, and 21 days after injection. Kidney sections were subjected to immunofluorescence staining for claudin-1, a marker of PECs, and cathepin C or cathepsin B. Images were acquired by confocal microscopy.

Results: Claudin-1, cathepsin C, and cathepsin B co-localized to glomerular parietal epithelial cells lining Bowman’s capsule in vehicle control mice. On day 4 after anti-Thy-1.1 administration, claudin-1 staining showed migration of PECs into glomerular tufts in more than half of the glomeruli. Both cathepsins B and C co-stained to positive cells within glomerular tufts. PECs in the Bowman’s capsule with hypertrophied morphology, suggesting activation, demonstrated increased expression of cathepsins C and B. Claudin-1 and cathepsins B and C co-localized within glomerulitis on day 7 and 21 after anti-Thy-1.1 administration, however, the number of stained cells per glomerulus and the percent glomerulus with positively stained cells in the glomerular tuft appeared decreased.

Conclusions: Glomerular PECs migrate into glomerular tufts and show increased expression of cathepsins C and B in the anti-Thy-1.1 model of cFSGS, recapitulating our findings in human cFSGS biopsies. The Thy-1.1 mouse model of cFSGS can be used to define the role of PEC expression of cathepsins B and C in the pathogenesis of human cFSGS.

Funding: Clinical Revenue Support

PB01399
Effects of Enzymatic Cross-Linking and Increased Stiffness on Glomerular Basement Membrane and Podocyte Function
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Background: The Glomerular basement membrane (GBM) is a critical component of the glomerular filtration barrier. Stiffening of the extracellular matrix is an important regulator of cellular function. How GBM stiffening affects podocyte function is not fully understood. This work aims to investigate the effect of GBM stiffening on molecular permeability and the podocyte function using a biomimetic in vitro model directly derived from kidney glomeruli.

Methods: Decellularized glomeruli isolated from porcine kidneys were pressure compacted on a Transwell membrane. GBM stiffness was tuned by crosslinking with Ficoll and AF488-BSA. Effects of GBM stiffening on gene expression of markers of podocyte differentiation (NPHP1, WT1, Synaptopodin) were screened by qPCR.

Results: The stiffness of the decellularized glomeruli showed a dose-dependent increase after incubating with TG for 1 day and 4 days. On stiffer GBM, immunofluorescence imaging showed translocation of YAP to the podocyte nucleus. Passive molecular permeability of GBM was similar for native and the TG crosslinked GBM. Podocytes cultured on both native and TG crosslinked GBM forms a stringent barrier to large molecules. qPCR results show an upregulation of differentiation markers as podocytes cultured on native and TG crosslinked GBM.

Conclusions: We developed a biomimetic in vitro model that fabricated directly from kidney tissue. mTG crosslinked glomeruli show a dose-dependent increase of stiffness. TG did not significantly effect the diffusive permeability of the GBM. GBM stiffness affects the YAP localization in the podocytes. The current in vitro model upregulates the gene expression of podocyte markers.

Funding: Other U.S. Government Support

PB01400
Effect of ANG-3070 in the Unilateral Ureteral Obstruction Mouse Model of Renal Fibrosis

Background: Tubulointerstitial inflammation and fibrosis are strong predictors of progression in all kidney diseases regardless of etiology. Receptor tyrosine kinases such as platelet-derived growth factor receptor (PDGFR) and discoidin domain receptors (DDRs), contribute to renal inflammation and fibrosis. ANG-3070 is an inhibitor of multiple tyrosine kinase receptors including PDGFR and DDR. This study evaluated whether ANG-3070 can slow the progression of fibrosis in the unilateral ureteral obstruction (UUO) mouse model of renal fibrosis.

Methods: Male mice were subjected to UUO and randomized to daily oral treatment with vehicle (n=15) or 100 mg/kg of ANG-3070 (n=15) for 10 days after UUO and then sacrificed. Control male animals were age-matched and were not subjected to UUO (n=10). At sacrifice, obstructed and control kidneys were collected and processed for renal damage by hematoxylin-eosin (H&E) staining and scoring (0-8; 0 no damage and 8 damage >80% of kidney) by blinded observers. Collagen deposition and myofibroblast transformation was determined by quantitative image analysis of picrosirius red (PSR)-stained slides and slides stained for α-smooth muscle cell actin (αSMA), respectively.

Results: Animals treated with ANG-3070 had a statistically significant reduction in histological damage as compared to vehicle (Vehicle, 6.4 vs ANG-3070, 4.3; p-value <0.001) and the histological markers of fibrosis, PSR (% control, vehicle, 1453 vs. ANG-3070, 5035; p-value <0.001), and αSMA (% control, vehicle, 511 vs. ANG-3070, 248; p-value <0.01) as shown in Figure 1.

Conclusions: Daily oral administration of 100 mg/kg ANG-3070 reduces renal damage and renal fibrosis in a mouse model of renal fibrosis induced by UUO.

Funding: Commercial Support - Angion Biomedica, Inc.

Figure 1

PO1401
Renal Outcome Using New Chronicity Scoring System in IgA Nephropathy: Nationwide Study in Korea
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Background: Many new grading systems of glomerulonephritis were proposed, recently. In 2019, new suggestion about standardized classification and reporting of GN is proposed by Mayo Clinic/Renal pathology society. Among the part of this new suggestion, grading the chronicity is an extremely important step and simple scoring system for chronic changes was devised. Therefore, the purpose of this study is predicting renal outcome with new grading system in IgA nephropathy (IgAN) patients.

Methods: 4,505 IgAN patients were enrolled from Korean Glomerulonephritis Study Group (KoGNET) registry. Validation of Oxford classification, chronicity index was predicting renal outcome with new chronicity grading system in IgA nephropathy (IgAN) patients.

Results: In validation of Oxford classification, both S and T scores were significantly associated with renal outcomes, but M and C scores were not. Multivariate linear regression analysis showed chronicity index was significantly associated with renal outcomes (P=0.05 for all). The severity of chronicity index was well correlated with renal outcomes in multivariate Cox regression analysis: minimal vs mild (HR, 1.95; 95% CI, 1.15 to 3.32; P=0.014), minimal vs moderate (HR, 2.98; 95% CI, 1.66 to 5.34; P<0.001), minimal vs severe (HR, 4.08; 95% CI, 2.27 to 7.35; P<0.001). Hypertension, eGFR, proteinuria and serum uric acid were also well correlated. In subgroup analysis,
POI1402
Comparison of Glomerular Proteome Profiles of Healthy Human Kidney and Minimal Change Disease Identifies Distinct Targets and Pathways
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Background: Minimal change disease (MCD) is a common cause of idiopathic nephrotic syndrome and is characterized by diffused podocyte foot process effacement. The pathogenesis of MCD remains unclear. We hypothesized that proteomics analysis of glomeruli could identify molecular markers that reflect the pathogenesis of MCD.

Methods: We included formalin-fixed paraffin-embedded kidney biopsies from patients with steroid-sensitive MCD (n=9) and normal donor kidneys (n=4). Glomeruli were isolated using laser capture microdissection and HPLC MS/MS was done using Orbitrap eclipse mass spectrometer. After data normalization, groups were clustered using principal component analysis (PCA) and compared by paired t-tests.

Results: PCA showed separate clustering of healthy glomeruli and MCD samples (FDR<0.1). Out of the 6729 unique proteins identified in MCD glomeruli, 1088 proteins were significantly differentially expressed compared to controls. Pathway analysis showed upregulation of complement pathway components (C1R, C1S, C1QA, C2, C3, C4A, C4B, C5, C7, C8B, C9) and downregulation of carbohydrate and amino acid metabolic pathway enzymes (FBP1, FBP2, ALDOC, ALDOB, AKR1A1, ALDH1A1, ALDH5A1, ACAT1). MCD glomeruli showed a significant reduction in expression of ECM proteins FREM2, FRAS1, CDH12. Surprisingly, the expression of podocyte slit diaphragm-associated proteins (SYNPO, NPHS2, CD2AP) was not significantly altered in MCD compared to controls. We did not observe differential expression of MCD associated proteins, KANK, CFL1, CMIP. No peptides from SMPD3L8 or ANGPTL4 were identified in MCD glomeruli.

Conclusions: Glomeruli from MCD showed differential proteomic signature compared to healthy human glomeruli. Activation of innate immune pathways including the complement system and loss of extracellular matrix and basement membrane-specific components in glomeruli of MCD are novel observations. The role of these markers in the pathogenesis of MCD needs to be investigated.

Funding: Clinical Revenue Support

POI1403
Effects of ANG-3070 in a Mouse Model of Alport Syndrome

Background: Alport syndrome (AS) is a hereditary kidney disease that presents in childhood and progresses to end stage kidney disease (ESKD) in adolescence. There are no approved therapies. AS is caused by mutations in type IV collagen genes Col4a3, a4 or a5, that result in reduced structural integrity of the glomerular basement membrane, triggering activation of fibrionic cytokines, including platelet derived growth factor (PDGF) and transforming growth factor beta (TGFβ1) causing proteinuric disease and fibrosis. We hypothesize that an antifibrotic therapy may decrease proteinuria-induced fibrosis, and evaluated ANG-3070, a novel tyrosine kinase inhibitor, in a Col4a3 knockout mouse model of AS.

Methods: After confirming the Col4a3 mutation by genotyping, 4-week-old male and female mouse were randomized to Vehicle (oral, twice-daily) or ANG-3070 (oral, 25 mg/kg, twice-daily) for 5 weeks (n=12/group). Age-matched, wild-type mice were included (n=9) as a control. Animals were sacrificed after 5 weeks of treatment, after collecting spot urines to measure protein to creatinine ratio (PCR). Renal tissue was analyzed for hydroxyproline (HYP) content by Western blot or tissue fibrotic markers, and for histopathology using hematoxylin-eosin (H&E) staining for renal damage score and picrosirius red (PSR) staining for fibrosis. All histological analyses were performed by two independent observers using a 0-4 scale (0 being normal, 4 ≥75% injured or stained).

Results: ANG-3070 treatment reduced mortality (survivors; Vehicle: 8/12 vs ANG-3070: 12/12). In surviving mice, proteinuria was reduced (mg/mg; Vehicle 6.2 vs ANG-3070 3.1, p<0.05) along with renal damage (Vehicle 2.6 vs ANG-3070: 1.2; p = 0.002) along with renal fibrosis (Vehicle 2.4 vs ANG-3070 1.2; p<0.001). When kidney lysates were evaluated, HYP content was reduced (mg/kg; Vehicle, 132 vs ANG-3070, 57; p<0.05) along with fibrosis (mg/g kidney; Vehicle, 132 vs ANG-3070, 57; p<0.05). When kidney lysates were evaluated, HYP content was reduced (mg/kg; Vehicle, 132 vs ANG-3070, 57; p<0.05) along with fibrosis (mg/g kidney; Vehicle, 132 vs ANG-3070, 57; p<0.05). When kidney lysates were evaluated, HYP content was reduced (mg/kg; Vehicle, 132 vs ANG-3070, 57; p<0.05) along with fibrosis (mg/g kidney; Vehicle, 132 vs ANG-3070, 57; p<0.05). When kidney lysates were evaluated, HYP content was reduced (mg/kg; Vehicle, 132 vs ANG-3070, 57; p<0.05) along with fibrosis (mg/g kidney; Vehicle, 132 vs ANG-3070, 57; p<0.05).

Conclusions: Treatment with a novel tyrosine kinase inhibitor, ANG-3070, was effective in AS mice compared to Vehicle. ANG-3070 may represent a novel therapeutic for AS.

Funding: Commercial Support - Angion Biomedica, Inc.
**PO1406**

Collapsing FSGS Is Strongly Associated with Microvascular Injury
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**Background:** Recent studies have suggested that the collapsing variant of focal segmental glomerulosclerosis (FSGS) might be a common secondary feature in renal disease influenced by microvascular injury. Here, we investigated glomerular and arteriolar microvascular injury in patients with collapsing FSGS, including primary FSGS, and HIV-associated FSGS, and compared these lesions to patients with other variants of FSGS.

**Methods:** Biopsies of patients with FSGS were collected, including primary FSGS in native biopsies or transplant biopsies, as well as HIV-associated FSGS. Cases of FSGS secondary to renal diseases known to be caused by microvascular injury were excluded. We assessed all glomeruli in a biopsy for the presence of lesions associated with FSGS or ischemic injury, assessed microvascular lesions in glomeruli and arterioles, and studied interstitial lesions.

**Results:** We included 53 cases of FSGS, of which 19 cases with collapsing FSGS, 18 cases with FSGS not otherwise specified (NOS), 11 cases with FSGS tip, 3 cases with perihilar FSGS and 2 cases with cellular FSGS. Compared to other variants of FSGS, glomerular endothelial swelling of the vascular pole was more common in patients with collapsing FSGS (11% vs 0.9%; p=0.05). Associations between thrombotic injury and FSGS variant were not found. Arteriolar abnormalities were seen in 58% of collapsing FSGS and 38% of other variants of FSGS (p=0.17). When evaluating the concomitant occurrence of FSGS lesions and microvascular injury in individual glomeruli, we found that collapsing lesions and FSGS NOS lesions were associated with endothelial swelling in the same glomerulus (OR=22;p<0.001 and OR=3.8;p=0.01, respectively). Endothelial swelling was more common in glomeruli with collapsing lesions than glomeruli with FSGS NOS (OR=2.7;p=0.044). Collapsing FSGS was also associated with endocapillary hypercellularity (OR=4.3;p<0.001).

**Conclusions:** Here, we demonstrate that collapsing FSGS lesions are strongly associated with microvascular injury such as endothelial swelling and endocapillary hypercellularity, and often co-exist in the same glomerulus. In addition to collapsing FSGS occurrence, the secondary phenomenon in renal microangiopathies, these results indicate that endothelial injury could also be involved in the pathophysiology of collapsing FSGS due to primary podocyte injury.

**PO1407**

Danhog Injection (DHI) Inhibits Lipopolysaccharide-Enhanced Cell Proliferation of Rat Renal Mesangial Cells via NF-κB Signaling Pathway
Hua Liu. The First Affiliated Hospital of Xi’an Jiaotong University, Xi’an, China.

**Background:** To explore the mechanisms of DHI in the treatment of Mesangioproliferative glomerulonephritis (MsPGN), we investigated the effects of DHI on LPS-induced NF-κB activation and its downstream inflammatory mediators, such as ICAM-1, TGF-β1, iNOS and FN protein expression in rat MCs.

**Methods:** The rat MCs treated with different concentrations of DHI (0, 50, 100, 200, 500, 1000, and 2000 uL/L) for 12 h,then incubated with or without 100 ng/ml LPS for another 24 h. Then, cell proliferation was determined by CCK8. The MCs treated with low-dose DHI (250 uL/L), median-dose DHI (500 uL/L) and high-dose DHI (1000 uL/L) for 12 h or PDTC for 30 min before 24h treatment of LPS. Then the activation of NF-κB was detected by Western blot and immunofluorescence. The protein levels of ICAM-1, TGF-β1, iNOS and FN in rat MCs were detected by Western blot.

**Results:** DHI significantly suppressed LPS-induced cell proliferation by CCK8 results (Fig 1). LPS stimulation resulted in a significant increment of p65 contents in nucleus and a decrement of p56 contents in cytoplasm in rat MCs compared with NC. PDTC and DHI exerted potent inhibitory effect on increasing expression of p65 in nucleus and decreasing in cytoplasm compared with LPS-treatment group. The inhibitory effect on NF-κB nuclear translocation of DHI was in a dose-dependent manner (Fig 2). The protein level of iκB-α in cytoplasm treated by LPS decreased significantly compared with that in control (Fig 3) and this decrement was significantly reversed by PDTC and DHI. In addition, the protein expression of ICAM-1, TGF-β1, iNOS and FN was also inhibited by PDTC and DHI (Fig 4).

**Conclusions:** DHI significantly repressed LPS-induced cell proliferation and FN expression in rat MCs through inhibiting the activation of NF-κB signaling pathway also its downstream inflammatory mediators.

**PO1408**

Effect of ANG-3070 in the Passive Heymann Nephritis Rat Model of Primary Proteinuric Kidney Disease

**Background:** Primary proteinuric kidney diseases (PPKD) as a group are an important cause of end-stage kidney disease (ESKD). Many receptor tyrosine kinases, including platelet-derived growth factor receptor (PDGFR), contribute to the progression of PPKD to ESKD. ANG-3070 is a novel and proprietary inhibitor of multiple tyrosine kinases including PDGFR. This study evaluated the effects of ANG-3070 in a passive Heymann's nephritis (PHN) rat model of membranous glomerulopathy.

**Methods:** Male Sprague Dawley rats (300g) were administered anti-FX1A serum. Treatment groups included 15mg/kg ANG-3070 (n=11), Vehicle (n=11) and Sham (n=5). Animals were dosed orally, twice daily, for 12 weeks, and 24-hour urines were collected biweekly. At sacrifice, kidney tissue was harvested.

**Results:** Twelve-week treatment with orally dosed ANG-3070 significantly reduced the protein to creatinine ratio as compared to Vehicle (mg/mg: 5.3 vs 9.4; p=0.05). It also led to a significant reduction in total kidney hydroxyproline content (mg/kidney: 952 vs. 1416; p=0.05), indicating a reduction in fibrotic tissue. When periodic acid-Schiff staining from kidney sections were evaluated for glomerular damage by two blinded observers on a scale of 0 (normal/no injury) to 4 (severe injury), ANG-3070 significantly reduced glomerular damage (1.7 vs. 2.6; p=0.05), indicating a reduction in glomerulosclerosis. The evaluation of PDGFRβ levels from total kidney lysates by Western blot indicated an increase in the Vehicle treated group compared to Sham (PDGFRβ/GAPDH; 2.6 vs 0.7, p=0.05). ANG-3070 treatment significantly reduced these levels when compared to Vehicle (PDGFRβ/GAPDH; 1.0 vs 2.6, p=0.05), which was comparable to the levels observed in the Sham group.

**Conclusions:** Twice-daily oral administration of the novel tyrosine kinase inhibitor ANG-3070 reduces proteinuria, renal fibrosis, glomerulosclerosis and PDGFRβ expression levels in a rat model of PHN. These data suggest ANG-3070 may be an effective treatment in PPKDs.

**Funding:** Other U.S. Government Support, Commercial Support - Angion Biomedica, Inc.

**PO1409**

A Rare Case of Immunotactoid Glomerulopathy Associated with Rheumatoid Arthritis
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**Introduction:** Immunotactoid glomerulopathy (ITG) is a rare disease that is characterized by nephritic range proteinuria, hematuria, hypertension, and kidney failure. It is most commonly associated with hematologic disorders. Rarely it presents as a polyclonal process and associated with autoimmune disorders such as rheumatoid arthritis (RA).

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Fibrillary Glomerulonephritis: A Rare Entity, Responsive to Rituximab
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Introduction: Fibrillary glomerulopathy (FGN) is a rare proliferative type of glomerular disease with poor prognosis and limited therapeutic options. Literature review showed very few cases of FGN where Rituximab has been used.

Case Description: A 69-year-old Caucasian woman with a history of DM, HTN presented to the hospital with complaints of dyspnea and leg swelling. Lab work revealed BUN/Ser of 34/3.88 mg/dL (baseline Ser of 1.4 mg/dL, proteinuria (7.902 mg/dL). Renal biopsy was performed which showed fibrillar deposits as shown in the picture. Hepatitis panel and work up of malignancy including bone marrow biopsy was negative. She was started on Rituximab 1gm every 14 days for 2 doses. Pt initially required HD but with treatment her symptoms and Cr improved and was taken off HD. Most recent Cr was1.8.

Discussion: The diagnosis of FGN can only be established with kidney biopsy. Most of the patients present with renal insufficiency, nephrotic picture. Most idiopathic but can be associated with hepatitis C, dysproteinemia, autoimmune diseases and to lesser extent malignancies. The prognosis is very poor with very limited therapeutic options to date. Rituximab has been used in few cases in literature showing good clinical response. Our patient tolerated and responded very well to Rituximab with significant improvement in kidney function and hence we propose the use of Rituximab in FGN.

Focal Segmental Glomerulosclerosis: A Rare Cause of Nephrotic Syndrome in Graft vs. Host Disease

Introduction: Nephritic syndrome (NS) is a very rare complication of allogeneic hematopoietic cell transplantation (HCT) and is usually associated with chronic graft versus host disease (GVHD). In such patients, membranous nephropathy and minimal change disease are the most frequently observed renal pathology. However, focal segmental glomerulosclerosis (FSGS) is an extremely uncommon etiology of NS in patients with HCT and GVHD. We herein describe a case of a patient with HCT and chronic GVHD who developed NS secondary to FSGS.

Case Description: A 24-year-old man with medical history of Sickle Cell Disease status post splenectomy and HCT, epilepsy, arterial hypertension and chronic GVHD with cutaneous and esophageal manifestations who presented to the emergency department with a one-month history of progressive lower extremity edema and intermittent hematuria. Vital signs were remarkable for uncontrolled blood pressure. Home medications were lisinopril 20mg daily, levetiracetam 500mg twice daily and prednisone 10mg daily. Physical examination was remarkable for edema of the lower extremities, ascites, and cachexia. Laboratories revealed: BUN 35 mg/dL, serum creatinine 1.15 mg/dL, total bilirubin 0.9 mg/dL, serum albumin 1 g/dL, glucose 110 mg/dL, total cholesterol 425 mg/dL, triglycerides 335 mg/dL, VLDL 67 mg/dL and LDL 316 mg/dL. Urine protein/creatinine ratio resulted in 30,000mg/g. Laboratory findings of hypalbuminemia, hyperlipidemia, and nephrotic range proteinuria were consistent with NS. A renal biopsy was performed and the findings consistent with a diagnosis of FSGS, not otherwise specified. Partial remission of NS was achieved at 3 months of treatment with mycophenolate mofetil 500mg twice daily and prednisone 15mg twice daily.

Discussion: GVHD is a significant cause of morbidity and mortality in patients after HCT. Renal involvement can be a serious manifestation and prompt recognition is essential for adequate management and prevention of renal disease. FSGS is an extremely rare complication of HCT and very few cases have been reported in the literature linking FSGS to HCT. Further documentation of this phenomenon is important to further characterize the clinical and pathological features of this complication.
Catastrophic COVID-19-Associated Nephropathy (COVAN) in an Asymptomatic Patient

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Introduction: Glomerular lesions were reported in a minority of patients with COVID-19, with collapsing focal segmental glomerulosclerosis (FGS) also called COVID-associated nephropathy (COVAN). This typically occurs in the setting of prominent COVID symptoms. We describe a COVAN occurring in an asymptomatic patient.

Case Description: A 48-year-old, African American female patient who had CKD stage 3 secondary to hypertension, with serum creatinine of 1.2 mg/dl and absent proteinuria at baseline, presented to the hospital for evaluation of an asymptomatic elevation of her serum creatinine to 9.9 mg/dl, discovered during a routine evaluation by her PCP. Her urine Protein/Creatinine was 6.15. Six weeks prior to her presentation, she endorsed 7 days of nausea and intermittent vomiting associated with non-bloody diarrhea without respiratory symptoms. Her GI symptoms has resolved on its own. She had multiple family members, including her husband and daughter, who had tested positive for COVID around the same time. Her nasal PCR for COVID was negative. She had not been vaccinated for SARS COVID. She has no family history of kidney disease; she denied IV drug use and had no risk factors for HIV. She was on Amlodipine for her hypertension. She was afebrile on admission with blood pressure of 170/80 mm Hg. She had 1+ pedal edema with an unremarkable physical exam. A percutaneous kidney biopsy was performed to evaluate the cause of her renal dysfunction. This showed collapsing FSGS. HIV and ANA were negative. A subsequent testing for COVID nucleocapsid and spike protein was positive. Results of APOL1 genotype is pending. She was started on high dose steroids and followed up as an outpatient.

Discussion: COVAN is recognized as a serious complication of COVID. However, the typical presentation is in the setting of prominent respiratory involvement. Recognizing the minor fleeting symptoms of COVID preceding a catastrophic kidney disease and testing for it is an important in patients presenting with features of collapsing FGS.

POI1415

Siglec-9 Agonism Reduces ANCA-Mediated Neutrophil Responses

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Background: Siglec-9 (Siglec-9), a high molecular weight sialic acid-binding Ig-like lectin, is a monocyte and neutrophil membrane protein that is expressed on neutrophils and monocytes. The expression and potential role of siglec-9 in ANCA-associated vasculitis (AAV) is not yet to be determined. We aimed to examine the expression of siglec-9 in patients with AAV and explore the impact of siglec-9 agonism on AAV-associated neutrophil responses in vitro.

Methods: Neutrophils and monocytes were isolated from peripheral venous blood of AAV patients and siglec-9 expression was measured by flow cytometry and ELISA, respectively. Immunohistochemistry was performed on kidney biopsies of AAV patients with AAVN and stained for siglec-9 and leukocyte markers. Functional studies were done using healthy donor neutrophils and monocytes. The expression and potential role of siglec-9 in AAVN-associated vasculitis (AAV) is yet to be determined. We aimed to examine the expression of siglec-9 in patients with AAV and explore the impact of siglec-9 agonism on AAV-associated neutrophil responses in vitro.

Results: We found increased serum siglec-9 expression in active AAV compared to remission AAV and a positive correlation with disease activity. Neutrophils and intermediate (CD14+CD16+) monocytes from PR3-ANCA patients displayed higher siglec-9 expression compared to MPO-ANCA patients. Siglec-9 expression in AAGN was restricted to areas of active inflammation. We observed increased siglec-9 shedding in neutrophils following AAGN stimulation. Siglec-9 agonism in these neutrophils was associated with increased apoptosis and reduced ROS production compared to isotype control and unstimulated neutrophils.

Conclusions: Our study suggests that siglec-9 expression correlates with disease activity in AAV. Our functional studies support a potential role for siglec-9 in modulating AAV-mediated neutrophil responses. Further evaluation is required to determine the relevance of these findings on neutrophil-endothelial interactions.

Funding: Government Support - Non-U.S.
non-renal AAV and remission in all cohorts, and healthy control urine in C1 (Kruskal- Wallis, P<0.001). sCD206 was significantly higher in active ANCA GN compared to HC in cohorts C1 & C2 (Kruskal-Wallis, P=0.01). sCD163 had a specificity of 100% in all cohorts, whereas sensitivity was 71% (C1), 88% (C2) and 64% (C3). The addition of sCD206 increased the sensitivity to detect active ANCA GN in all cohorts to 83% (C1), 100% (C2) and 81% (C3). IHC revealed CD163+ and CD206+ cells in the kidneys of active ANCA GN patients (n=8). IF showed glomerular presence of CD163+ and CD206+ cells were mainly found in the tubulointerstitium.

Conclusions: sCD206 complements sCD163 and reduces false negative rates in the detection of active ANCA GN. Histological assessment revealed distinct glomerular and tubulointerstitial populations of CD163+ and CD206+ cells.

PO1418
Urine and Plasma Complement Ba Levels During Flares of Nephritis in Patients with ANCA-Associated Vasculitis
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Background: The alternative complement pathway has been implicated in the pathogenesis of ANCA-associated vasculitis (AAV), however it is not clear whether activation of complement occurs systemically or in affected organs such as the kidney. This study measured levels of urinary and plasma complement fragment Ba (uBa and pBa) respectively at multiple timepoints in patients with AAV.

Methods: Ba was measured by ELISA in serial samples of urine (uBa) and plasma (pBa) from 20 AAV patients who developed a renal flare, 20 who developed a non-renal flare, and 20 in long-term remission. Changes in Ba levels were modeled using linear mixed effect models.

Results: Cohort characteristics are given in Figure 1. uBa levels increased at renal flare, but did not increase at non-renal flare, and remained stable in long-term remission. Changes in Ba levels were modeled using linear mixed effect models.

PO1419
Alterations in Amino Acid and Lipid Metabolism in ANCA-Stimulated Monocytes
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Background: Multiple metabolic pathways and intermediates are involved in inflammation. Altered immune cell metabolism is involved in the pathogenesis of autoimmune diseases such as anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). In particular, monocytes stimulated with ANCA show increased oxidative phosphorylation and glycolysis, with a more profound response to myeloperoxidase (MPO) ANCA than proteinase-3 (PR3). The aim of this work was to profile the metabolome of ANCA-stimulated primary monocytes.

Methods: Monocytes from healthy donors (n=24) were isolated and stimulated with monoclonal anti-MPO, anti-PR3 for 4 hours. Metabolites were extracted using an optimised extraction protocol and analysed by liquid chromatography–mass spectrometry (LC-MS). Targeted and untargeted analyses were carried out using Agilent MassHunter Profiler and Mass Profiler Professional. Cytokine production was measured by ELISA and flow cytometry was used to assess surface expression of MPO and PR3.

Results: Targeted metabolomic analysis showed increases in several amino acid and TCA cycle metabolites relative to unstimulated cells, notably phenylalanine, isomers leucine & isoleucine, and fumarate. Untargeted analysis confirmed alterations in amino acid and lipid metabolism in ANCA-stimulated monocytes (Figure 1). These metabolic differences did not correlate with the increased cytokine expression observed in anti-MPO-treated monocytes. Anti-PR3 stimulation did not induce major changes in metabolism or cytokine production. Monocytes expressed high levels of surface MPO and PR3, with MPO expression showing a significant inverse correlation with age.

Conclusions: Inflammatory and metabolic activation of primary human monocytes occurs with anti-MPO but not anti-PR3 stimulation. Early increases in amino acid and lipid metabolism are evident in anti-MPO treated cells. Further work is needed to validate these findings and determine their physiological relevance in AAV.

Funding: Commercial Support - Agilent Technologies Ireland Limited
Conclusions: Depletion of LFA-1 or Mac-1 blocks MPO-ANCA induced NCGN in mice, thus both of these β2-integrins are required for ANCA disease induction. Depletion of LFA-1 or Mac-1 does not block MPO-ANCA induced neutrophil activation. These observations indicate that blockade of either of these β2-integrins abrogates MPO-ANCA NCGN by inhibiting the recruitment of neutrophils that is required to induce inflammatory vascular injury in ANCA disease. These data suggest that pharmacologic blockade of β2-integrins may have a therapeutic role in ANCA disease.

Funding: NIDDK Support

Anti-MPO IgG-Induced Glomerular Lesions in Different Strains of Mice

POI421

Drilling into a Potential Correlation Between ANCA-Associated Vasculitis and Natural Gas Wells

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Background: ANCA-associated vasculitis (AAV), a systemic necrotizing disease affecting small and medium blood vessels, is caused by antineutrophil cytoplasmic autoantibodies which target neutrophilic proteases such as proteinase 3 (PR3) or myeloperoxidase (MPO). The incidences of PR3-AAV and MPO-AAV vary geographically with PR3-AAV most commonly reported in the United Kingdom and MPO-AAV the predominant type seen in Japan. Environmental exposure has been implicated in the pathophysiology of MPO-AAV. The aim of this study is to evaluate a potential relationship between AAV and environmental factors in north central West Virginia.

Methods: This is a retrospective cohort study of 212 patients diagnosed with AAV at West Virginia University and its affiliated hospitals from January 1, 1990 to December 31, 2019. Patients were mapped by zip code and prevalence of AAV assessed over time.

Results: The proportion of MPO-ANCA cases increased (37.5% in 2010 vs 71.7% after 2016 (p = 0.008)) with a resultant increase in the prevalence of AAV overall after 2010 (Table). During this time, the production of natural gas through fracking increased with barrel production rising more than 5-fold after 2010. Regional heat mapping reveals that the increase in cases of AAV occurred in areas of increased fracking activity (Figure)

Conclusions: The increase in prevalence of MPO-ANCA AAV correlates temporally and geographically with escalations in fracking activity. These findings suggest that exposure to toxins from fracking could be operative in the pathophysiology of AAV and the increase in case numbers seen in north central West Virginia.

Prevalence of AAV before and after 2010

Pictured on the left is a map of all the gas fracking wells (pictured in red) and gas and oil fracking wells (pictured in yellow) (BWGES Maps and GIS Data Memo [swnet.edu]). Pictured on the right is a map of the ANCA cases diagnosed after 2010.

POI422

Maintenance of ANCA Vasculitis Remission by Intermittent Rituximab Dosing Based on B Cell Reconstitution vs. a Serologic ANCA Flare (MAINTANCVAAS)

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Background: ANCA vasculitis is caused by autoantibodies to proteinase 3 (PR3) or myeloperoxidase (MPO). Rituximab (RTX), an anti-CD20 monoclonal, is effective at induction and maintenance of remission. However, RTX is associated with adverse events; hypogammaglobulinemia, infections, and late onset of neutropenia. The ideal strategy for long-term maintenance of remission remains unknown.

Methods: This is an interim analysis of an open-label, single center, randomized, two-arm controlled trial (ClinicalTrials.gov Identifier: NCT02749292) to evaluate maintenance of remission strategies that provides the best relapse-free survival in patients with ANCA vasculitis at 36 months. We enrolled subjects with ANCA vasculitis on RTX-induced continuous B cell depletion for a minimum of two years to one of two arms as follows: intermittent B cell depletion with RTX re-dosing upon (1) B cell return (a 10 B cells/mm3) or (2) upon a significant ANCA titer increase. The primary outcome was number of relapses defined by a Birmingham Vasculitis Activity Score (BVAS/WG) ≥ 2. Other outcomes, including serologic relapse and serious adverse events are not included in this analysis.

Results: From May 2016 to June 2021, 113 patients (mean age, 61 years; 48% women) were randomized, 57 to the ANCA arm and 56 to the B cell group. 52 patients were positive for anti-MPO, and 61 for anti-PR3. Relapse-free survival estimates at month 60 were 76% (95% CI, 62% to 86%) and 91% (95% CI, 74% to 97%) in the ANCA and B cell groups, respectively (hazard ratio of 3.85 (CI, 1.40 to 10.60) (P = 0.024 by logrank).

Conclusions: B cell driven RTX dosing appears to be highly efficacious at preventing relapses compared to ANCA titer driven dosing. Full trial analysis, including differences in adverse events, is needed to balance the benefit of reduced relapses against the infectious complications that may be associated with increased RTX use.

Funding: Private Foundation Support

POI423

Pulsed Steroids Impede T Memory Cell Recruitment to the Kidney in Human and Experimental Crescentic Glomerulonephritis

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Background: Despite undesirable side effects and understudied modes of action steroids still constitute a cornerstone of therapeutic regimes for autoimmune kidney diseases presenting as rapidly progressive glomerulonephritis (RPGN), e.g. anti-neutrophil cytoplasmatic antibody associated glomerulonephritis (ANCA-GN). However, if the rapid clinical effects of steroids are due to a direct impact on leukocytes, i.e. CD3+ T cells, or mediated indirectly by attenuation of an inflammatory environment is still unknown.

Methods: Kidney biopsies of patients with ANCA-GN with and without pulsed steroids before biopsy were analysed by immunohistochemistry, flow cytometry and single cell RNA sequencing. Furthermore, corresponding studies were conducted in untreated or steroid pulsed mice with crescentic glomerulonephritis (cGN), respectively. Additionally, steroid effects were studied in mice lacking the glucocorticoid receptor specifically in T cells and in CD4 T cell transfer experiments in nephritic recombination activating gene 1 (RAG1) knockout mice.

Results: Combined high-dimensional single-cell analysis and IHC showed that intravenous steroid pulses rapidly reduced renal T-cell infiltrate in human ANCA-GN patients but did not significantly regulate the immune response of a specific T-cell subset (e.g., Th1, Th2, Th17, Treg). Almost identical effects were observed in a murine cGN model (nephrotoxic nephritis), including reduced glomerular crescent formation, after steroid pulse treatment. Functional studies using CD4+ T-cell-specific glucocorticoid receptor-deficient mice showed that T-cell reduction was not caused by T-cell-intrinsic factors. Mechanistically, we demonstrated in CD4+ T-cell transfer experiments that steroid-induced attenuation of intrarenal effector T cells in cGN was a consequence of reduced expression of the T-cell-attracting chemokines CCL5, CCL20, CXCL9, and CXCL10 by resident kidney cells, which was further confirmed by in vitro and ex vivo trafficking experiments.

Conclusions: Our findings demonstrate that pulse steroid therapy rapidly reduce renal T-cell infiltrate in human and murine cGN by inhibiting the production of T-cell-attracting chemokines by resident renal cells. In summary, we have identified a previously unrecognized therapeutic mechanism of steroids in immune-mediated glomerular disease.

Funding: Government Support - Non-U.S.
**PO1424**

Immune Checkpoint Molecule BTLA Attenuates Inflammation and Glomerular Damage in Experimental Glomerulonephritis  
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**Background:** An imbalance of pro- and anti-inflammatory signals in the kidney can result in irreversible damage and destruction of glomeruli leading to end stage kidney disease. Current treatment of the glomerulonephritis (GN) consists of unspecific, highly toxic immunosuppressive therapies with detrimental adverse effects. More specific therapies are therefore warranted. T Lymphocytes are not only key players in the nephritogenic nephritis (NTN) model in rodents but also during GN in humans, representing potential targets for tailored therapies. As an immune checkpoint molecule, B and T lymphocyte attenuator (BTLA) is crucial in the regulation of T Lymphocyte activation and has been shown to mediate anti-inflammatory effects in other T cell-mediated disease models.

**Methods:** NTN was induced in BTLA knock out mice (BTLA-KO) and littermate controls. Regular urine analysis (ACR) was performed throughout the course of the study. 14 days after NTN induction, blood, kidneys and spleens were harvested for further analysis. Histological assessment of the kidneys was used to evaluate the severity of NTN. Local immune response in the kidney and systemic immunity was analyzed by flow cytometry and qPCR.

**Results:** Wild type mice (WT) showed an increased BTLA expression on renal T cells and dendritic cells throughout the course of NTN. No immune-phenotype was observed in unstimulated BTLA-KO and WT mice. However, BTLA-KO resulted in aggravation of NTN compared to WT. Quantification and characterization of renal immune cells revealed an increase in proinflammatory cells. Interestingly, especially T Lymphocytes were significantly expanded in BTLA-KO mice.

**Conclusions:** BTLA attenuates inflammation in experimental GN through suppression of proinflammatory T Lymphocytes. These results build the foundation of a checkpoint inhibitor based therapy of inflammatory glomerular disease.

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**PO1425**

Collapsing FSGS or Crescentic GN or Both: A Diagnostic Challenge  
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**Introduction:** The finding of an ANCA associated necrotizing & crescentic GN with collapsing FSGS is a rarity with only few reported cases in literature.

**Case Description:** A 53-year-old AA female was admitted to hospital with difficulty in swallowing, poor oral intake, hemoptysis & AKI superimposed on CKD-III with hx of HTN & use of NSAIDs. Urine analysis showed hematuria, proteinuria & UPC ratio of 20. Blood analysis showed S.Cr 8.7mg/dl, BUN 60mg/dl, Albumin 2.4gm/dl, positive ANA titer, positive MPO ANCA & ANA titers. By light microscopy 36 glomeruli were present, 20% showed A-Tuft collapse(arrow), podocytes hyperplasia/hypertrophy. B-Fibrinoid necrosis (arrow) & crescent formation(Trichrome stain x20)

**A-Tuft collapse(arrow), podocytes hyperplasia/hypertrophy. B-Fibrinoid necrosis (arrow) & crescent formation(Trichrome stain x20)**

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**PO1426**

CD11b Activation Suppresses Pro-Inflammatory IL-1β in Myeloid Cells and Protects Against Lupus Nephritis  
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**Background:** Lupus nephritis (LN) is a debilitating glomerular disease and a comorbidity of systemic lupus erythematosus (SLE). CD11b, the alpha-chain of integrin CD11b/CD18, plays a critical role in cell signaling. Mutations in the ITGAM gene, encoding CD11b, are associated with LN and reduce integrin function. Interleukin-1β (IL-1β) is produced by myeloid cells as a propeptide and cleaved by caspase-1 where it mediates the inflammatory response. IL-1β is downstream of toll-like receptor and IL-1β receptor signaling. We previously showed that activation of CD11b suppresses TLR-dependent pro-inflammatory signaling. Here, we investigate if this mechanism includes control of IL-1β and/or if CD11b influences IL-1β by another mechanism, which may provide novel therapeutic options for proinflammatory diseases.

**Methods:** To investigate TLR-dependent signaling affected by CD11b activation, we utilized in vitro assays using primary macrophages. Cells were treated with TLR agonists, IL-1β protein, or IL-1β antibody and changes in protein expression was assessed by western blot and proinflammatory cytokine levels were assessed by ELISA. For complementary in vivo studies, we utilized our newly generated mouse model, where we incorporated a constitutively active CD11b point mutation (I332G) globally in mice to generate a model for CD11b activation – CD11b knock-in model. C57BL-6 wild type mice, CD11b knock-out, and CD11b knock-in mice were used to determine the effect of CD11b activation on circulating IL-1β levels.

**Results:** TLR-stimulation increased IL-1β levels in vitro and in vivo. Importantly, CD11b activation resulted in significantly reduced IL-1β levels in both systems, suggesting a novel mechanism for controlling inflammation in glomerular disease. Additional mechanistic studies are on-going to define the exact molecular mechanism of action. Murine models of SLE and LN display significant decreases in IL-1β when CD11b is activated, both genetically or pharmacologically, showing potential protection against LN.

**Conclusions:** Using these models, we have identified a possible link between CD11b activation and IL-1β secretion in myeloid cells. These studies will provide understanding of the influence CD11b has on signaling pathways and inflammation associated with inflammatory diseases such as LN.

**Funding:** NIDDK Support

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**PO1427**

Deletion of Smad3 Worsens Lupus Nephritis by Promoting B Cell Activation  
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**Background:** TGF-β signaling has been shown to play a critical role in many autoimmune diseases. However, its regulatory role in lupus nephritis remains unknown, which was investigated in the present study in a mouse model of lupus nephritis (LN) in which Smad3 gene was deficient.
Intrarenal B Cells in Systemic Lupus Erythematosus Upregulate Na+/K+-ATPase to Facilitate Survival in a High-Sodium Environment

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Background: The kidney is a unique microenvironment characterized by high sodium concentrations, yet susceptible to infiltration by lymphocytes in autoimmune diseases, such as systemic lupus erythematosus. The effects of sodium-immune cell interactions on tissue injury in autoimmune disease and the mechanisms used by infiltrating lymphocytes to survive the high sodium environment of the kidney are not known.

Methods: We investigated the mechanisms utilized by B cells from lupus-prone mice and B cells in vivo and in vitro.

Results: We successfully deleted the Smad3 gene from B6. NZMSle1-3 mice with unexpected findings that Smad3KO-LN mice developed much more severe LN with higher mortality rate (50%), higher circulating autoAb, lower creatinine clearance rate (Ccr, 20%), more severe glomerular necrosis (50%), massive renal immune complex deposition and complement activation, and progressive renal inflammation and functional injury. Mechanistically, we observed that lupus mice lacking Smad3 largely promoted Th1, Th2 and Th17 populations which resulted in autoAb immune responses in the kidneys. Unexpectedly, deletion of Smad3 largely increased macrophage inducible lectin-receptor (Mincle) expression by B220⁺ B cells (80%). Further studies showed that B cells lacking Smad3 were largely promoted Cytosine-phosphorothioate-guanine oligodeoxynucleotides ( CpG ODN)-induced but failed to respond to the inhibitory effect of TGF-β on Mincle-Syk-NFκB signaling, and IgG production by splenic B cells.

Conclusions: TGF-β/Smad3 signaling plays a protective role in LN by maintaining the balance of T cell immunity and B cell function. Loss of Smad3 worsens LN by shifting Treg to Th1, Th2 and Th17 and promoting B cell activation and autoantibody production via the Mincle-Syk-NFκB-dependent mechanism. Thus, outcomes from this study will be of great significance both scientifically and clinically.

Funding: Government Support - Non-U.S.

POI1428

Anti-SOD2 Antibodies in Lupus Nephritis as Second Wave Antibodies

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Background: Superoxide dismutase-2 (SOD2) is an enzyme with antioxidant action. Anti-SOD2 antibodies (anti-SOD2 IgG2) were recently described in the serum of subjects with Membranous Nephropathy, as antigens of a possible second wave injury. The presence of anti-SOD2 IgG2 correlates with worse outcomes in terms of response to treatment [1]. The presence and role of anti-SOD2 IgG2 in Systemic Lupus Erythematosus (SLE) and Lupus Nephritis (LN), a secondary autoimmune glomerulonephritides, are to be clarified.

Methods: We measured serum levels of anti-SOD2 IgG2 (Homemade designed ELISA), every six months, in 1.052 patients (459 LN and 573 SLE) enrolled at different times from the diagnosis (i.e., 0-1 month, 2-12 m, 13-24 m, 25-48 m, 49-96 m, and >96 m). We also evaluated the main markers of the SLE activity, such as serum complement C3 and C4, ANA, ENA, anti-dsDNA and proteinuria. Of note, 91 LN and 130 SLE had a relevant follow-up of 36 months.

Results: As main characteristics, we report median age of 40 (IQR 28-54) years, the predominance of females (88%), disease activity (SLEDAI) of 4 (IQR 2-8). At the cross-sectional analysis, serum levels of anti-SOD2 IgG2 at T0 are significantly higher in LN than in SLE (Fig 1a). Considering LN, the serum levels of anti-SOD2 IgG2 at T0 were significantly higher than the other time points (Fig 1a). No correlation with the histological class of LN is reported. In LN, the reduction of anti-SOD2 IgG2 was in accordance with proteinuria. Anti-dsDNAs did not result as a valuable marker of disease activity (Fig 1b).

Conclusions: Circulating anti-SOD2 IgG2 are elevated in active LN. Serum levels of Anti-SOD2 IgG2, also considering the concomitant negative serum levels of anti-dsDNAs in all phases of LN, support the hypothesis of direct involvement of anti-SOD2 antibodies in LN as second wave antibodies that actively contribute to the manifestations of autoimmune glomerulonephritides.

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Underline represents presenting author.
Altered Propanoate Metabolism and gut Lachnospiraceae Composition in Lupus Nephritis Patients

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Background: There are growing evidence for the role of gut microbiota in the pathogenesis systemic lupus erythematosus (SLE), especially lupus nephritis (LN). Recently, high abundance of Ruminococcus gravis belonging to the family Lachnospiraceae has been noticed in featural sample of LN patients. However, the functional role of gut microbiota and its metabolic pathway which affect host metabolism in LN are less understood.

Methods: Shotgun sequencing of fecal samples from biopsy-proven LN patients and matched controls was performed. We used Kraken2 for taxonomic analysis and humann2 with customized KEGG database for gene family analysis. Comparison of taxonomic abundance and gene families were assessed by Maaslin2.

Results: Control and LN group were included 24 and 20 patients, respectively. Both groups had similar age, sex, and eGFR. In the comparison of relative abundance of major species, Roseburia intestinalis, Butyricimonas fagi, and Eubacterium elgins were significantly decreased while Ruminococcus gravis was significantly elevated in LN group, respectively. Interestingly, 3 of these 4 species were included in the same Lachnospiraceae family showing a significantly different composition between the two groups (PERMANOVA p=0.042). Furthermore, we found 161 differentially expressed gene families including 65 metabolism-associated and 29 carbohydrate metabolism-associated genes. Considering Lachnospiraceae is known to play a role in propanoate pathway, we further assessed the propanoate pathway (ko00046). As a result, LN patients revealed more prone to propanediol pathway rather than in succinate pathway in the propionate pathway. This tendency was more pronounced in the contribution to the pufd: gene by R. gravis having well-known pathogenic linkage with SLE.

Conclusions: LN patients showed altered propanoate metabolism associated with the differential species composition of Lachnospiraceae including R. gravis. Functional role of this alteration on the pathogenesis of LN should be clarified by further investigations.

Gut Microbiome Changes in NZBWF1/J Murine Lupus Nephritis

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Background: Lupus nephritis is an important cause of acute kidney injury and chronic kidney disease. There is preliminary data that gut dysbiosis may be involved in the pathogenesis of lupus nephritis. We investigated gut microbiota burden in murine lupus nephritis.

Methods: Eight-week old NZBWF1/J mice were randomized to receive drinking water alone or containing ampicillin (1.0 mg/ml) and neomycin (0.5 mg/ml) for 18 weeks. Renal and colonic histopathology was examined, and intestinal mucosal permeability investigated with LPS-FITC. Quantitative changes in gut microbiota were assessed by 16S rRNA sequencing.

Results: Serum LPS and urea levels, and proteinuria were significantly lower in antibiotic-treated mice (P<0.05, for all). Histopathologic manifestation of active nephritis and podocyte foot process effacement were associated with increased LPS-binding protein, CD14 and TLR-4 expression in proximal renal tubular epithelial cells, and increased interstitial α-smooth muscle actin, fibronectin and collagen expression. Mice with active nephritis showed increased gut permeability to LPS-FITC given orally, and decreased ZO-1 expression in the colonic epithelium. 16S rRNA sequencing data showed that active nephritis was associated with a progressive decrease in Gram-positive bacteria phyla Actinobacteria and Firmicutes and increased Gram-negative bacteria phyla Bacteroides and Proteobacteria. Antibiotic treatment significantly decreased Bacteroides, which was associated with lower levels of serum LPS and urea, proteinuria, and ameliorated histopathologic features in the colon and kidney.

Conclusions: Murine lupus nephritis is associated with gut dysbiosis, which may contribute to the pathogenesis of nephritis progression.

Funding: Government Support - Non-U.S.
Results: 43 patients (21%) exhibited TLTs in the kidneys. There were no significant differences in ISN/RPS classification between LN patients with TLTs and those without TLTs. TLT development was not associated with disease activity indicators, such as SLEDAI, dsDNA titer, proteinuria, or complement factors, but it was associated with reduced eGFR (60.2 versus 83.8 ml/min/1.73m², P = 0.001) and higher histological kidneyn scores (P = 0.0038). A higher prevalence of TLTs was observed with age over 40 years old and non-treatment history of immunosuppressive drugs. Additionally, TLT development was associated with incidence of hypertension.

Conclusions: Association between TLT development and reduced eGFR and higher histological scores suggest the potential of TLTs as an additional histological marker for evaluation of LN disease activity. Dissociation between TLT development and SLE disease activity indexes such as SLEDAI and dsDNA antibody titers also suggest that TLTs development are, at least partly, independent of the severity of glomerulonephritis.

Funding: Government Support - Non-U.S.

PO1435

New Drugs and Evolving Treatment Patterns in Lupus Nephritis: How Nephrologists and Rheumatologists Are Responding Differently to New Treatment Options


Background: Each uptake and experience with recently approved lupus nephritis (LN) drugs belimumab and voclosporin reveal different perceptions, comfort levels, and prescribing intentions between nephrologists and rheumatologists.

Methods: Data were collected over four waves of research between February and May 2021 via online surveys with 50 US nephrologists and 50 US rheumatologists who are currently treating LN. Each wave was followed-up with a subset of qualitative interviews.

Results: In a notable trend, rheumatologists deem more of their LN patients as candidates for belimumab, while nephrologists increasingly see their patients as better suited for voclosporin. Rheumatologists tend to rate belimumab higher overall than voclosporin, particularly on safety and tolerability, thanks to long term history with the product in SLE patients. Both physician types generally use belimumab as a later-line therapy in mild-to-moderate LN, often to reduce steroid burden. It is generally used with at least one other advanced agent like an immunosuppressant, steroid, or MMF. Recent initiation patients are most often in CKD Stage 3, with proteinuria and fatigue. Nephrologists favor voclosporin, likely due to their familiarity with the CNI drug class. Both physician-types are using voclosporin even later-line than belimumab for moderate-to-severe LN patients given the drug’s perceived quicker onset of action, efficacy, and steroid-sparing effect. Voclosporin is nearly always used concomitantly with advanced drugs like immunosuppressants, steroids, or MMF’s. Rheumatologists appear to be initiating voclosporin most often in CKD Stage 2, while nephrologists are initiating most often in CKD Stage 3. Rheumatologists are the leading prescribers of belimumab, and currently have a slight edge with voclosporin patient initiations as well. Nephrologists are tending to wait longer to initiate, due to cost- and risk-benefit uncertainty compared to other options like tacrolimus. Rheumatologists currently view both drugs as a greater treatment advance than nephrologists; nephrologists believe voclosporin is more of an advance in LN treatment than belimumab.

Conclusions: Physician understanding and comfort level with belimumab and voclosporin MOAs are driving early use and perceptions of the two new LN drugs.

PO1436

Treatment of Crescentic Lupus Nephritis with Voclosporin

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Introduction: Crescent glomerulonephritis (CGN) is a rare complication of Lupus nephritis (LN) and carries a worse prognosis. There is paucity of data regarding effective treatment options for CGN. We present a case of crescentic ANCA negative LN treated with voclosporin (VSN).

Case Description: 19-year-old African American female with 2-year history of Class II LN, treated with hydroxychloroquine 200 mg/day, prednisone 10 mg/day, mycophenolate mofetil 1 gm twice daily and Belimumab, presented with a 2-week history of anaemia and generalized bullous skin rash. On exam BP 126/78 mm Hg, HR 96/min, afebrile, RR 18/min, O2 saturation 97% on room air. Investigations revealed hemoglobin 9.2 g/dL, serum creatinine (SCr) 1.2 mg/dl (baseline 0.6), albumin 1.9 g/dL, platelet 310,000, WBC 10.0, neutrophils 71%, lymphocytes 13%, eosinophils 3%, mononuclear cells 4%. CT and MRI of chest, abdomen and pelvis was normal. Urinalysis revealed microscopic hematuria (3+), proteinuria 3+, protein casts, RBC casts 1+, WBC casts 1+. Nephrology consultation was obtained and she was started on high dose IV methylprednisolone 1 gm over 3 days, however she became anuric, CRF peaked at 5.0 mg/dl, and was commenced on hemodialysis and 7 sessions of plasma exchange. She was started on VSN 15.8 mg BID and after 10 days of therapy, CRF improved and dialysis was discontinued. On discharge, SCR was 2.0 mg/dl and plasma exchange was discontinued. She was started on VSN.

Discussion: There has not been any published case report of Crescentic LN being treated successfully with VSN. Given poor prognosis of CGN, early diagnosis and treatment is imperative. Our patient had rapid recovery of renal function and resolution of proteinuria following treatment with VSN. VSN may be effective in combination with plasma exchange in ANCA negative Crescentic LN. Larger studies with longer follow-up are needed to assess the efficacy of VSN in CGN.

PO1437


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Background: Lupus nephritis (LN) occurs in ~40% of adults with SLE. Despite the high burden of LN, current care management and utilization data are limited. This longitudinal study evaluated US healthcare resource utilization (HRU) and costs over 5 years in patients (pts) with SLE newly diagnosed with LN.

Methods: This retrospective cohort study (GSK Study 214102) used data from the Optum Research Database. Index date was the first claim with a renal diagnosis code indicating LN during the identification period (Aug 1, 2011–Jul 31, 2018). Inclusion criteria: age ≥18 years; ≥2 renal diagnosis codes during the identification period; ≥1 inpatient or ≥2 outpatient SLE diagnosis codes in the 12 months pre index; and continuous enrollment of ≥12 months pre and post index. HRU and costs for the cohort with 5 years of continuous enrollment post index are reported.

Results: Overall, 2159 pts met the study criteria (mean [standard deviation, SD] age, 45.0 [14.9] years; 86.7% female) and 335 had ≥5 years of continuous enrollment post index. HRU and costs were highest in the first year post LN diagnosis (Figure). Mean healthcare costs were $44,205 in Year 1 and ~$30,000/year in Years 2 through 5. Approximately 50% of patients incurred an inpatient stay in Year 1, with ~25% of patients hospitalized in each subsequent year.

Conclusions: Patients with newly diagnosed LN incur substantial HRU and costs, which were highest in the year of diagnosis. These data highlight the need for interventions to prevent renal worsening in SLE.

Funding: Commercial Support - GSK

Figure. Longitudinal HRU and costs among patients with ≥5 years of follow-up (N=335)

PO1438

Association of TNIP1 Variants with Disease Severity and Progression and IP-10 Chemokine Levels in Lupus Nephritis Patients

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Background: African American SLE patients experience higher rates of LN, increased progression to ESKD, and higher mortality when compared with white patients, but etiology for this disparity is unclear. We reported that a TNIP1 polymorphism, rs4958881, is a risk variant for lupus nephritis (LN) in African American patients. TNIP1 encodes the protein ABIN1, which negatively regulates the transcription factor NF-kappaB. We generated mice with inactivation of ABIN1 (AbBin1−/−) and C. P:AS and Silver strains show no glomerular basement membrane remodeling. D. Trichrome stain with moderate interstitial fibrosis and tubular atrophy (35%).

Conclusions: Association between TLT development and reduced eGFR and higher histological scores suggest the potential of TLTs as an additional histological marker for evaluation of LN disease activity. Dissociation between TLT development and SLE disease activity indexes such as SLEDAI and dsDNA antibody titers also suggest that TLTs development are, at least partly, independent of the severity of glomerulonephritis.

Funding: Government Support - Non-U.S.
Increased tissue levels of IP-10 have been implicated in pathogenesis and as a diagnostic marker. LN, but the mechanism is unknown. The current project tested a hypothesis that LN severity and enhanced IP-10 levels are associated with the TNPI1 rs4958881 risk allele.

Methods: All endpoints were compared for LN patients w/o TNPI1 variant rs4958881 genotyping. Classifications were compared for 125 African American and 133 White American LN patients. Urine and serum IP-10 levels were measured in 33 LN patients using ELISA. Progression of disease was assessed and compared from follow up (mean = 3 yrs) for 33 LN patients. Urine, plasma, and kidney levels of IP-10 were compared for LN controls. Flow cytometry analysis of T helper cell phenotypes was assessed for LN patients. Conclusions: The current work compared the tissue distribution of IP-10 in LN and that of NF-E2 or neutralization of IP-10 is a promising personalized therapeutic direction for these patients.

Funding: NIDDK Support, Other U.S. Government Support, Clinical Revenue Support

PO1419

Inflammatory Dendritic Cell and Th17 Polarization in Mouse Model of Lupus Nephritis

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Background: To examine if these infDC are necessary or sufficient to cause LN. The current project tested a hypothesis that LN severity and enhanced IP-10 levels are associated with the TNPI1 rs4958881 risk allele.

Methods: All endpoints were compared for LN patients w/o TNPI1 variant rs4958881 genotyping. Classifications were compared for 125 African American and 133 White American LN patients. Urine and serum IP-10 levels were measured in 33 LN patients using ELISA. Progression of disease was assessed and compared from follow up (mean = 3 yrs) for 33 LN patients. Urine, plasma, and kidney levels of IP-10 were compared for LN controls. Flow cytometry analysis of T helper cell phenotypes was assessed for LN patients. Conclusions: The current work compared the tissue distribution of IP-10 in LN and that of NF-E2 or neutralization of IP-10 is a promising personalized therapeutic direction for these patients.

Funding: NIDDK Support, Other U.S. Government Support, Clinical Revenue Support

PO1440

SeqStain Is a Novel, Multiplex Imaging Method for Spatially Profiling of Human Kidney Tissues

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Background: Chronic Kidney Disease (CKD) is the ninth leading cause of death in the United States, an emerging global health challenge affecting 10-15% of the population. Lack of reliable biomarkers precludes early diagnosis of CKD. The progression of CKD is known to be dictated by renal tissue changes. For instance in Diabetic Nephropathy, disease progression is accompanied by considerable changes to the glomeruli, reduced podocyte number, inflammation in the renal tissue, influx of immune cells that ultimately lead to tissue damage. Understanding these tissue-centered events on a deeper level is important for future therapies.

Methods: To understand molecular and cellular composition of tissues and their relative organization in three-dimensional space, we developed a novel multiplex staining method called SeqStain. The SeqStain multiplex platform uses fluorescently labeled DNA oligonucleotides (termed “SeqStain antibodies”) to stain white while endocytosis are used to achieve gentle de-staining after each round. This methodology can fluorescently label primary antibodies, secondary antibodies and Fabs of secondary antibodies to efficiently analyze multiple tissue sections. With SeqStain, mouse kidney was stained with antibodies that would probe different histological regions relevant to the kidney

Results: Normal kidney was stained with SeqStain antibodies and de-stained using endocytosis. Using SeqStain methodology, we built ~20-plex panel on kidney tissue and provided a gentle and rapid technique for multiplex imaging. Stripping de-staining using the SeqStain method was rapid and removed ~99% of the signal in <1min without affecting tissue integrity. The method was implemented using a simple perfusion setup with readily available components, allowing staining of tens of antigens on a single tissue section. Alignment of images and their analyses provided spatiotemporal data on multiple cell types in tissue

Conclusions: The SeqStain method offers a gentle, easy-to-use, and effective multiplex imaging technique that provides a unique platform for obtaining spatiotemporal insights. SeqStain method can profile the CKD kidney tissues and comprehend the tissue-centered events that could play a role in disease progression. Currently, we are profiling the CKD tissues in multiplex staining experiments in comparison to healthy human kidney to generate spatial maps

Funding: Commercial Support - Eledon Pharmaceuticals

PO1442

High Expression of Mince in Intermediate Monocytes of Patients with Autoimmune Diseases

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Background: Macrophage- inducible C-type lectin (Mince) is a transmembrane C-type lectin receptor that is predominantly expressed on macrophages’ surface and results in broad range of self and foreign antigens as part of innate immune sensing, thus playing a pivotal role in tailoring immune response. Mince’s function associates with its expression levels on immune cells’ surfaces. However, the differential expression of Mince in various types of immune cells between patients with autoimmune disease (AD) and healthy controls (NCs) is yet to be examined, and its clinical relevance remains unclear. Therefore, this study aimed to investigate Mince expression and distribution in different types of immune cells in patients with AD and NCs, and to explore the clinical relevance and potential mechanisms of Mince expression levels in immune cells of peripheral blood in patients with systemic lupus erythematosus (SLE).

Methods: Mince expression levels in leukocyte subgroups and monocyte subsets of peripheral blood from all participants were analyzed using flow cytometry and real time PCR, and the clinical characteristics of patients with SLE were collected for correlation analysis. Hematological parameters were also used to distinguish intermediate monocytes from naïve T cells, and the differentiations of naïve T cells were detected by flow cytometry.

Results: Mince was expressed predominantly in myeloid cells, both in peripheral blood and cell lines. Moreover, monocytes expressed higher levels of Mincle than macrophages. Mincle expression levels in peripheral blood in patients with systemic lupus erythematosus (SLE)
Cathy how "poised Trm17 cells" use the integrated stress response - stress granules pathway to rapidly produce IL-17A upon re-stimulation. Our study identifies a novel mechanism of is stored in stress granules and not translated into protein. In contrast, these Trm cells willi

Nariaki

Activation of the Integrated Stress Response Regulates the Production of PO1444

Jonathan


Background: Macrophages are part of the phagocyte mononuclear system constantly replaced by the circulating blood monocytes. In the steady state, the myeloid cell compartment is highly heterogeneous, containing various subtypes. These cells include macrophages and dendritic cells, and each play important roles in tissue maintenance, including development, homeostasis, immunity and repair following tissue injury. The composition of kidney macrophages is not well known.

Methods: A multi-parameter flow cytometry approach was used to identify the resident and recruited macrophage population in the kidneys of male and female C57BL/6J mice aged -7, -21 and -84 days in the steady state. Resident and recruited macrophage populations were characterized based on 33 cell surface and intracellular markers.

Results: Both resident and recruited macrophages were identified in the kidneys of male and female mice aged -7, -21 and -84 days in the steady state. We observed two distinct resident macrophage populations in young mice (7 and 21 days old) by 84-days, male and female mice displayed 4 and 5 resident populations, respectively. The resident macrophage population in 7-day old mice displayed low surface expression of MHC II and began to shift to an increased expression of MHC class II at 21 days, and high MHC class II expression at 84 days. We detected three recruited macrophage populations in 7- and 21-day-old mice, and two populations by 84-days of age. The recruited macrophage population displayed low MHC class II at all ages in both sexes. Analysis of the global macrophage populations at 84-days of age revealed female mice had twice as many recruited compared to resident macrophages, whereas male mice had an equal distribution.

Conclusions: The data indicate a dynamic change in the kidney macrophage population with age and resident macrophage phenotype. The composition of macrophage populations also differs by sex and age. These data suggest each population plays a role in kidney homeostasis. Future studies will be directed towards elucidating the functions of each of the identified macrophage populations.

Funding: NIDDK Support

PO1444

Activation of the Integrated Stress Response Regulates the Production of IL-17 in Tissue Resident Memory T Cells


Background: CD4-positive T cells produce cytokines and play a central role in immunity. Tissue-resident memory T (Trm) cells remain in organs after infection and contribute to efficient host defense by immediate production of cytokines, such as IL-17A. More recently, it was demonstrated that Trm cells also promote autimmunity. Therefore, the regulation of cytokine production by Trm cells is of great importance to achieve efficient host defense without excessive inflammation. However, the control mechanisms of cytokine production by Trm cells are not well understood.

Methods: Human and mouse T cells including renal Trm cells were analyzed by single cell RNA sequencing (scRNAseq), polysome profiling combined with bulk RNA sequencing, RT-PCR, flow-cytometry, immunocytochemistry, and mRNA FISH. Mouse models for Staphylococcus aureus infection and crescentic glomerulonephritis were used to induce and study Trm cells in vivo.

Results: Combined scRNAseq, polysome profiling and tissue signature analysis of human and mouse tissue samples revealed that resting CD4+ Trm cells in the kidney express IL17A mRNA but do not produce or secrete the cytokine protein without re-stimulation. Mechanistically, we demonstrate that the phosphorylation of eIF2α, a key feature of the integrated stress response (ISR) activation, resulted in recruitment of IFN17A mRNA into stress granules, which are organelles crucial for regulating mRNA translation during ISR, thereby inhibiting mRNA translation in resting Trm cells. Finally, we show that re-stimulation of human renal Trm cells through T cell receptor resulted in eIF2α dephosphorylation, leading to efficient translation of IFN17A mRNA and subsequent IL-17A secretion.

Conclusions: Tissue-resident memory CD4+ T cells in the kidney express high levels of IL-17A cytokine mRNA. Under homeostatic conditions the cytokine mRNA is stored in stress granules. In contrast, these Trm cells rapidly produce IL-17A upon re-stimulation. Our study identifies a novel mechanism of how “poised Trm17 cells” use the integrated stress response - stress granules pathway to regulate IL-17A cytokine mRNA translation. Disregulation of this pathway might have a pathogenic role in infection-related and renal inflammatory diseases.

Funding: Government Support - Non-U.S.

PO1445

Differential Cell Cycle and Kinase Activation in IgA1-Producing Cells from IgAN Patients and Healthy Controls Mediated by Cytokine Stimulation Colin Reilly, Dana Rizk, Jan Novak. The University of Alabama at Birmingham, Birmingham, AL.

Background: Some cytokines increase production of galactose-deficient IgA1 (Gd-IgA1) in immortalized IgA1-producing cells derived from peripheral blood of patients with IgAN. Previous work has indicated dysregulated cytokine induced signaling may be responsible, but minimal work investigating the overlapping pathways has been performed. Using single-cell transcriptomics, we analyzed pathway responses in immortalized IgA1-secreting cells derived from IgAN patients and healthy controls (HC) before and after response to a mixture of cytokines.

Methods: A mixture of cytokines mimicking those produced by T-follicular helper (Th) cells (IL-4, IL-6, IL-21, CD40L; 50 ng/mL) was used to stimulate immortalized IgA1-producing cells for 30 min before single-cell transcriptomic analysis. Gd-IgA1 level was determined by lectin ELISA. Standard data processing using Seurat was performed along with Alteryx for IgA1 separation. Differential markers for genes in unstimulated and stimulated conditions were analyzed for pathway differences using the GSEA MSig database, and kinase-transcription factors were imputed using X2K analysis.

Results: Th cytokines mediated overproduction of Gd-IgA1 in IgAN cells but not HC. IgA1-secreting subpopulations were separated, and UMAP was used for unsupervised dimension reduction analysis. Within these UMAP groups, pathway analysis found multiple significant associations, including down-regulation of cell cycle processes (FDR<0.05) in IgAN cells compared to an increase in HC (FDR<0.01) after cytokine stimulation. Analysis of imputed kinases changes in IgAN stimulated IgA1 cells compared to HC identified MAPK14 (p<1X10^-20 and AKT1 (p<1X10^-10), which have been associated with controlling O-glycosylation expression.

Conclusions: Significant changes in imputed kinases previously associated with O-glycosylation were found in IgA1-secreting cells in IgAN compared to HC in response to Th cytokine stimulation. When stimulated with cytokines, there were significant decreases in cell cycle and proliferation pathway responses in the IgA1-secreting cells from IgAN vs. HC samples. Further investigation is needed to determine the role of cell cycle and MAPK14 pathways in driving Gd-IgA1 overproduction mediated by cytokine stimulation.

Funding: NIDDK Support

PO1446

Serum and Glomerular Complement Component as Biomarkers in the First South Asian Prospective Longitudinal Observational IgA Nephropathy Cohort (GRACE-IgAN)

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Background: The Glomerular Research And Clinical Experiments- IgA Nephropathy in Indians is a prospective longitudinal cohort. The study protocol has been published and is registered with WHO trial id: ISRCTN36834159. The role of serum and glomerular complement components in South Asian IgAN is unknown.

Methods: 201 consenting adult IgAN patients were consecutively recruited post kidney biopsy. 192 (97%) patients completed 3 years. Serum complement C3 and C4 levels and glomerular C3d and C5b-9 by IHC were quantified at baseline in IgAN patients. Composite outcome (CO) was defined as a 50% fall in eGFR from baseline and/or eGFR <15ml/min/1.73m² or RRT/death.

Results: 195 patients (97%) completed 3 year longitudinal follow-up. Lower serum C3 was significantly associated with S1, T1/T2 according to the Oxford MEST grading and with global glomerulosclerosis (GS>33%) whereas higher C4 levels were associated with S1 scores. Increased mesangial C3d deposition correlated with increased mean arterial pressure, proteinuria, decreased serum albumin, decreased eGFR and with GS>33%. Inversely, increased mesangial C4d correlated with increased systemic blood pressure, decreased serum protein and decreased eGFR and with GS>33%. Mesangial deposition of C5b-9 did not have any clinical associations. Lower serum C3, higher serum C4 and increased mesangial C3d was significantly associated with CO over three years.

Conclusions: Serum and tissue complements could be potential biomarkers for severity and progression in the GRACE-IgAN cohort. This requires further validation.

Funding: Government Support - Non-U.S.
Immune Complexes Containing Galactose-Deficient IgA1 Deposit on Mesangium Through Damage to Endothelial Cells

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Background: Galactose-deficient IgA1 (Gd-IgA1) plays a crucial role in the pathogenesis of IgA nephropathy (IgAN). However, the pathogenic role of mesangial Gl-IgA1-containing immune complexes (ICs) remains unclear. The endothelial surface glycocalyx modulates microvascular function. Loss of the glomerular endothelial glycocalyx is known to be involved in albuminuria. Here, we examined whether the deposition of Gl-IgA1-containing ICs in the mesangium may lead glomerular endothelial cell dysfunction in this disease.

Methods: Gl-IgA1 and recombinant anti-glycan IgG were used to form ICs to inject into nude mice. The renal microvascular endothelial glycocalyx removal of the injected nude mice was evaluated by real-time glycocalyx imaging. Human renal glomerular endothelial cells (HRGECs) were used to assess the potential capacity of Gl-IgA1-containing ICs to activate endothelial cells.

Results: After co-culture of Gl-IgA1-containing ICs with HRGECs, mRNA expression levels of endothelial adhesion molecules (ICAM-1, VCAM-1, and E-selectin) were significantly upregulated (P<0.01). Expression levels of proinflammatory mediators (TNFα and IL-6) that are able to induce the expression of the adhesion molecules on endothelial cells were also increased (P<0.01). Nude mice injected with Gl-IgA1-containing ICs showed podocyte and endothelial injuries with IgA, IgG, and C3 co-deposition along the glomerular capillaries and in the mesangium. Moreover, albuminuria and hematuria were also induced. Real-time glycocalyx imaging showed that renal microvascular glycocalyx was decreased immediately after the injection of Gl-IgA1-containing ICs and then mesangial IgA deposition was increased.

Conclusions: Present data suggest that Gl-IgA1-containing ICs may induce glomerular endothelial injuries resulting in mesangial deposits.

Immune Complexes in the Peripheral Blood of Patients with IgA Nephropathy Contain Polymeric Galactose-Deficient IgA1 Associated with IgG and Complement C3

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Background: IgA nephropathy (IgAN) is an autoimmune disease wherein immune complexes (IC) consisting of IgA1 with some hinge-region O-glycans deficient in galactose (Gd-IgA1) and IgG autoantibodies deposit in the kidneys and induce injury. Although the glomerular immunodeposits are enriched for Gd-IgA1, not much is known about the association of different molecular forms of Gd-IgA1 in circulation.

Methods: Total serum IgA1 was isolated from 7 Caucasian and 10 African American patients with IgAN by jacalin-affinity chromatography. Different molecular forms of IgA1 were then separated by size-exclusion chromatography (SEC). Gd-IgA1 was detected by lectin ELISA. IgA1-IC were isolated by SEC from sera of 4 IgAN patients. Biological activity of the isolated IC was assessed measuring the proliferation of cultured primary human mesangial cells (MC). IgA1, IgG, and complement C3 were analyzed by SDS-PAGE/immunoblotting.

Results: Total serum IgA1 included monomeric and polymeric forms and IgA1 bound in IC. Monomeric IgA1 presented ~88-92% of total IgA1, whereas polymeric IgA1 represented ~8-12%. IgA1 in IC was the least abundant form, representing ~0.4% of total IgA1. Relative representation of Gl-IgA1 was highest in IC, followed by polymeric forms, and lowest in monomeric forms. Gl-IgA1 in IC had minimally sialylated O-glycans, whereas polymeric and monomeric forms were substantially sialylated. Caucasian patients had higher content of Gd-IgA1 in polymeric and monomeric forms of IgA1 compared to those of African American patients (P<0.03 and P<0.05, respectively). Gl-IgA1 in sera of IgAN patients had molecular mass >700 kDa and stimulated proliferation of MC. These ICs consisted of polymeric IgA1, IgG, and complement C3.

Conclusions: Biologically active IC in the circulation of IgAN patients contain polymeric, minimally sialylated Gl-IgA1 associated with IgG and C3. These findings support the pathogenic role of Gd-IgA1-IgG IC in IgAN.

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PO1451

Histopathological Association of Lambda Light Chain Predominance in IgA Nephropathy
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Background: A relative predominance of lambda (λ) over kappa (κ) light chain deposition has long been recognized in IgA Nephropathy (IgAN), which is unique among other glomerular disease. The reason for this predominance is unknown but may be related to a purported predominance of λ, chain expression by gut associated lymphoid tissue B cells. There is limited information regarding the histopathological findings, if any, associated with predominant λ, light chain deposition. Utilizing the CureGN IgAN cohort, we evaluated if predominant λ chain deposition was associated with histologic markers of disease activity by examining MEST characteristics and other variables.

Methods: We divided the CureGN IgAN cohort into two groups based on the intensity of light chain deposition by immunofluorescence. The λ, dominant group (LD) was defined by a difference in intensity score of staining of λ, minus κ ≥ 1, while the κ codominant group (KL) by a difference of λ, minus κ < 1. Fisher’s exact test was used to compare the histopathological changes between the groups with respect to M, E, S, T, scores, total crescents, percent (%) of globally sclerotic glomeruli, % of glomeruli with fibroin necrosis, degree of interstitial inflammation, and the intensity of IgG, C1q, and C3 staining.

Results: Among 695 IgAN patients, the kidney biopsy digital images of 269 patients were reviewed by CureGN pathologists and 234 patients had reported λ and κ staining intensity. Of these, 96 (41%) patients were classified as LD (including 7 patients (3%) with λ, monotypic staining) and 138 (59%) classified as KL. The two groups did not differ significantly in age, sex, or race. Compared to the KL group, the LD group had a greater frequency of endocapillary hypercellularity (E1, 51.1% vs 36.3%, p=0.04) and IgG staining intensity ≥ 1.5 (37.3% vs 21.9%, p<0.01). There were no significant differences between groups with respect to any other histologic finding.

Conclusions: In IgAN, patients with predominantly λ, mesangial deposition are more likely to have increased endocapillary hypercellularity and IgG deposition, two findings previously linked with greater histologic disease activity and possibly worse prognosis. Further studies are needed to elucidate if the predominance of λ, chains represents a unique pathogenesis in a subset of patients, or if it imparts a more severe disease course.

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PO1452

Plasmacytoid Dendritic Cells from Murine IgA Nephropathy Have a Capacity to Enhance IgA Production ThroughTLR9/APRIL Signaling
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Background: Our recent study revealed that chronic Toll-like receptor 9 (TLR9) stimulation induce a proliferation-inducing ligand (APRIL) expression on naïve B cells and such APRIL-B cell may contribute to nephritogenic IgA production in IgA nephropathy (IgAN). On the other hand, APRIL from TLR9 activated dendritic cell (DC) is generally known to be involved in B cell maturation and IgA class switching. In this study, we evaluated IgA production through TLR9/APRIL signaling by DCs from murine IgAN.

Methods: Splenic B cells and DCs from group dLyg (gdy) mice, which are known as the spontaneous IgAN model, and Balb/c mice were isolated using magnetic cell sorting system. In addition, DCs were further divided into three DC subsets; i.e., plasmacytoid DCs (pDCs), CD8+ conventional DCs (cDCs), and CD11b+ cDCs by cell sorter. We co-cultured these isolated DCs and B cells with or without Cpg-ODN, a synthetic oligonucleotide TLR9 ligand, and IgA in the culture supernatants was measured by ELISA. We also measured the expressions of TLR9 and APRIL in each DC.

Results: The gdy-derived, but not Balb/c-derived, DCs could dramatically enhance IgA production by co-culture with B cells derived from both gdyL and Balb/c mice, and further enhance under Cpg-ODN stimulation. Moreover, pDCs from gdyL mice strongly induced the IgA production in B cells, compared with cDCs. The expressions of APRIL and TLR9 in the pDCs were higher than those in cDCs.

Conclusions: Present findings suggest that the gdyL DCs, especially pDCs, strongly enhance IgA synthesis from B cells through TLR9 and APRIL signaling.

PO1453

Targeted Release Formulation Budesonide (Nefecon) Selectively Reduces Circulating Levels of Chemokines Critical to Immune Cell Trafficking to Peyer Patches in IgA Nephropathy
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Background: Evidence supports a pivotal role of gut-derived chemokines in the direction of immune cell trafficking to the intestine in homeostatic and inflammatory conditions. It is well established that chemokines and their receptors control the influx
of T cells and B cells into Peyser’s patches (PP). T-cell homing to the PP depends on CCR7 and its ligands, CCL19 and CCL21, whereas B-cell homing to PP depends on the coordinately signaling of CCR7, CXCR4, CXCR5 and CCR6. The PP are believed to be a major source of the poorly O-galactosylated IgA1 in IgA nephropathy (IgAN). The therapeutic potential of targeting PP was demonstrated in the Phase 2 NEFIGNAN trial (NCT01738035), which assessed the safety and efficacy of a novel targeted-release investigational formulation of budesonide (TRF-budesonide [Nefecon]), designed to deliver budesonide to the PP-rich distal ileum in patients with IgAN. The trial comprised a 6-month run-in, 9-month treatment, and 3-month follow-up phase: 49 patients received Nefecon 8 mg/day, 51 patients received Nefecon 8 mg/day and 50 patients received placebo. Nefecon 16 mg/day, added to optimized renin-angiotensin system blockade, reduced proteinuria and stabilized eGFR in patients with IgAN. This study investigated whether Nefecon treatment altered serum levels of chemokines.

Methods: Serum levels of a panel of 20 chemokines were measured by Luminex. Changes in log-transformed levels of each biomarker with treatment were compared by one-way ANCOVA. Significance was p<0.05.

Results: A significant, dose-dependent modulation in serum levels of key chemokines directing T and B cell trafficking to the intestine (CXCL5), and more specifically to the PP (CCL11, CCL19, CCL20) was seen with Nefecon, which reversed on cessation of treatment. These observations paralleled significant reductions in the levels of soluble CD23, CD27 and CD30, and are consistent with our previous reports describing a dose-dependent increase in BAFF, soluble BCMA, TACI, IgA-IgG immune complexes, secretory IgA and galactose-deficient IgA levels with Nefecon.

Conclusions: Nefecon, which targets the PP-rich distal ileum, modulates key chemokine signals which direct immune cell trafficking to the intestine in IgAN.

Funding: Commercial Support - Caliditas Therapeutics

PO1454 The Dual Endothelin Angiotensin Receptor Antagonist (DEARA) Sparansen Protects from Glomerular Hypercellularity and Associated Immune/Inflammatory Gene Network Activity in a Model of IgA Nephropathy Colin Reily,1 Zina Moldoveanu,1 Tiziano Pramparo,2 Stacy D. Hall,1 Lea Novak,1 Radko Komers,2 Celia P. Jenkinson,1 Jan Novak,1 1University of Alabama at Birmingham, Birmingham, AL; 2Traverese Therapeutics Inc, San Diego, CA

Background: IgA Nephropathy (IgAN) is an autoimmune glomerulonephritis wherein immune complexes (IC) composed of galactose-deficient IgA1 (Gd-IgA1; autoantigen) and Gd-IgA1-specific IgG autoantibodies (AuAb) deposit in the glomeruli (glomerular hypercellularity) and activate the alternative complement pathway (Amp) and C1q pathways, and result in Nephrotic Syndrome. In the current study we aimed to investigate the potential anti-inflammatory role for Sp in IgAN.

Methods: In a mouse model of IgAN induced by IC formation by human Gd-IgA1 and a recombinant AuAb, we used whole-kidney RNAseq profiling to assess how Sparsentan (Sp) affects the gene expression of pathways dysregulated by IC.

Results: IC were injected into ~7-week-old nude mice every other day for a total of 6 doses (n=5/group). Sp (8 mg/kg or 16 mg/kg) or vehicle (Veh) were given by gavage once daily, starting from the first day of IC injections. Negative-control mice received only V. Kidney histopathology and RNAseq was harvested on day 12. RNAseq raw data processed using DESeq2 identified differentially expressed genes. WGCNA was used for network-level profiling and to identify co-expressed genes associated with hypercellularity and Ki-67 positivity of gl. GSEA and X2 assessed changes at the pathway level and imputed correlated upstream cell-signaling networks. Pathway enrichment p-values were adjusted with FDR.

Results: Sp ameliorated IC-induced hypercellularity (P<0.01) and Ki-67-positive gl (P<0.05). WGCNA clustered genes into co-expressed modules associated with hypercellularity and Ki-67 positivity. GSEA-identified top 5 pathways were enriched for immune processes (FDR <1x10^-10). The top pathway, signaling pathways. The expression of the top module gene dysregulated by IC, was corrected by Sp administration. GSEA analysis revealed correlated expression of top hub genes, kinases MAPK14, GSK3B, CSN2K2A1 (z-score <1x10^-12) and transcription factors SPI1 and RUNX1 (z-score <0.05), highlighting the role of the ERK1/2-SP1 axis known to regulate cell proliferation.

Conclusions: In a mouse model of IgAN, kidney transcriptomics revealed gene networks, enriched in inflammatory/inflammatory functions, correlating with IC-induced hypercellularity. The top dysregulated genes were normalized by Sp and were linked to kinases and transcription factors with correlated functional activity. These data suggest a potential anti-inflammatory role for Sp in IgAN.

Funding: Commercial Support - Traverese Therapeutics, Inc, San Diego, CA

PO1455 Treatment with Targeted Release Formulation Budesonide (Nefecon) Modulates the Complement System in Patients with IgA Nephropathy Laura Pérez Alanís,1 Karen Molyneux,2 Bengt C. Feltstrom,3 Jonathan Barratt,2 Peter Garred,1 1Københavns Universitet Sundhedsvidenskabelige Fakultet, København, Denmark; 2University of Leicester, Leicester, United Kingdom; 3Akademiska sjukhuset, Uppsala, Sweden.

Background: The NEFIGNAN trial (NCT01738035) evaluated the effect of a novel targeted-release investigational formulation of budesonide (TRF-budesonide [Nefecon]) in the treatment of IgA nephropathy (IgAN). Participants in this Phase 2b trial were randomized to receive either placebo, Nefecon 8 mg or 16 mg/day, and samples were collected at baseline (0 months), at the end of the treatment (9 months) and at the end of the study (12 months). In this exploratory study we evaluated the effect of Nefecon treatment on the circulating levels and urinary excretion of a panel of complement components.

Methods: Plasma and urine levels of complement proteins (C4c, C3b and soluble C5b-9) and MASP-3 and PTX-3 were measured using in-house sandwich-ELISAs. Treatment differences between baseline, end of treatment and end of study were assessed by mixed-effects model analysis. The effect of the treatment correcting for the baseline was assessed by multiple linear regression. Significance: p<0.05. Urinary proteins were adjusted for creatinine excretion.

Results: Circulating levels of MASP-3 were decreased in a dose-dependent manner after treatment (p=0.0313 Nefecon 8 mg/day, p=0.0080 Nefecon 16 mg/day). MBL-creatinine was significantly reduced in the urine by both doses of Nefecon compared with placebo (p=0.0001 Nefecon 8 mg and 16 mg/day). CL-11/creatinine levels were also significantly reduced in a dose-dependent manner after Nefecon administration (p=0.0411 Nefecon 8 mg/day, p=0.0095 Nefecon 16 mg/day). Complement activation markers and ficolin-3 levels were detectable in urine but levels remained unaltered.

Conclusions: Treatment with Nefecon modulates components of both the alternative (MASP-3) and lectin (MBL- and CL-11) pathways of complement, two pathways known to be important in mediating kidney damage in IgAN. These initial observations warrant further investigation.

Funding: Commercial Support - Caliditas Therapeutics

PO1456 Defining Cell Type Specificity of TNF Targets in Nephrotic Syndrome Phillip J. McConn,1 Scan Eddy,1 Fadhil Alakawa, Jennifer L. Harder, Jannal El Saghir,1 Wenyun Ju, Matthias Kretzler, Laura H. Mariani. Nephrotic Syndrome Study Network (NEPTUNE) University of Michigan Medicine, Ann Arbor, MI.

Background: Mechanistic, targeted therapies are needed for patients with FSGS and MCD, as diverse biological processes produce similar histologic injury patterns. Bulk transcriptionic data from kidney biopsy tissue can be used to find subgroups with shared molecular features, but cellular signaling networks need to be defined.

Methods: Consensus clustering was applied to bulk RNA sequencing data from the tubulointerstitial (TI) compartment of 220 participants from the NEPTUNE cohort, a study of children and adults with nephrotic syndrome enrolled at the time of kidney biopsy. Clusters were assessed for association with clinical outcome. Differential gene expression analysis was analyzed for enrichment of canonical pathways and functional grouping between patient clusters. Nuclei were extracted from renal biopsies, processed, and quality control analyzed to remove low quality nuclei. Nuclei identity were assigned by comparisons of enriched genes in a cluster to previously identified cell-type specific genes.

Results: One cluster of 59 patients was associated with a higher risk of loss of kidney function over time and observed TNF activation. To test the cellular source of the TNF pathway biomarker candidate, we performed mRNA-seq on 10 NEPTUNE biopsies, 5 with high TF activity scores and 5 with moderate to low TF activity scores in TI gene expression profiles. We pooled 45,175 nuclei into 15 clusters, which included all major kidney cell types. TNF expression was found in nuclei from immune clusters and in a proximal tubule and loop of Henle cluster. TNFRSF1A was universally expressed across cell clusters, while TNFRSF1B showed more restrictive expression. TNF targets CCL2 and TAZ were higher in all patients with activated TNF scores with maximal increase in epithelial cells (proximal and podocytes). Kidney organoids confirmed MCP1 (encoded by CCL2) and TIMP1 upregulation by TNF treatment.

Conclusions: TNF, TNF receptors, and TNF-responsive biomarkers reflect alterations in inflammatory and intrinsic kidney cell populations in patients with a TNF-associated signaling profile and are currently assessed as TNF target engagement biomarkers in a clinical trial of FSGS patients (NCT04096683).

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PO1457

Dysregulated T Cell Metabolomic Profile in Patients with Steroid-Resistant Nephrotic Syndrome

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Background: We have recently reported early relapse following rituximab in patients with minimal change disease was associated with baseline reduction in regulatory T-cells and T-cell hyporesponsiveness to activation, suggesting chronic T-cell activation. This study aimed to compare T-cell activation and characterise the metabolic alterations associated with T-cell hyporesponsiveness in patients with steroid-dependent (SDNS) and steroid-resistant nephrotic syndrome (SRNS) in relapse.

Methods: A total of 48 patients with childhood-onset SDNS (n=31) and SRNS (n=17) were recruited during relapse. T-cell activation assay was performed on whole blood while metabolomic profiling was performed on purified stimulated CD4 T-cell culture supernatants (n=23) using GC-MS/MS and analysed using Shimadzu Smart Metabolites Database. Differences in the metabolomic profile between SDNS and SRNS were identified using PLS-DA (SIMCA), and pathway analysis was performed using MetaboAnalyst 4.0. Metabolomic validation assay was performed using Glucose 6 Phosphate Dehydrogenase (G6PD) assay kit.

Results: SRNS patients had significant lower T-cell expression of CD69 (98±2.3% vs 91±3.1%, P = 0.024) and IFNγ (1.9±0.73% vs 6.6±1.35%, P = 0.016) compared to SDNS patients. PLS-DA modeling of the 93 metabolites identified in CD4 culture supernatants yielded one fitted component, in which 24% of the variability in metabolites measured (R2X) could explain 58% of the variation in steroid-response (R2Y). Of note, 85% of the metabolites tended to be lower in SRNS compared to SDNS patients. Pathway analysis of the 38 metabolites with VIP>1 implicated the biosynthetic pathways glyoxylate and dicarboxylate metabolism, ascorbate and aldarate metabolism as well as galactose metabolism (Benjamini-Hochberg P<0.05). Interestingly, the 2 metabolites with the highest VIP score have been implicated as downstream products in the pentose phosphate shunt and were reduced in SRNS compared to SDNS patients (P<0.001). G6PD activities in SDNS patients in relapse negatively correlated with T-cell expression of CD69 (r=-0.58, P = 0.047).

Conclusions: We demonstrated that muted T-cells response to in vitro stimulation in SRNS patients was associated with metabolic quiescence, with dysregulated biosynthetic pathways including the pentose phosphate shunt.

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PO1458

Blocking the IL-1β/IL-1R1 Signaling as a Potential Therapy for Multidrug-Resistant Nephrotic Syndrome

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Introduction: In idiopathic nephritic syndrome (NS), Steroid-resistant patients with complete or partial resistance to the combination of prednisone and steroid sparing-agents are at high risk to progress to end-stage kidney disease. Considering the toxicities associated with chronic use of these drugs, alternative interventions are urgently needed. IL-1β/IL-1R1 has been recently suggested as a possible mechanism of complement-mediated progression of Focal Segmental Glomerulosclerosis.

Case Description: A 26-year-old white woman had FSGS (kidney biopsy) presenting with NS and kidney failure. Serum creatinine level was 1.6 mg/dL, urinary protein excretion 20.4 g/day and serum albumin 0.9 g/dL. She received methylprednisolone, 1g rituximab, and CAN with partial remission. Three months later, she presented relapse of NS and acute kidney failure requiring 5 HD: CAN was switched to MMF. Immunglobulins IV were administered. After 3 months, serum creatinine was 5.1 mg/dL, urinary protein excretion was 18 g/d. Given the lack of improvement/worsening of proteinuria, new started anakinra, the anti-IL-1R1 (subcutaneously, 2 mg/kg/d for the first week and then 4 mg/kg/d). After 1 year, serum creatinine is 3.4 mg/dL, urinary protein excretion is 5.2 g/d and serum albumin level was 1.3 g/dL. No side effects were reported (Fig 1).

Discussion: We administered Anakinra in MRCN due to FSGS and CKD Stage IV. After Anakinra, multiple ongoing immunosuppressive treatments were stopped. We acknowledge that Anakinra did not promote full disease remission, but it was associated with a significantly amelioration of the disease clinical. By slowing the rapid progression of kidney failure, the young patient better faced all future perspectives: a pre-emptive kidney transplant in case kidney function worsens is now available. In conclusion, our data indicate that Anakinra, by antagonizing IL-1β/IL-1R1 signaling, may represent a useful therapeutic option to prevent the progression of kidney injury in advanced forms of nephrotic syndrome.

IHC staining for STING on kidney tissue obtained from MCD patients (classified into negative (A), 1+ (B), 2+ (C), and 3+ (D) according to the signal intensity) and IgAN patients, the glomerulus was exclusively stained in MCD patients (Figure). MCD patients were divided into the high (n = 6) and low (n = 14) intensity subgroups according to the signal intensity based on 2+ or more or less, respectively. TA-proteinaemia and frequency of relapses during the follow-up period were higher in the high intensity group than in the low intensity group (1.18 ± 0.54 vs 0.57 ± 0.45 g/day, p = 0.022; and 0.72 ± 0.60 vs 0.09 ± 0.22 episodes/year, p = 0.022, respectively).

Conclusions: These findings suggest that more severe mitochondrial injury, as represented by a high signal intensity of IHC staining for STING at the time of diagnosis, could be used as a prognostic marker to predict poor prognosis in MCD.

PO1460

Maturation of Decay Accelerating Activity Response Across the Natural History of C3 Glomerulopathy

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Background: C3 Glomerulopathy (C3G) is an ultra-rare complement-mediated renal disease characterized by dysregulation of the alternative pathway (AP) of complement. Dysregulation is often driven by a nephritic factor (C3NeF), an autoantibody to the C3 convertase (C3BbBb) of the AP. We hypothesized that the properties of Nefs change

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
over time and that changes will be associated with changes in underlying complement dysregulation.

**Methods:** IgG was purified from normal human serum and from sera collected across six time points of a well characterized C3G patient. Using SPR (Biacore), the C3 convertase (C3bBb) was formed on a CM5 sensor chip. Purified test or control IgG was injected to form the Nef-C3bBb complex. The ability of naive complement regulators to decay the Nef-C3bBb complexes was assessed by injecting Decay Accelerating Factor (DAF), Complement Receptor 1 (CR1), Factor H (FH), or control reagent. Residual C3bBb was determined by the ratio of post- to pre-regulated convertase. Data were compared to time-matched complement biomarker results.

**Results:** The presence of Nef conferred resistance to the normal decay accelerating activity (DAIA) by DAF, CR1, and FH. Resistance to DAA was highest in the earliest sample (S1, p = 0.0001), with a reduction in subsequent samples. This change was independent of Nef titer and coincident with reduced complement activity. Low DAF resistance was maintained in later samples, whereas CR1 and FH resistance gradually increased.

**Conclusions:** Nef-stabilized C3bBb resistance to native DAA proteins matures over time and is independent of Nef titer. Changes in response to regulators is accompanied by a relative change in underlying complement dysregulation as reflected by complement biomarkers. How this variance (in time and across regulators) impacts disease course and outcome in patients with C3G or whether the phenomenon represents a novel treatment target warrants further study.

**Funding:** NIDDK Support

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**PO1462**

**Complement-Activating Polymorphonuclear Neutrophil Contribution to C3G Pathogenesis**

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**Background:** C3G is caused by dysregulation of the complement alternative pathway, but there is a gap in the pathogenic cascade from complement activation (intravascular space) to inflammation and complement deposition in the glomeruli (extravascular space). Recently, biopsies have shown the presence of (activated) polymorphonuclear neutrophils (PMNs) in C3G glomeruli indicating an underappreciated role for PMNs in C3G pathogenesis.

**Methods:** PMNs were investigated in a transwell chamber allowing for different environments. Conditions were chosen to resemble the intravascular space (top well; serum containing) versus extracellular space (bottom well; serum-free conditions). PMNs were stimulated in the top well via various agonists, including complement, and allowed to transmigrate to the bottom well where they were monitored for the formation of Neutrophil Extracellular Traps (NETs) via immunofluorescence and SYTOX assay. Circulating C3G patient PMNs were examined for priming via flow cytometry.

**Results:** Upon complement stimulation, PMNs showed evidence for priming in serum conditions (top well). PMNs travelled to the bottom well following chemotactic factor (MLP) where they then completed the process of NET formation (NETosis) in serum-free conditions (bottom well). Results were validated ex vivo using C3G patient PMNs and autologous serum (Figure). In addition, incubation of control PMNs in C3G patient serum revealed a correlation between serum-albumin levels and the degree of NET formation. C3G patient PMNs showed upregulation of CD11b compared to controls.

**Conclusions:** Assigning a pathogenic role to PMNs in C3G identifies a new treatment and monitoring strategy with the potential for improved long-term outcomes and quality of life.

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**PO1461**

**C3 Glomerulonephritis with Nephritic Factor Treated with Rituximab**

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**Introduction:** C3 Glomerulonephritis (C3GN) is a well described cause of kidney disease that results from dysregulation of the alternative complement pathway. Kidney biopsy demonstrates a membranoproliferative pattern of injury and mesangial C3 staining with minimal or no staining of immunoglobulins on immunofluorescence. C3GN can be due to genetic mutations, autoantibodies against the alternative complement regulators, or monoclonal gammopathy. C3 nephric factor (C3NeF) is an auto-antibody that stabilizes C3 convertase due to genetic mutations, autoantibodies against the alternative complement regulators, or monoclonal gammopathy. C3 nephric factor (C3NeF) is an auto-antibody that stabilizes C3 convertase which leads to an increase in activity of the alternate complement pathway. Steroids, mycophenolate mofetil (MMF), rituximab, and abatacept have been used with varying results. We present a patient with biopsy proven C3GN with C3NeF who was successfully treated with rituximab after failing therapy with MMF.

**Case Description:** Patient is a 64-year-old male diagnosed with biopsy proven C3GN after being found with decreased kidney function with a peak creatinine of 1.97 mg/dL and nephrotic range proteinuria with a maximal urinary protein excretion of 4.3 mg/dL. Evaluation revealed low C3 and C4 at 60 mg/dL and 5 mg/dL respectively, negative monoclonal testing, and a C3NeF of 21 unit/mL (reference range 0). Patient was initiated on prednisone 60 mg/day with taper, MMF with a maximal dose 3 grams/day, and valacyclovir for 2 years with little improvement in clinical parameters. Therapy was switched to rituximab 1 gram on weeks 0, 2, 26. Within 3 months patient had; normalization of complements, negative C3NeF, 0.7 urine protein-to-creatinine ratio (UPCR), and serum creatinine 1.5 mg/dL. Since his initial rituximab regimen 2 years ago, he remains off maintenance therapy, with negative C3NeF, normal complements, 0.1 UPCR, and serum creatinine 1.04 mg/dL.

**Discussion:** C3GN was successfully treated with rituximab based on the disappearance of C3NeF and improvement in clinical parameters. Rituximab was chosen to target CD20 cells to halt the production of the C3NeF autoantibody. Laboratory response (complements and C3NeF) was seen within 3 months of initial rituximab dosing, and UPCR and serum creatinine required a longer follow up for a nadir. Recurrence of relapse is being monitored using serial C3NeF measurements. We believe that targeted B cell therapy should be considered in the treatment of C3GN cases which are C3NeF antibody mediated.

**PO1463**

**Differential Expression of Complement and Non-Complement Proteins in C3 Glomerulonephritis and Dense Deposit Disease**

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**Background:** C3 glomerulopathy comprising dense deposit disease (DDD) and C3 glomerulopathies (C3GN) results from overactivation of the alternative pathway of complement. Mass spectrometry (MS) studies have previously shown accumulation of complement proteins in C3GN and DDD. However, complete MS analysis of non-complement proteins and comparison of complement proteins in C3GN and DDD has not been done.

**Methods:** We performed laser microdissection of glomeruli followed by MS in 12 cases each of biopsy-proven C3GN and DDD, and 6 control cases of time 0 transplant biopsies.

**Results:** Compared to the controls, C3GN showed increased intensity based absolute quantification (iBAQ) values of C3 (20-fold), C5 (52-fold), C6 (76-fold), C7 (90-fold), C8 (66-fold), C9 (30-fold), CFHR1 (146-fold) and CFR5 (65-fold). Similarly, DDD showed also increased iBAQ values compared to controls of C3 (26-fold), C5 (365-fold), C6 (473-fold), C7 (261-fold), C8 (353-fold), C9 (159-fold), and CFHR1 (73-fold). When DDD was compared to C3GN, there was a 2-5 fold increase in iBAQ values in C5, C6, C7, C8 and C9 (p<0.001), although there was no significant difference in C3. Among the non-complement proteins Apolipoprotein E (APOE) and A-II and V (APO-A-II and V), Serine protease HTRA1, Ryonandine receptor 1 (RYR1), and Translational activator GCN1 were expressed 3-7 fold higher in DDD compared to C3GN (p<0.001). On the other hand, proteoglycans 2 and 3 (PRG2 and 3), angiotensin (AGT) and proopitide (CFF) were expressed 2-5 fold higher in C3GN compared to DDD (p<0.001).

**PMNs were seeded in the top well of a transwell system and allowed to transmigrate for 12 h. PMNs from both wells were stained for IF with DAPI (blue), Citrullinated histone 3 (ChH3; green) and Myeloperoxidase (MPO; red). Scale bar 20 um. 63x magnification.**

*Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only*
Conclusions: MS of C3GN and DDD show high iBAQ values of complement proteins. DDD shows a higher iBAQ values in terminal complement proteins compared to C3GN. In addition, proteins such as APOE and APOA IV are increased in DDD compared to C3GN, while PRG2/3 and properdin are increased in C3GN compared to DDD suggesting a role for the proteins in the pathophysiology of C3GN and DDD.

PO1464
Clinical and Histological Features of Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits: A Single-Center Retrospective Study from China
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Background: PGNMID is a new entity of monoclonal gammopathy affecting the kidney characterized by intact monoclonal immunoglobulins (mlg) deposits that result in membranoproliferative pattern of glomerular injury. In this study, clinical and histological of PGNMID cases were evaluated.

Methods: A total of 23 patients with biopsy-confirmed PGNMID in native kidney diagnosed between December 2015 to April 2021 were enrolled in this study. Clinical, histological, hematologic, and follow-up data were abstracted from the medical record.

Results: Of 23 cases, majority were male (65.2%), and the mean age was 49.5 years with 8 cases (34.8%) under 40 years old. At the time of biopsy, 19 cases had proteinuria with a mean 24h urine protein of 3.99g (0.28 to 8.96), 11 of 22 cases had nephrotic syndrome, and 18 of 22 cases had hematuria. The mean serum creatinine was 1.52mg/dl (0.6 to 7.8). 15 cases (65.2%) had eGFR<90 mL/min (CKD-EPI), and 4 cases had eGFR <60mL/min. Eleven of 23 cases (47.8%) showed MPGN, 6 cases showed EGPG, 2 cases showed MesPGN, and 2 cases showed MN. By IF, 21 cases (91.3%) showed mIgG (12 IgG3, 5 IgG1, 1 IgG1A, 1 IgG2, and 2 IgGk without determined subclass) and 2 cases (8.7%) showed mIgA deposits. All cases showed C3 co-deposits, and 6 of 18 cases (33.3%) had a low serum C3 level. EM revealed unorganized and granular deposits in the mesangial area (17 of 17), subendothelial area (15 of 17), and subepithelial area (12 of 17). Three of 4 cases whose eGFR<60 mL/min showed EMG. SIFE showed mIg that matched the renal deposits in 2 of 13 cases (15.3%). After mean follow up of 3 months in 3 cases, 1 patient treated with bortezomib+ CTX+DXM and another patient treated with rituximab both achieved partial renal remission. But the third patient treated with rituximab had a persistent renal dysfunction. Of note, previous or concurrent chemotherapeutic agents and adequate blood pressure control, her creatinine continued to increase with subsequent development of nephrotic range proteinuria. All serologies (including anti-nuclear, anti-dsDNA, anti-Smith, anti-SLA/B, anti-Ro/La, anti-SS A and B, anti-RNP, anti-Jo) were negative. Kidney biopsy demonstrated TMA. Despite the discontinuation of all chemotherapeutic agents and adequate blood pressure control, her creatinine continued to increase, peaking at 6.8 mg/dl 2 months after the biopsy. She was started on Eculizumab with an improvement in creatinine to 3.49 mg/dl 2 months later.

Conclusion: Fifty-seven patients with TMA on kidney biopsy and a normal activity of von Willebrand factor cleaving protease were screened for deregulated complement using ex vivo C5b9 formation on the endothelium and genotyping. Massive ex vivo C5b9 formation and/or rare complement gene variants defined C-TMA. Clinico-pathologic features that may distinguish C-TMA from secondary TMA were studied. Regression models were used to assess the prognostic value of chronic damage on kidney biopsy.

Results: C-TMA was diagnosed in 30 patients (coexisting conditions, n=26 [87%]), including 16 (53%) cases with rare complement gene variants; 27 patients had secondary TMA related to autoimmunity (n=13), hypertension (n=10), and other etiologies (n=4). Patients presented with acute kidney injury, while systemic hemolysis was uncommon in both groups (n=14/30 vs. n=6/27; P=0.05). C-TMA was linked to younger age (37 [±14] vs. 46 [±15] years; P=0.04), low plasma C3 (n=16/29 vs. n=3/22; P=0.01), and glomerular thrombosis (n=19/30 vs. n=8/27; P=0.02) as compared to secondary TMA: glomerular thrombosis, however, was common in patients with autoimmunity (n=6/13; P=0.05 vs. C-TMA). These characteristics, when combined, had a specificity and sensitivity for C-TMA of 100% and 33%, respectively. Eculizumab treatment was associated with clinical remission in C-TMA (n=12/14; P<0.01 vs. n=3/16 untreated patients). Morphologic features of chronic damage, i.e., glomerulosclerosis, interstitial fibrosis/tubular atrophy, and arteriosclerosis, did not predict prognosis; 5 out of 6 patients with C-TMA and moderate-to-severe chronicity scores treated with eculizumab recovered and/or improved kidney function.

Conclusion: Patients with TMA, low plasma C3, and glomerular thrombosis who present at younger age (i.e., <45 years) are at high risk for C-TMA. Although a kidney biopsy is often needed to detect the TMA, morphologic features of chronic damage cannot predict prognosis.

PO1466
Limited Therapeutic Arsenal for the Thrombotic Microangiopathy Spectrum
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Introduction: Thrombotic microangiopathy (TMA) is a common renal pathologic finding with an associated broad spectrum of clinical diseases. Complement-mediated TMA (C-TMA) is a frequently recognized cause of TMA due to uncontrolled complement activation. Terminal complement inhibitors such as Eculizumab have been shown to improve renal function in C-TMA. Multiple case reports have demonstrated a benefit in patients without identifiable complement disorder.

Case Description: 41-year-old Ethiopian female with a history of metastatic ovarian cancer treated with omentectomy, partial hepatectomy, salpingo-oophorectomy, splenectomy one year before admission was admitted for renal biopsy for evaluation of an increasing creatinine and proteinuria. Following her surgery she had been treated initially with paclitaxel and carboplatin and subsequently she had received bevacizumab and doxorubicin; the last doses of these latter agents were six months before admission. Four months prior to admission she developed new onset hypertension and her creatinine began to increase with subsequent development of nephrotic range proteinuria. All serologies were negative. Kidney biopsy demonstrated TMA. Despite the discontinuation of all chemotherapeutic agents and adequate blood pressure control, her creatinine continued to increase, peaking at 6.8 mg/dl 2 months after the biopsy. She was started on Eculizumab with an improvement in creatinine to 3.49 mg/dl 2 months later.

Discussion: There are no randomized trials evaluating terminal complement inhibitors for c-TMA. The indication for these medications becomes even more unclear when we factor in drug-induced TMA, cancer-associated TMA, malignant hypertension, and other TMA with readily identifiable complement disorders. More research on the use of genetic testing and complement inhibition is warranted for the entire spectrum of TMA.

PO1465
Diagnostic and Risk Factors for Deregulated Complement in Thrombotic Microangiopathy
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Background: The syndromes of thrombotic microangiopathy (TMA) are diverse and represent severe endothelial damage caused by various etiologies. The early recognition of complement-mediated (C)-TMA is of utmost importance to select patients for complement inhibition. Whether or not clinicopathologic features at presentation can distinguish C-TMA from secondary TMA was studied. Regression models were used to assess the prognostic value of chronic damage on kidney biopsy.

Results: Of 23 cases, majority were male (65.2%), and the mean age was 49.5 years with 8 cases (34.8%) under 40 years old. At the time of biopsy, 19 cases had proteinuria with a mean 24h urine protein of 3.99g (0.28 to 8.96), 11 of 22 cases had nephrotic syndrome, and 18 of 22 cases had hematuria. The mean serum creatinine was 1.52mg/dl (0.6 to 7.8). 15 cases (65.2%) had eGFR<90 mL/min (CKD-EPI), and 4 cases had eGFR <60mL/min. Eleven of 23 cases (47.8%) showed MPGN, 6 cases showed EGPG, 2 cases showed MesPGN, and 2 cases showed MN. By IF, 21 cases (91.3%) showed mIgG (12 IgG3, 5 IgG1, 1 IgG1A, 1 IgG2, and 2 IgGk without determined subclass) and 2 cases (8.7%) showed mIgA deposits. All cases showed C3 co-deposits, and 6 of 18 cases (33.3%) had a low serum C3 level. EM revealed unorganized and granular deposits in the mesangial area (17 of 17), subendothelial area (15 of 17), and subepithelial area (12 of 17). Three of 4 cases whose eGFR<60 mL/min showed EMG. SIFE showed mIg that matched the renal deposits in 2 of 13 cases (15.3%). After mean follow up of 3 months in 3 cases, 1 patient treated with bortezomib+ CTX+DXM and another patient treated with rituximab both achieved partial renal remission. But the third patient treated with rituximab had a persistent renal dysfunction. Of note, previous or concurrent infections by fungi, HIV, HBV, HPV or other undetermined pathogen, were observed in 5 cases (21.7%). We also found 1 patient with autoimmunity and another with malignancy.

Conclusion: Compared with previous reports, our PGNMID cases showed similar clinical and histological features. EPGN pattern seems to be associated with more severe renal function damage. Previous or concurrent infections, autoimmunity and malignancy were observed in 21.7% of cases.
Hematopoietic Stem Cell Transplant Membranous Nephropathy Is Associated with Protocadherin FAT1
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Background: Membranous nephropathy (MN) is a common cause of proteinuria in patients with a hematopoietic stem cell transplant (HSCT). The antigen(s) responsible for MN in HSCT-associated MN is unknown.

Methods: We performed laser microdissection and mass spectrometry (MS/MS) of glomeruli of 230 cases of PLA2R-negative MN to detect novel proteins/antigens in MN. These included PLA2R-negative MN developing in the setting of HSCT and de-novo MN in the kidney transplant.

Results: We detected a novel protein Protocadherin FAT1 (FAT1) in 9 cases of PLA2R-negative MN. Of the 9 FAT1-associated MN cases, 7 patients followed HSCT and 2 followed kidney transplant (de-novo MN). HSCT was done for treatment of AML (5 cases), MDS (1 case) and essential thrombocytopenia (1 case). All 9 cases were negative for known antigens of MN including PLA2R, THSD7A, NELL1, PCDH7, NCAM1, SEMA3B and HTRA1. Baseline PLA2R spectral counts were detected in 7 of the 9 cases. The FAT1 total spectral counts ranged from 27 to 70 (mean 44.1 ± 13.1). FAT1 was not detected in MS/MS in 115 control cases that included time 0 transplant, minimal change disease, FSGS, diabetes and IgA nephropathy. FAT1 was also not detected in 28 cases of PLA2R-positive MN. No case of FAT1-associated MN was detected in a non-transplant setting. The mean age of patients with FAT1-associated MN was 36 ± 9.7 yrs, 7 patients were females and 2 were males. MN occurred 2.5 ± 0.8 yrs and 7.5 ± 1.2 yrs after HSCT and kidney transplant, respectively. The mean serum creatinine and proteinuria at kidney biopsy was 1.9 ± 1.2 mg/dL and 7.4 ± 5.4 gms/L, respectively. Kidney biopsy showed IgG (2-3+) and minimal C3 (0-1+) along glomerular capillary walls; electron microscopy showed stage II MN in 8 out of 9 cases.

Conclusions: FAT1 appears to be a unique protein found in MN developing in the setting of HSCT and de-novo MN following kidney transplant. Further studies to localize FAT1 on the glomerular basement membranes and detect circulating antibodies are ongoing.

POI1468
Netrin G1 Is a Novel Target Antigen in Membranous Nephropathy
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Background: PLA-R is the main target antigen in membranous nephropathy (MN) representing 70-80% of cases. In the past years a number of confirmed, or potential target antigens, such as THSD7A, NELL1, HTRA1, Semai3B and PCDH7 have been reported, showing that the pathophysiology of PLA-R-antibody (ab) negative MN represents a diverse repertoire of antigens with low frequency.

Methods: Western blot (WB) analysis was used to identify sera of MN patients with IgG4 specific signals binding to antigens in the membrane fraction of human glomerular extracts (HGE). Only sera which were negative for PLA2R- and THSD7A- and PCDH7 were used. Recombinant protein was used to confirm the reactivity of patient sera by WB and identify other patients in a large cohort of MN patients. The deposition of the target antigen in the glomerular immune deposits was confirmed by immunohistochemistry (IHC).

Results: Using this approach, we identified Netrin G1 (NTNG1) as a novel target antigen in MN. NTNG1 is a 50 kDa secreted glycoprotein, which is attached to the cell surface by a GPI anchor (Fig. A, B). We identified NTNG1-1 in two out of 110 PLA-R- and THSD7A-negative MN patients. A follow-up of 5 years was available for the index patient. During this time, both proteinuria and NTNG1 persisted while renal function was stable. Further, a granular positivity for NTNG1 along the glomerular capillary wall was confirmed in the kidney biopsy by IHC (Fig. C), but was undetectable in the negative control (PLA-R- and THSD7A-negative MN).

Conclusions: We report NTNG1 as a novel target antigen in MN, occurring with low frequency and expanding the repertoire of antigens in patients with MN. The prevalence, pathogenic and clinical roles remain to be defined.

Funding: Government Support - Non-U.S.
PO1470

Epitode Spreading and Immune Complex Rearrangement in Membranous Nephropathy

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Introduction: We present a rare case of ANA and anti-dsDNA negative, anti-GBM positive lupus nephritis (LN) patient with two biopsies demonstrating LN Class III+V with possible immune complex (IC) rearrangement and/or epitope spreading (ES).

Case Description: A 62-year-old white male presented with a year-long history of purpuric rash and hematuria. His hospital admission laboratory data is detailed in Table 1. The first renal biopsy showed crescents in 2/4 glomeruli with mild (+) granular and segmentally linear deposits by immunofluorescence (IF). The patient received cyclophosphamide, corticosteroids and one session of therapeutic plasma exchange due to rapidly worsening renal function and an initial presumptive diagnosis of anti-GBM disease. The second biopsy demonstrated no crescents but features of combined class III + V LN with IF findings suggestive of a full-house pattern with a change in the deposits from segmentally linear to pure granular. He began therapy with mycophenolate mofetil and prednisone resulting in a decrease in his UPCR from 2.3 to 0.3 mg/mg (complete remission) over the next four months and significant improvement in renal function.

Discussion: A link has been reported between anti-GBM histopathology and membranous nephropathy. Evidence suggests IC rearrangement and/or ES as possible explanations. ES refers to the molecular conformational changes of secondary, non-membranous nephropathy. Evidence suggests IC rearrangement and/or ES as possible explanations. ES refers to the molecular conformational changes of secondary, non-membranous nephropathy. Evidence suggests IC rearrangement and/or ES as possible explanations. ES refers to the molecular conformational changes of secondary, non-membranous nephropathy. Evidence suggests IC rearrangement and/or ES as possible explanations. ES refers to the molecular conformational changes of secondary, non-membranous nephropathy. Evidence suggests IC rearrangement and/or ES as possible explanations. ES refers to the molecular conformational changes of secondary, non-membranous nephropathy. Evidence suggests IC rearrangement and/or ES as possible explanations. ES refers to the molecular conformational changes of secondary, non-membranous nephropathy. Evidence suggests IC rearrangement and/or ES as possible explanations.

We believe our case suggests this possible pathogenic mechanism. More research is needed to improve understanding of the sequential change observed on immunofluorescence microscopy.

Laboratory Data

PO1471

Generation of Anti-THSD7A Antibodies Using a Human Antibody Phage Display Library

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Background: Membranous nephropathy (MN) is an antibody-mediated autoimmune renal disease. In the majority of cases, autoantibodies target podocyte membrane proteins such as PLA2R1 and THSD7A. We could previously demonstrate that autoantibodies in THSD7A-associated MN cause disease and recognize several extracellular domains of the target antigen. However, the clinical relevance of this antibody polyclonality remains unclear as disease pathogenicity. The aim of this study was the generation of anti-THSD7A antibodies using a human antibody phage display library for further diagnostic and pathomechanistic studies.

Methods: In the antibody phage display technology, antibody fragments are displayed on the phage particle and the corresponding gene fragment encoding the antibody fragment is packaged in the phage particle. A selection process called panning enables the selection of antibody fragments against virtually any target structure in vitro. In this project, a naïve antibody gene library was used to select binders to the extracellular part of human and mouse THSD7A. Binders were sequenced, cloned into scFv-Fc format - an IgG like format - and produced in HEK293 cells. Binding of scFv-Fc to human and mouse THSD7A was investigated using Western blot, ELISA and indirect immunofluorescence testing (IFT). Epitope regions were mapped using an ELISA.

Results: Four binders (SAK79-B1, SAK78-C12, SAK78-E6, SAK78-F8) could be obtained. While SAK78-F8 exclusively bound human THSD7A, the other binders reacted with both human and murine THSD7A in Western blot, ELISA and IFT. A domain-specific ELISA revealed binding of SAK78-C12, SAK78-E6 and SAK78-F8 to the regions d8, d9, d11, d2 and d6, d7, respectively. SAK79-B1 did not react with any domain combination, but showed strong binding to murine and human d1, d2. We suspect a conformational epitope that was not conserved in the coated domain fragments. SAK78-C12 and SAK78-E6 were successfully cloned into human IgG subclass backbone IgG1-IgG4. We generated recombinant antibodies using a human antibody phage display library for further diagnostic and pathomechanistic studies.

Conclusions: Antibody phage display represents a powerful method to generate recombinant antibodies. The antibodies selected show different binding characteristics in vitro. In vivo binding characteristics, pathogenicity and potential as a diagnostic tool in THSD7A in patient biopsies, need to be determined.

Funding: Government Support - Non-U.S.

PO1472

A Comparison of aPLA2Rab Assays on Treatment with Cyclophosphamide and Steroids

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Background: Anti-PLA2R antibodies (aPLA2R) are present in ~75% of patients with primary membranous nephropathy (MN). A qualitative immunofluorescence test (IFT) allows accurate detection of aPLA2R, additionally ELISA and ChLIA provide quantitative analysis. Sensitivity of the two latter methods after start of immunosuppressive therapy is not well studied.

Methods: We retrieved stored samples of patients with aPLA2R associated MN, who were treated with cyclophosphamide and steroids(CP), collected at baseline and 8 weeks after start of therapy. Assays were performed by the EUROIMMUN research lab, Lübeck, Germany. All samples were analysed by IIFT, ELISA and ChLIA. We categorized ELISA results to cut-off values used in literature: 2, 14, and 20 RU/ml resp.

Results: We included baseline samples of 50, and 8 week samples of 51 patients. At baseline, all patients tested IIFT positive; ELISA test was positive in 94% or 98% of samples using cut-off values of 20 RU/ml or 14 RU/ml resp., indicating high sensitivity. Agreement between IIFT and ChLIA was 100%. After 8 weeks on CP, 37/51 patients had immunological remission by IIFT. ELISA test results are given in Table 1. In the IIFT positive samples collected after 8 weeks, ELISA titers were < 20RU/ml or < 14 RU/ml in 9/14 and 5/14 patients respectively, suggesting lower sensitivity. All IIFT negative samples had ELISA titers < 14 RU/ml. When analysing IIFT negative patients with ELISA titer <2 U/ml (N=23) vs. 2-14 U/ml (N=14), persistent immunological and clinical remission was better in the first group (74% vs 58%), however not statistically different. With ChLIA only 4/51 (8%) had different results (2 IIFT-/ChLIA+, 2 IIFT+/ChLIA-); resulting in a sensitivity of 86% and a specificity of 95%, when comparing IIFT.

Conclusions: Using immunological remission as treatment target, as described here after 8 weeks of CP, requires evaluation of the applied assay for this purpose. Of the examined quantitative methods, ChLIA demonstrated the highest agreement with IIFT. ELISA titers below the recommended cut-off for initial diagnosis still show a tendency towards the clinical outcome, which could be investigated by further studies.

Funding: Commercial Support - EUROIMMUN research lab, Lübeck, Germany.

PO1473

The Classical Pathway Triggers Pathogenic Complement Activation in Membranous Nephropathy

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Background: Membranous nephropathy (MN) is characterized by severe proteinuria, circulating autoantibodies against podocyte antigens such as PLA2R1 and THSD7A, and glomerular deposition of IgG and complement components (CCs). However, the pathways triggering the complement cascade (classical, alternative or lectin) and the significance of local glomerular complement action for podocyte damage and proteinuria are poorly understood.

Methods: Complement activation was investigated in 20 biopsies from patients with PLA2R1- and THSD7A-associated MN using immunofluorescence and proximity ligand blotting to visualize the assembly of CCs/convertases. Experimental autoimmune MN (EAMN) was established in 12-week-old BALB/c mice by immunization with THSD7A. Anti-THSD7A antibodies, proteinuria, serum parameters, and histological signs of MN were analyzed. The role of the complement system was studied by induction of EAMN in C3-/- mice. The efficacy of complement-targeted treatment was evaluated by weekly injection of a C3-silencing siRNA after the onset of proteinuria.

Results: The assembly of the classical/lectin convertase was identified in 19/20 MN biopsies, which was accompanied by detection of IgG and C3 in the majority of cases. The alternative convertase and MBL deposits were detected in fewer cases. Upon immunization, mice developed classical and histopathological features of MN. Proteinuria ranged from mild to severe nephrotic syndrome and histopathological features included granular glomerular deposition of IgG and CCs including C1q and C3 as well as loss of the integral podocyte proteins nephrin and nephrin. Strikingly, severe disease with ascites was prevented in C3-/- mice and overall proteinuria was reduced in comparison to WT littermates. Finally, treatment with C3-silencing siRNA after the onset of proteinuria attenuated disease.
Conclusions: The complement system is dominantly activated via the classical path in MN patients. Experimental data in the first author’s membranous model suggests an antigen that is pathogenically relevant in patients suggest complement-targeted treatment as a promising strategy for MN patients with severe disease, but also hint at a role of complement-independent mechanisms in the pathogenesis of MN.

Funding: Government Support - Non-U.S.

PO1476
Compelent Activation and Suppression Profile Reveals Distinct Subtypes in C3 Glomerulonephritis

Background: The complement pathway is an innate immune defense mechanism, and uncontrolled activation can cause damage to host tissues including the kidney. C3GN is characterized by deposits in the glomerulus made up entirely of complement C3 protein without the presence of immunoglobulins.

Methods: The activity of the alternative complement pathway (ACP) was determined in serum derived from C3GN patients, IgA Nephropathy (IgAN) and Polycystic Kidney Disease (PKD) and healthy controls (HC) by measuring the lysis of rabbit red blood cells (rRBC). Complement factor H (CFH) was added to the serum of C3GN patients to test if CFH is capable of inhibiting the ACP in C3GN patients.

Results: Analysis of the ACP using the serum of C3GN, IgAN, PKD patients and healthy controls can be calculated by the lysis of rRBC. The percent lysis at specified time points (5, 10 and 15 minutes) was calculated using the maximal lysis for each sample. Serum from C3GN patients result in more significant lysis (one way ANOVA, p = 0.01) at 5 and 10 minutes (22.9% ± 11% and 42.7% ± 12%, respectively) compared to HC (7.1% ± 3% and 21.7% ± 6%, respectively), IgAN (10.9% ± 7% and 27.3% ± 15%, respectively) and PKD (8.6% ± 6% and 24.4% ± 12%, respectively). However, at 15 minutes, there were no statistically different differences in the lysis of the rRBC between these groups, suggesting that the ACP is more rapidly activated in C3GN patients, leading to a faster depletion of C3. Addition of CFH to the serum of C3GN patients reduced the ACP activity to control levels in 6 out of 14 patients. We did not detect CFH specific antibodies in the serum of patients who did not respond to CFH, indicating additional mechanisms are involved with the rapid activation of the ACP in C3GN.

Conclusions: The ACP is rapidly activated by the serum of C3GN patients compared to other kidney diseases and HC. Although the addition of CFH to the serum reduced the ACP activation compared to controls in 42% of C3GN patients, not all the serum samples responded to CFH. Future work may elucidate additional mechanisms of the continued ACP activation in C3GN patients and have implications for therapy of these patients.

Preexisting Autoimmune Dysregulation Unmasks a Role for Silica Dust Exposure in Nephrotrophic Autoantibody Production
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Background: Pathogenic autoantibodies (autoAb) promote severe glomerulonephritis in ANCA vasculitis and lupus. Genetic susceptibility and environmental exposures, particularly inhalation of silica (Si) dust, are implicated in dysregulated autoreactivity and are targets for therapeutic intervention. Using a mouse reporter system expressing a regulated nephrotropic autoAb transgene (Tg) targeting basement membrane (BM) and instilling Si by oropharyngeal aspiration (OAP), we demonstrated that central B cell tolerance and anergy to BM are preserved in multiple lupus strains despite induction of lung inflammation and ectopic lymphoid tissue. Nonetheless, Si exposure increased local and systemic anti-DNA Ig levels in wildtype (WT) B6 and lupus mice, suggesting subversion of alternative regulatory checkpoints. Herein we leverage the aberrant M7 anti-BM Tg lineage that demonstrates partial escape from tolerance and evidence of glomerular Ig deposition to study the interaction of Si exposure with preexisting defects in autoreactive cell regulation.

Methods: M7 Tg mice (WT at Ig light chain, or LC, locus) were exposed to Si or vehicle (V) by OAP, organs harvested at 5-6 weeks, and cells cultured aToll-like receptor ligand (TLR-L). To restrict Ig specificity, a subset of mice (TgK) was bred to heterozygosity for the Vκ8.8/κ V8. Ig LC knock-in. Tg autoAb were measured by ELISA; mean OD±SD.

Results: Presence of serum Tg autoAb and induction of high levels of autoAb by TLR-L stimulated splenocytes (OD 2.61±0.49; TLR7/9, v 0.06±0.03; medium, p=0.0001) confirmed Tg phenotype, and bronchoalveolar lavage fluid cell counts confirmed exposure (237.1±130 vs 18±1.7, x1000, Si vs V, p<0.05). Among Tg WT mice, more autoAb were produced by TLR7/9-stimulated lung cells from Si vs V mice (OD 0.13±0.15, Si, vs 0.03±0.01, V, p<0.05), indicating that Tg B cells recruited by Si exposure contribute to local autoAb production. Among Si-exposed mice, Tg autoAb levels were higher in Tg vs Tg/Ki mice: OD 1.23±0.47 for TLR4-L stimulated splenocytes, Tg/Ki vs 0.51±0.43, Tg/Ki, p<0.05. Increased CFH was added to the serum of C3GN patients to test if CFH is capable of inhibiting the ACP in C3GN.

Conclusions: The method is rapid activated by the serum of C3GN patients compared to other kidney diseases and HC. Although the addition of CFH to the serum reduced the ACP activation compared to controls in 42% of C3GN patients, not all the serum samples responded to CFH. Future work may elucidate additional mechanisms of the continued ACP activation in C3GN patients and have implications for therapy of these patients.

PO1477
Preexisting Autoimmune Dysregulation Unmasks a Role for Silica Dust Exposure in Nephrotrophic Autoantibody Production

Funding: Other NIH Support - NIEHS, Veterans Affairs Support

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Underline represents presenting author.
**POI1478**

**Characteristics of Membranous Nephropathy Patients with IgA and IgA Co-Deposits on Capillary Wall**

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**Background:** Membranous nephropathy (MN) is characterized by immune deposits on glomerular capillary wall, predominantly IgG. There have been several reports of MN combined with IgA nephropathy with features of IgA immunofluorescence staining in the glomerular mesangium. However, we found that IgA can also be deposited on the capillary wall with IgG. This study aimed to investigate the prognostic, clinical and renal histopathological characteristics of adult MN patients with IgA and IgA co-deposits on capillary wall.

**Methods:** A retrospective study was conducted in biopsy-proven MN patients of our renal department during January, 2007 to May, 2020. Clinical data were collected at time of biopsy and the latest followed-up. Pathological parameters included immunofluorescence staining, pla2 staining, membranous Chang’s stages, sclerosis, crescent, focal segmental sclerosis lesion, chronic tubulointerstitial injury and et al. Indirect immunofluorescence experiment was conducted in 293T cells transfected with pla2 plasmid.

**Results:** Out of 531 cases diagnosed with MN, 53 patients have moderate IgA deposit on capillary walls with IgG. 19 cases were determined to be secondary MN, which were 10 cases of autoimmune disease, 4 cases of Hepatitis B, 3 cases of kidney transplantation, 1 case of chemical exposure and 1 case of AL amyloidosis-associated secondary MN. 31 Idiopathic MN patients with both IgA and IgG depositing on capillary wall were followed up for a median interval of 49months (interquartile-range, 17-82) and 3 patients were transferred to stage 3 (6.5%) patients progressed to ESKD or death, 2 (6.5%) patients had their eGFR declined by half, 11 (35.5%) patients had no remission and 15 (53.6%) patients withdrew. 3 (9.8%) patients progressed to ESKD or death, 2 (6.5%) patients had their eGFR declined by half.

**Conclusions:** IgA and IgG could be co-depositing on glomerular capillary wall in MN patients, secondary causes should be screened with cation. IgA and IgG type of autoantibodies linked to MN co-existed in serum of idiopathic MN patients, whose prognosis might be poor.

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**POI1479**

**Humanistic Burden of Rare Kidney Diseases: Understanding the Impact of FSGS and IgAN on Patients and Caregivers: The HONUS Rationale and Study Design**

**Justyna Szklarzewicz. HONUS Advisory Board Members and HONUS Study Team University Hospitals of Leicester NHS Trust, Leicester, United Kingdom.**

**Background:** While both Immunoglobulin A Nephropathy (IgAN) and Focal Segmental Glomerulosclerosis (FSGS) conditions have been shown to be associated with significant clinical and economic burden to healthcare systems, less is known about the humanistic burden associated with these diseases. Here we describe the Humanistic Burden of Rare Kidney Diseases: Understanding the Impact of FSGS and IgAN on Patients and Caregivers Study (HONUS), which aims to elucidate the impact of these conditions.

**Methods:** HONUS is being designed in consultation with patient and clinical community members at inception of study design, ensuring the right elements are informed decision making. For industry, data supports value assessments and ensures therapeutic options, but also has broader benefits. For patients and care-partners, insights into patient and caregiver burden, particularly in the context of disability or Quality-Adjusted Life Years (DALYS or QALYS), is commonly quantified in population health context as Disability- or Quality-Adjusted Life Years (DALYS or QALYS). Quantifying humanistic burden is foundational for value assessment of new therapeutic options, but also has broader benefits. For patients and care-partners, insights can validate and support individual experiences and coping. For patient advocacy groups, information can be used to raise awareness, facilitate education and develop resources for affected families. For the clinical community, evidence supports patient/ family communication, education of the broader clinical community and contributes to informed decision making. For industry, data supports value assessments and ensures the patient and care-partner voice is heard. This begins with engagement of patient and clinical community members at inception of study design, ensuring the right elements are included in the study, the design fits with the evidence generation goal, and results are disseminated in a comprehensive and useful way.

**Conclusions:** HONUS will provide evidence quantifying the humanistic burden of FSGS and IgAN from patient and care-partner perspectives.

**Funding:** Commercial Support - Travere Therapeutics

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**POI1480**

**Mystery Cryoglobulinemic Glomerulonephritis Treated with Rituximab**

**Mohamed Hassanein, Hanny Sawaf, Leal C. Herltitz, Michael Lioudis. Cleveland Clinic, Cleveland, OH.**

**Introduction:** Cryoglobulinemic Glomerulonephritis (GN) is characterized by the deposition of immunoglobulins (IG), also known as cryoglobulins (CG), in the kidney. We report a case of idiopathic mixed cryoglobulinic GN treated with rituximab and prednisone.

**Case Description:** A 42-year-old tri-athlete with a history of pediatric meningitis with hydrocephalus requiring placement of a ventriculoperitoneal shunt presented with lower extremity swelling limiting his ability to exercise. He denied non-steroidal anti-inflammatory drug and illicit drug use, and was not on any prescribed medications. Laboratory workup showed serum creatinine: 1.2 mg/dL (normal 0.7 – 1.2), serum albumin: 2.1 mg/dL (normal 3.9 – 4.9), CG: 140 mg/mL (normal 0 – 50), C3: 39 mg/dL (normal 86 – 166), C4: 7 (normal 13 - 46), and a urine protein to creatinine ratio (UPCR) 5.9 g/g. Kidney biopsy showed diffuse proliferative GN with polyclonal IG deposits consistent with mixed cryoglobulinic GN (figure 1). An infectious workup, including human immunodeficiency virus (HIV), viral hepatitis, blood and urine culture, and a lumbar puncture were unremarkable. Computed tomography of the chest, abdomen, and pelvis revealed splenomegaly. Echocardiogram and bone marrow biopsy were non-diagnostic. He was treated with rituximab and prednisone with normalization of CG, C3, and C4, a reduction in UPCR to 0.5 g/g and return to full exercise capacity five months later.

**Discussion:** Mixed cryoglobulinic GN is a rare disorder caused by polyclonal deposition of Ig in the kidney. Autoimmune disease, hematological malignancies, and infectious etiologies such as endocarditis, HIV, and viral hepatitis should be ruled out prior to immunosuppressive therapy. Our patient elected to proceed with treatment due to his poor quality of life and evidence of end-organ involvement. Although workup for hematological malignancies was unremarkable, it is unclear if his splenomegaly could be reflective of an underlying indolent lymphoma, which could have simultaneously responded to rituximab treatment.
Vancymycin-Induced Thrombotic Microangiopathy: A Rare Association
Gaurav Rajashekar, Anuja Java. Washington University in St. Louis Washington University in St. Louis, St Louis, MO.

Introduction: Thrombotic microangiopathies (TMAs) are life-threatening conditions characterized by hemolytic anemia, thrombocytopenia and AKI. Drug-induced TMA (DITMA) is a diagnostic challenge because specific tests to identify a drug etiology are not available.

Case Description: A 40 yr-old female with history of neurofibromatosis type 2 underwent resection of a T10-11 schwannoma. The surgery was complicated by wound dehiscence which was treated with incision and drainage followed by intravenous vancomycin and cefazolin. The next day, she developed fever, altered mental status and a diffuse purpuric rash (Fig 1). Labs showed anemia (Hgb 6.2 g/dl), thrombocytopenia (PLT 15 k/µL), elevated LDH and anuric AKI requiring dialysis. C3 and C4 were low. Coombs test was negative. She subsequently developed disseminated intravascular coagulation and elevated liver enzymes. Skin biopsy revealed a leukocytoclastic vasculitis with IgG and complement deposition within vessel walls. Given the concern for DITMA versus thrombotic thrombocytopenic purpura, vancomycin was discontinued. Treatment with prednisone and plasmapheresis was initiated which led to improvement for DITMA versus thrombotic thrombocytopenic purpura, vancomycin was discontinued. Unfortunately, later during the hospitalization, she developed acute respiratory failure leading to cardiac arrest.

Discussion: This is a rare case of vancomycin-induced TMA. We speculate the mechanism is immune-mediated given the presence of low complement levels (although we did not test for vancomycin-dependent antibodies). Patients with immune-mediated DITMA present with sudden onset of severe systemic symptoms after a short exposure to the implicated drug. Greater awareness with improved methodology for diagnosis of DITMA is critical for clinicians evaluating such patients. Recognition of DITMA and documentation of the drug etiology are essential for patient safety.

Cryoglobulinemic Vasculitis in a Patient with Known Thrombotic Microangiopathy
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Introduction: Acute kidney injury (AKI) is a ubiquitous presentation, but thrombotic microangiopathy (TMA) and cryoglobulinemia are uncommon causes that are not easily diagnosed. We highlight a case of AKI that was found to be cryoglobulinemic vasculitis, an unexpected diagnosis in a patient with history of TMA.

Case Description: A 68-year-old female was diagnosed with giant cell arteritis, with temporal artery biopsy showing inflammation of the adventitia consistent with small vessel vasculitis. She received prednisone and tocilizumab. 6 months later, she was admitted for hypertensive crisis with thrombocytopenia and schistocytes, with creatinine (Cr) elevation to 3.5 from baseline of 1.0. Renal biopsy showed TMA. Tocilizumab was discontinued. She was transitioned to eculizumab, eventually resulting in renal recovery (Cr 1.5) after 1.5 months. However, she continued to feel poorly and returned to the hospital, where she was found to have Cr 4.0. Physical exam was significant for hypertension and tender retiform purpura. Urine studies were consistent with cellular casts. Dermal biopsy showed dermal necrosis but no intravascular thrombi. Renal biopsy ultimately revealed cryoglobulin deposition, resulting in a diagnosis of cryoglobulinemic vasculitis. She was treated with prednisone, rituximab, and cyclophosphamide with good renal response, and discharged with Cr 2.4.

Discussion: The finding of cryoglobulin on this patient’s renal biopsy was subtle, causing a near-miss in her diagnosis. Her history and repeat clinical evidence of TMA further confounded her presentation. Therefore, when TMA is on the differential, workup should also evaluate for cryoglobulinemia. Her prior diagnosis of GCA also acted as a confounder, though absence of panarteritis and large vessel involvement on temporal artery biopsy may have hinted at underlying systemic vasculitis. While eculizumab is a standard therapy for TMA, there is limited evidence for its use in treating cryoglobulinemic vasculitis. This patient’s positive renal response to eculizumab supports the potential role of complement inhibitors in treating cryoglobulinemia. It remains possible that the patient could have had TMA and cryoglobulinemia concurrently, with renal biopsy during this presentation only capturing the latter. Therefore, further research into the role of complement inhibitors for cryoglobulinemia is needed.
POI1485

Minimal Change Disease as a Novel Manifestation of Cytomegalovirus
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Introduction: Cytomegalovirus (CMV) infection is typically asymptomatic among the immunocompetent or can cause a mononucleosis. Among immunosuppressed patients common presentations are colitis, hepatitis, encephalitis, retinitis and even Guillain-Barre syndrome. This case is a rare dissemination of CMV manifesting as acute glomerulonephropathy.

Case Description: A 67 year-old female with past medical history of lupus, rheumatoid arthritis, and Sjogrens syndrome on maintenance steroids presented with a prolonged cough, joint swelling, shortness of breath and rash consistent with livedo reticularis. She developed worsening weakness in the arms and legs. High dose IV steroids were initiated for presumed rheumatoid vasculitis. Nephrology was consulted for worsening renal function with urine protein to creatinine ratio of 42 g, later requiring hemodialysis for volume management. Work up for nephritic range proteinuria including hepatitis B/C, HIV, SLEP, UPEP, and complement screen was unrevealing. Renal ultrasound demonstrated an 11.7 cm right kidney and 14 cm left kidney. Renal biopsy demonstrated diffuse podocyte effacement and large atypical mononuclear cells within the glomerulus. No immune deposits seen on electron microscopy. Immunohistochemical staining confirmed glomerular CMV. Six weeks after starting treatment with ganciclovir and tapering steroids, CMV viral load was undetectable and renal function recovered to baseline.

Discussion: CMV involvement of the kidney is unusual aside from tubulointerstitial nephritis. Rare cases of collapsing glomerulopathy and focal segmental glomerulosclerosis are found in literature. We report a novel presentation of CMV glomerulonephropathy with minimal change disease and renal failure. To prevent tissue invasive CMV in a chronically immune suppressed patient one needs to maintain clinical suspicion for infectious pathogens and perform tissue biopsy.

POI1486

Minimal Change Disease Following the mRNA-1237 Vaccine in a Kidney Transplant Recipient
Juanly N. Rodriguez, Shobana Sivan, Mariella O. Goggins. University of Miami School of Medicine, Miami, FL.

Introduction: Kidney transplant recipients (KTR) are susceptible to post-transplant glomerulopathies. Minimal change disease (MCD) is seen rarely. Few cases have been reported post-immunization, recently with the Pfizer-BioNTech vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We report a case of de novo MCD after mRNA-1237 vaccine in a deceased donor KTR, with a sudden onset nephrotic syndrome (NS) and acute kidney injury (AKI) a week after the first dose.

Case Description: 45-yr-old woman with history of ESKD from lupus nephritis, underwent DDKT on 09/2019 from a 20-yr Caucasian male, kidney donor profile index (KDP) 1. She was a Transplant Recipient (TTR) with mild membranous nephropathy on prior baseline. Her creatinine was 0.9 mg/dL but increased to 1.8 mg/dL within 2 months. She follows with maintenance prednisone. Her creatinine has stabilized to 1.4 mg/dL and urine protein to creatinine ratio (UPCR) 9.6 g/g, albumin 2.1 g/dl consistent with NS.

Discussion: This is a seropositive SARS-CoV-2 KTR from previous COVID-19 pneumonia who developed NS following mRNA-1237 mRNA vaccine. Biopsy consisted of MCD. Immunogenicity to mRNA vaccines in transplant recipients is blunted after the first dose but higher in seropositive patients. Timing from vaccine exposure to development of MCD ranges from days to months, our patient mounted an immune response in 4 days. The acute tubular injury seen in LM is atypical, unclear if this is a cell mediated process from allograft rejection or part of the pathogenesis post-immunization. In cases of AKI with NS, days to weeks following either class of mRNA vaccine a prompt initiation of steroids and further investigation with kidney biopsy is warranted.

POI1487

COVID-19-Associated Collapsing Focal Segmental Glomerulosclerosis During Pregnancy in a Woman with Lupus Nephritis
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Introduction: Lupus nephritis (LN) is a common clinical entity in patients with systemic lupus erythematosus (SLE). LN is classified on the basis of renal biopsy findings. We present a woman with a history of LN who was diagnosed with COVID and AKI during pregnancy. Kidney biopsy showed collapsing FSGS and class V LN with APOL1 gene mutation.

Case Description: A 32-year-old G4P0012 African American female presented to a multidisciplinary Nephrology Maternal-Fetal Medicine program at 12 weeks gestation for management of LN in pregnancy. She was diagnosed with SLE at age 8, previously treated with rituximab and belimumab for rash, and other extrarenal manifestations. Three years ago she was diagnosed with LN Class 3 + Class V treated with MMF with partial remission. She was switched from MMF to azathioprine at pregnancy diagnosis. She was diagnosed with COVID 4 days prior to the telemedicine office visit with GI symptoms and fever and admitted to the hospital. Her creatinine was 3.9 mg/dL, increased from the prior baseline of 1.3 mg/dl. Urinalysis showed proteurina, and 24-hour urine collection contained 13.6 grams of protein. Her renal function continued to worsen despite intravenous fluid administration. Laboratory results included anti-Ds DNA titer 1:80, C3 61 mg/dl (90-180 mg/dl), and C4 34 mg/dl (10 -40 mg/dl). Kidney biopsy revealed class V LN and FSGS potentially related to COVID. As per biopsy finding and ethnicity, we sent APOL1 genetic analysis which came back positive. Treatment was started with IV steroids. The creatinine peaked at 4.7 mg/dL on hospital day 8 and subsequently improved. She did not require RRT and was continued on her maintenance IS. Unfortunately, she had fetal demise at 18 weeks 3 days of gestation with stable renal function.

Discussion: This is a case of COVID-associated FSGS in a pregnant woman with a history of LN. The initial impression included prerenal azotemia, LN flare, and COVID-associated kidney injury. Serologies were consistent with an LN flare, but renal biopsy showed both class 5 LN and FSGS potentially related to COVID. Kidney biopsy should be considered in pregnant patients with hematuria, proteinuria, to rule out alternative etiologies, even when LN is suspected on clinical grounds. The threshold of RRT is very narrow in pregnancy and requires increasing dialysis frequency for adequate pregnancy outcomes.

POI1488

Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis (SAPHO) Syndrome and IgA Nephropathy
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Introduction: Immunoglobulin A nephropathy (IgAN) is the most common form of glomerulonephritis (GN). It is characterized by IgA deposits within glomeruli, classically caused by poorly galactosylated immunoglobulin A1 that trigger autoantibodies. Other forms of IgA nephropathy include IgA vasculitis with nephritis (Henoch-Schönlein purpura) and secondary forms arising from chronic lower respiratory disease, chronic infections and neoplasms.

Case Description: Patient is a 50 year old female with anemia, hypothyroidism and chronic joint pain who presented for rising creatinine and hematuria. Baseline creatinine was 0.9 mg/dl, increased to 1.8 mg/dl within 2 months. She follows with maintenance IS. Unfortunately, she had fetal demise at 18 weeks 3 days of gestation with stable renal function.

Discussion: This is a seropositive SARS-CoV-2 KTR from previous COVID-19 pneumonia who developed NS following mRNA-1237 vaccine. Biopsy consisted of MCD. Immunogenicity to mRNA vaccines in transplant recipients is blunted after the first dose but higher in seropositive patients. Timing from vaccine exposure to development of MCD ranges from days to months, our patient mounted an immune response in 4 days. The acute tubular injury seen in LM is atypical, unclear if this is a cell mediated process from allograft rejection or part of the pathogenesis post-immunization. In cases of AKI with NS, days to weeks following either class of mRNA vaccine a prompt initiation of steroids and further investigation with kidney biopsy is warranted.

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Kidney biopsy for IgA case depicting membranoproliferative pattern of glomerular injury in patient with SAPHO syndrome

PO1489
Crescentic Pauci-Immune Glomerulonephritis in a Patient with Sickle Cell Anemia and Cocaine Abuse
Marimar Contreras Nieves, Stanford Medicine, Stanford, CA.

Introduction: Levamisole is an anthelminthic agent and a common contaminant found in cocaine. It has been linked to ANCA-associated vasculitis with cutaneous, and more rarely, renal and pulmonary manifestations. This is the case of a patient with sickle cell anemia and cocaine abuse presenting with acute kidney injury (AKI) and nephrotic-range proteinuria in sickle cell anemia, return to baseline, which could have been due to his degree of kidney injury and ongoing crescentic glomerulonephritis, transmural arteritis, and sickle cell nephropathy. He was evaluated for ANCA vasculitis. Pathology showed pauci-immune necrotizing and crescentic glomerulonephritis, transmural arteritis, and sickle cell nephropathy. He was treated with pulse dose steroids and rituximab, followed by maintenance prednisone and additional doses of rituximab after discharge. His renal function improved, but did not return to baseline, which could have been due to his degree of kidney injury and ongoing cocaine use after discharge.

Discussion: This case demonstrates the importance of keeping a broad differential diagnosis in the evaluation of AKI and nephritic-range proteinuria in sickle cell anemia, particularly in the setting of cocaine use and its known association with vasculitis. A kidney biopsy was performed, with pathology showing a pauci-immune necrotizing and crescentic glomerulonephritis, transmural arteritis, and sickle cell nephropathy.

PO1490
A Case of Rapid Progressive Glomerulonephritis Associated with Disseminated Gonococcal Infection
Safa Osman, Nihal M. Ali, Pradeep Varilla, Franco H. Cabeza Rivera. The University of Mississippi Medical Center, Jackson, MS.

Introduction: Disseminated gonococcal infection (DGI) results from bacteremic spread of the sexually transmitted pathogen, Neisseria gonorrhoeae. Direct and immunological damage of multiple organs can be seen. We are reporting a case of sterile DGI with RPGN as part of the initial presentation.

Case Description: A 60-year-old male with a 5-year history of seronegative spondyloarthropathy, hypertension, heart failure, poor dentition who presented to the hospital with shortness of breathing, diarrhea, joint pain, and palpable purpura ongoing for several weeks. Work-up revealed severe anemia and rapidly progressive acute renal failure (Baseline creatinine unknown, peaked at 7.2 mg/dL on admission), urine showed 9.3 g of proteinuria, hematuria, and pyuria. Serological work-up showed low C3 with normal C4, ASO, ANA, ANCA and anti-GM. Negative HIV, hepatitis B, C, syphilis serologies, monoclonal and cryoglobulins. Skin biopsy showed leukocytoclastic vasculitis which improved with steroids. Kidney biopsy showed crescentic glomerulonephritis (GN) with 10% IFTA likely due to infectious GN (RPGN). Patient completed 3-day course of ceftriaxone but left before cyclophosphamide could be initiated. A week later he presented with persistent hematuria and oliguria. Echocardiogram showed tricuspid endocarditis and leaflet perforation. Blood cultures were negative. Patient started on vancomycin and Ropeschin for culture negative endocarditis. Extensive infectious disease workup, metagenomics test showed Neisseria gonorrhoeae as the cause of endocarditis. Kidney function improved. Due to disseminated GC and concern for complement deficiency, he was referred to Adult Immunology clinic.

Discussion: DGI is estimated to occur in up to 3 percent of patients infected with N. gonorrhoeae. The probability that a localized gonococcal infection will spread to joints and other tissues depends upon specific host, microbial, and possibly immune factors.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

RPNG is unusual presentation, the immunopathogenesis is uncertain but immunological and hypersensitivity damage is postulated based on the frequent lack of N. gonorrhoeae growth from blood, skin, and synovial fluid cultures during disseminated infection. Congenital or acquired complement deficiencies (C5, C6, C7, or C8) predispose to DGI as a result of decreased complement-mediated killing of N. gonorrhoeae.

PO1491
Proliferative Glomerulonephritis with Monoclonal IgM Deposits in ANCA Vasculitis
Rama Kethninen, Marc Barry, Monica P. Revelo Penafiel, Janame J. Kottey, Niraj K. Yadav, Josephine Abraham. University of Utah Health, Salt Lake City, UT.

Introduction: Proliferative glomerulonephritis with monoclonal immunoglobulin deposition (PGNMID) is a rare entity of unclear etiology that can be occasionally associated with an underlying hematological malignancy. We report a case of PGNMID in a patient with ANCA vasculitis.

Case Description: A 78 yr old female with hypertension presented with a history of recurrent sinusitis over 6 months that was treated with steroids and antibiotics. She had progressive weight loss, fatigue, cough, and dyspnea. Chest X-ray was normal prompting a CT chest, which showed bilateral pulmonary nodules. Her creatinine was 0.96mg/dL. Urine analysis was notable for hematuria. Antineutrophil cytoplasmic antibodies were positive at 1: 640 with myeloperoxidase Abs IgG of 199. Serum protein electrophoresis showed a normal pattern with no monoclonal spike on immunofixation electrophoresis. Her Kappa/Lambda light chain ratio was normal at 1.04, infections were ruled out, and cryoglobulin was not detected. She was started on prednisone 60 mg and had a renal biopsy. Renal biopsy showed focal segmental necrotizing glomerular lesions, mesangial hypercellularity with deposition of IgM with lambda light chains restriction on immunofluorescence and occasional mesangial and subendothelial granular electron densities on electron microscopy. She was referred to hematology for concern with monoclonal gammopathy of renal significance and had a negative evaluation on serological tests, bone marrow biopsy and PET CT scan. She was treated with Rituximab. Her creatinine had remained stable with resolution of hematuria and respiratory symptoms.

Discussion: PGNMID is an immune complex glomerulonephritis that is occasionally associated with a hematological malignancy. The pathophysiology remains elusive and treatment can be challenging. We present a case of ANCA vasculitis with monoclonal IgM with light lambda chain restriction with an unusual association with ANCA vasculitis.
severe interstitial fibrosis and tubular atrophy indicating MPA. Patient was treated with pulse steroid and plasma pheresis initially, later received Rituximab. Patient improved clinically with therapy. Later, serum creatinine plateaued around 3.6 with eGFR 15.6 indicating patient’s CKD had progressed to advanced CKD stage 4/5.

Discussion: Though the presence of AAV is not common in MCTD, this case illustrates the importance of considering AAV for worsening pulmonary and renal function in overlap syndrome. Microscopic polyangiitis is one of the most common cause of pulmonary-renal syndrome, often manifested as diffuse alveolar hemorrhage and RPGN. Prompt diagnosis and early intervention can dramatically improve the patient outcome.

PO1493
Nephrotic Range Proteinuria due to ANCA-Associated Vasculitis in a Diffuse Systemic Sclerosis Patient: A Rare Presentation
Pranav Sharma, Steve I. Khalil, Jonathan Lebowitz. Rutgers University New Brunswick, New Brunswick, NJ.

Introduction: Scleroderma renal crisis (SRC) is a severe complication of SSC and typically presents with new-onset hypertension and a reduction in renal functioning. Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a rare co-occurrence with SSC. We present a rare case of diffuse systemic sclerosis who presented with features of SRC and AAV with nephrotic range proteinuria without significant renal failure.

Case Description: The patient is a 32-year old woman with diffuse systemic sclerosis complicated by pulmonary fibrosis who had been treated with Mycophenolate mofetil but she discontinued treatment in order to conceive. She reports having an uncomplicated pregnancy without proteinuria or hypertension, but she delivered 7 weeks early. After delivery, she began experiencing weakness of her lower extremities and was diagnosed with myasthenia gravis. She had been treated with intravenous immunoglobulin with partial response and received rituximab with full recovery. Several months later, she developed proteinuria and nephrotic range proteinuria. She was started on mycophenolate mofetil and azathioprine. After 6 months of treatment, she was on the waiting list for a renal transplant. She received a kidney from a deceased donor who developed glomerulonephritis secondary to G-CSF treatment.

Discussion: Clinicians should remain vigilant for concomitant autoimmune disorders in patients with scleroderma. In the background of systemic sclerosis, our patient developed AAV with neurologic and renal manifestations. Thus, renal injury, proteinuria or rapid onset of hypertension should not be assumed to be due to scleroderma renal crisis, particularly when there is nephrotic range proteinuria or an active urine sediment.

PO1494
Filgrastim-Induced ANCA-Associated Glomerulonephritis in the Presence of Membranous “Full House Nephropathy”
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Introduction: G-CSF is commonly used to stimulate progenitor cell collection for bone marrow transplantation. We present a seemingly healthy altruistic bone marrow donor who developed glomerulonephritis secondary to G-CSF treatment.

Case Description: A 34-year old man presented after altruistic bone marrow donation. During G-CSF treatment he developed headache, epistaxis, painless macrohematuria and AKI (creatinine -2.91mg/dL). Seven years and one year prior to this event he had similar presentations of macrohematuria, AKI and proteinuria. In between episodes he had persistent microhematuria. At this admission, Myeloperoxidase antibodies (MPO) were found to be elevated to 97 IU/ml. all other serologies were unremarkable. A kidney biopsy revealed glomerular inflammatory crescents (Figure 1). Capillary loop “spikes” were seen on silver staining (Figure 2). On immunofluorescence, there was a “full house” granular pattern. PL2AR and IgG4 stains were negative. Electron Microscopy revealed mainly subepithelial electron dense deposits. His current creatinine, without immunosupression, is 1.19 mg/dL.

Discussion: G-CSF induced ANCA associated glomerulonephritis developed on top of silent membranous “full house nephropathy”. Bone marrow donors should be asked about prior glomerulopathies and screened for proteinuria and hematuria before bone marrow donation is authorized.

PO1495
Ivermectin-Induced ANCA Vasculitis
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Introduction: Ivermectin is an antiparasitic agent that has demonstrated antiviral potential against HIV1, Dengue, Zika viruses and most recently, COVID-19. But the use of self-medication and off-label use for COVID prophylaxis in some countries is cause for concern. Here, we present what may be the first reported case of ANCA- associated vasculitis (AAV) from Ivermectin use.

Case Description: A 56-year male with no significant past medical history presented with dark urine, epistaxis, conjunctival redness, arthralgias, and malaise. His mother was on dialysis for the past few years for ESRD of unknown etiology. For several months, he had been taking Ivermectin imported from Peru for COVID prophylaxis per family advice. He was on no other medications. His creatinine, normal at baseline, was now 4.5mg/dL. He had hematuria, 3g/d proteinuria, dysmorphic RBCs and RBC casts. Serum C3, C4, ANA, anti-dsDNA, anti-GBM, hepatitis B&C screen, SPER&LUPE were negative. Atypical and p-ANCA were negative, but c-ANCA was 1:640. Kidney biopsy revealed pauci-immune necrotizing crescentic glomerulonephritis. He soon developed pulmonary hemorrhages. Ivermectin was discontinued. He received prednisone 1mg/kg, 3 biweekly doses of intravenous cyclophosphamide, 10 doses of plasmapheresis, and was initiated on dialysis. Four weeks later, he has no epistaxis or pulmonary hemorrhages and is off oxygen. He does remain dialysis-dependent. Drug exposure can trigger ANCA formation against myeloperoxidase(MPO) and, less commonly, proteinase 3(P33). Drug-associated AAV can’t be discerned from primary AAV based on clinical and pathological findings. Clues suggesting drug-associated AAV include a temporal relationship of symptom onset with suspected drug, a high ANCA titer, and positive autoantibodies like elastase and lactoferrin. Drug-associated AAV has a better prognosis than its primary counterpart, with symptoms often resolving with drug withdrawal. Though this may not suffice in cases with pulmonary and renal involvement, outcomes in drug-associated AAV remain comparable even with shorter induction and often no maintenance regimens. Commonly implicated drugs are hydralazine, levamisole-contaminated cocaine, propylthiouracil, allopurinol.

PO1496
Presence of Membranous “Full House Nephropathy”
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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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Although no case of Ivermectin-induced AAV has been reported, we recommend a high index of suspicion as prompt cessation of the offending drug can significantly improve prognosis in drug-associated AAV.

**PO1496**

Myeloperoxidase-ANCA and Takayasu Arteritis Overlap Syndrome Presenting as Rapidly Progressive Glomerulonephritis


Introduction: The spectrum of vasculitides is classified according to the size of the vessels involved and the clinical and histopathological findings. The simultaneous involvement of Takayasu arteritis and myeloperoxidase-ANCA vasculitis is extremely rare.

Case Description: A 12-year-old female with no previous medical history. In the last three years the patient developed lower limb claudication and unexplained intermittent fever. In recent weeks she developed edema and oliguria, she was admitted in another hospital where she was started on renal replacement therapy. Large vessel involvement was suspected so a contrast enhanced CT was ordered and was compatible with Takayasu arteritis. The patient was referred to our hospital for evaluation. During nephrology assessment she was found to have acute kidney disease with massive proteinuria (16 g/dL), so work up was directed towards rapidly progressive kidney disease. Percutaneous kidney biopsy was performed, and it revealed pauci-immune crescentic glomerulonephritis. ANCA and glomerular basement membrane antibodies were ordered, with a positive MPO-ANCA result. She was then started on IV methylprednisolone pulses and 5 cycles of plasma exchange therapy. After this, rituximab was started on a weekly basis. The biopsy was performed, and it revealed pauci-immune crescentic glomerulonephritis.

Discussion: This an extremely rare case which highlights the diagnostic and therapeutic difficulties in patients presenting with overlap clinical and serological features of different forms of systemic vasculitis.

**PO1497**

Granulocyte Colony Stimulating Factor-Associated Vasculitis: Adding Fuel to the Fire

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Introduction: Granulocyte colony-stimulating factor (G-CSF) is commonly used with chemotherapy to stimulate bone marrow production and prevent neutropenia. Although usually well tolerated, G-CSF can exacerbate underlying autoimmune diseases with the development or progression of glomerulonephritis (GN). We present a case of pauci-immune necrotizing GN that developed in a patient with rheumatoid arthritis (RA) after receiving G-CSF therapy.

Case Description: A 61 y/o man with ampullary adenocarcinoma and RA without prior renal involvement presented with AKI. One week prior to admission he had received G-CSF therapy. His creatinine (Cr) was 4.8 mg/dL from a baseline of 0.9 mg/dL. His urinalysis was notable for hematuria and urine protein-creatinine ratio (UPC) of 5.2 g/wk. Workup showed: +p-ANCA (1:320), + anti-histone Ab, + SSA and + ANA (1:1280 speckled pattern). A renal biopsy revealed necrotizing GN with crescents or crescents in 75% of the glomeruli. There was no evidence of immune deposits/c pauci-immune GN. He received steroids and rituximab for induction. His Cr peaked at 6.0 mg/dl but improved down to 1.1 and UPC improved to 0.6 g/wk after 3 months.

Discussion: G-CSF is used to prevent neutropenia and reduce infection risk by activating mature neutrophils and preventing neutrophil apoptosis. G-CSF can also have inflammatory effects including the release of proinflammatory cytokines and tissue infiltration by activated neutrophils with the potential of end-organ damage. In patients with preexisting GN or an autoimmune disease (e.g. RA, SLE), G-CSF administration can exacerbate or even initiate a de-novo GN. Pauci-immune GN is a rare but well established complication of RA. In our case, the almost immediate temporal relationship between the development of the GN and the G-CSF administration supports G-CSF as etiologic. This case demonstrates the importance of considering the possible renal complications and need for close monitoring while giving G-CSF in patients with autoimmune diseases.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

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POI1500

Pemphigus Vulgaris and PLA2R-Associated Membranous Nephropathy: Two IgG4-Related Diseases in the Same Patient
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Introduction: The relationship between bullous skin diseases and glomerulopathies has been increasingly recognized. Other bullous diseases were previously reported in association with membranous nephropathy (MN), but the association between pemphigus vulgaris (PV) and MN has not been reported in the literature yet.

Case Description: A 39-years-old smoker woman presented with trunk blisters and worsened mouth ulcers after stopping the treatment for MN. One year before, she had nephrotic syndrome and the kidney biopsy was positive for anti-PLA2R and IgG4 (and negative for THSD7A) in the immunohistochemistry (IHQ). Serum anti-PLA2R was negative. Four months earlier she was started on cyclopentone, but stopped it due to mouth ulcers. She had nephrotic range proteinuria, no edema, when the painful blisters spread out on the trunk, back, limbs, scalp as well as ulcers in the oral cavity and esophagus. The diagnosis of PV was confirmed by skin and esophagus biopsy and IHQ showed the presence of IgG4 subclass antibody in the epithelial tissue. She received pulse and oral steroids along with azathioprine for the PV. The skin lesions were slowly healing and no more new blisters have appeared.

Discussion: The humoral auto-immune response in pemphigus produces anti-desmoglein 1 and 3, both IgG4. Desmogleins are responsible for adhesion in stratified squamous epithelia, when damaged produces to the blistering eruptions. There is a genetic predisposition between PV and MN, with HLA-DQA1, HLA-DRB1 and the thrombospondin gene (THSD7A). Environmental factors such as smoking and air pollution could act as a second trigger for the development of auto-immune diseases. PLA2R can be expressed in the bronchiolar tissue and in macrophages of the lung, however there is no evidence of histological damage in the pulmonary tissue. Although we found no description on the expression of PLA2R in the skin, in an attempt to find a common antigen for both diseases, we did search for anti-PLA2R in the skin, but it was negative. In conclusion, this is the first described case of association of pemphigus vulgaris and PLA2R-associated MN, both IgG4-related conditions that involve the production of different autoantibodies directed to skin and kidney antigens.

POI1501

A Case of an Elderly Woman with Membranous-Like Glomerulopathy with Masked Monoclonal IgG Deposits Whose Renal Biopsy Revealed Renal Cell Carcinoma

Introduction: Membranous-like glomerulopathy with masked monoclonal IgG deposits (MGIMD) is a recently described form of glomerulopathy with a unique histopathology reported by Larsen et al. The pattern is characterized by subepithelial and/or supramembranous deposits that are “masked,” to immunoglobulin staining by routine immunofluorescence but strongly stained for IgG and kappa light chain after protease digestion. Patients with MGIMD are commonly young females and have a vague history of autoimmune diseases such as low titer antinuclear antibodies.

Case Description: A 65-year-old woman was referred to our hospital with urinary protein (0.80 g/gCr) and microscopic hematuria. Serum antinuclear antibody, rheumatoid factor, and M-protein were negative and serum C3 and C4 were normal. Plain CT showed no evidence of hepatic and ymphatic systems. Image 1 shows giant cells on PAS. She was started on prednisone 40 mg daily and azathioprine for PV. The skin lesions were slowly healing and no more new blisters have appeared.

Discussion: The humoral auto-immune response in pemphigus produces anti-desmoglein 1 and 3, both IgG4. Desmogleins are responsible for adhesion in stratified squamous epithelia, when damaged produces to the blistering eruptions. There is a genetic predisposition between PV and MN, with HLA-DQA1, HLA-DRB1 and the thrombospondin gene (THSD7A). Environmental factors such as smoking and air pollution could act as a second trigger for the development of auto-immune diseases. PLA2R can be expressed in the bronchiolar tissue and in macrophages of the lung, however there is no evidence of histological damage in the pulmonary tissue. Although we found no description on the expression of PLA2R in the skin, in an attempt to find a common antigen for both diseases, we did search for anti-PLA2R in the skin, but it was negative. In conclusion, this is the first described case of association of pemphigus vulgaris and PLA2R-associated MN, both IgG4-related conditions that involve the production of different autoantibodies directed to skin and kidney antigens.

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polycyclonal increase in gamma globulins. It is likely that in some patients with lupus, B cell regulation becomes impaired in a way that allows a clonal, but not necessarily neoplastic, an expansion that results in increased production of paraproteins, leading to MGUS. This case adds to the literature showing that there indeed may be an association between MGUS and lupus.

**PO1504**

**Bartonella Henselae Infective Endocarditis (BHEIE): A Rare Cause of Pauci-Immune Necrotizing GN (PINGN)**

**Muhammad A. Shahzad, Aji Purohit, Stephen M. Korbet. Rush University Medical Center, Chicago, IL.**

**Introduction:** Bartonella is the commonest cause of culture negative endocarditis. While, infection Related GN (IRGN) can mimic pauci-immune vasculitis, the majority of cases of BHE have been immune complex (IC) mediated. We present a case of BHE related PINGN. Timely recognition of this atypical presentation led to appropriate medical therapy.

**Case Description:** A 33 yo M with HIV on HAART and recent tooth extraction was admitted with a severe headache due to a sub arachnoid hemorrhage from a ruptured right anterior cerebral artery mycotic aneurysm. TEE showed a vegetation on the aortic valve (AV). Blood cultures were negative. Initial SCR was 3.3 mg/dl and urinalysis had 2+ protein, 3+ blood with 29 RBC/hpf and a UPro/Cr ratio was 1.7 g/g. The C4 was low (10.2 mg/dL) and PR3-ANCA elevated-4.0 (NL <3 .5 U/mL). The Bartonella henselae IgG titre was elevated 1.56 (NL <1.320). Renal biopsy revealed pauci-immune necrotizing GN (Figure) with no evidence of IC deposition. BHE associated PINGN was diagnosed and treatment with doxycycline, ceftriaxone and gentamicin initiated. The AV was replaced and was positive for BH by PCR. After a prolonged course of antibiotics the SCR improved to 2.5 mg/dl.

**Discussion:** B henselae associated GN is a rare cause of PR3-ANCA positive GN with only 6 cases previously reported. By immunofluorescence, 4 cases were immune complex deposition involving glomeruli, and arteries. Mass spectrometry performed at Mayo Clinic Laboratories confirmed renal involvement by Amyloidosis, AA (serum amyloid A Abs, meeting criteria for DM. Patient continued eculizumab. Within 7d, LDH decreased to 772, haptoglobin increased to 79 and platelets normalized. Further workup revealed elevated creatine kinase 1,271 U/L, aldolase 17 U/L, AST 566 U/L with normal ALT and positive anti-MDA5 and transcription intermediary factor-1-gamma (TIF-1-γ) Abs, meeting criteria for DM. Patient continued eculizumab and prednisone. Eventually developed invasive aspergillosis and expired.

**Discussion:** We report a case of STE-DM overlap with anti-MDA5 and TIF-1γ Abs complicated by aHUS and severe hypocalcemia in the setting of pancreatitis. The cutaneous manifestations and typical of MDA5-associated DM. Due to the risk of developing intestital lung disease, exemplifying range of variation from case to case. The presence of anti-TIF-1γ confers a 6-fold increased malignancy risk; finding of omental nodularity in this case would warrant further investigation. aHUS as a complication of SLE-DM overlap is rare, with mortality risk up to 52%. AKI, infection and low C3 are associated with highest mortality. Prompt diagnosis, high clinical suspicion and early initiation of eculizumab resulted in a rapid response.

**PO1506**

**Anti-LRP2 Nephropathy in a Patient with Chronic Lymphocytic Leukemia**

**Derek Tran, Chien-Wen Yang, Avantika Israni, Abdollah Sassine Garea, Al J. Lee, St Mary Medical Center, Longhorne, PA; Penn Medicine, Philadelphia, PA.**

**Introduction:** Anti-LRP2/anti-Brush Border nephropathy is a newly identified autoimmune tubulo-interstitial nephritis triggered by circulating antibodies to low-density lipoprotein receptor-related lipoprotein 2 (LRP2). We present a case of anti-LRP2 nephropathy in a patient with chronic lymphocytic leukemia (CLL).

**Case Description:** A 74-year-old Caucasian male patient known to have CLL presented following a fall with a forearm laceration. At presentation, he had acute renal failure (Scr of 5.04 mg/dL) and severe thrombocytopenia (platelets of 11,000/uL).

**Additional Evaluation showed positive ANA and p-ANCA. The patient had proteinuria of 1754 mg/g creatinine. The kidney biopsy showed moderate interstitial fibrosis and tubular atrophy involving 30-40% of the renal cortex. The tubular epithelium showed reactive-appearing nuclei as well as cytoplasmic thinning with loss of the proximal tubular brush border. Immunofluorescence showed IgG (3+ and C3 (3+)) for the glomerular capillary and the TBM. There was focal staining of the brush borders by IgG with positive LRP2 stain in the TBM. Electron microscopy revealed numerous subepithelial electron-dense deposits. The serum anti-LRP2 antibody titer was 1:100. The patient was started on dexamethasone and rituximab with improvement of the thrombocytopenia. Plasmaphenesis was prescribed for 5 sessions, the creatinine continued to worsen (Scr of 7.37 mg/dL), and the anti-LRP2 titer did not improve. The patient is being transitioned to renal replacement therapy.

**Discussion:** The mechanism that links the ABBA disease with lymphoproliferative disease is still unknown. The current reported cases suggest an association between direct lymphoma renal infiltration, progression of the lymphoproliferative disease and the presence of the ABBA disease. However, in our reported case, the patient’s underlying CLL was stable without evidence of renal infiltration. The poor response to treatment in this case is consistent with the poor outcomes of many anti-LRP2 reported cases. The renal biopsy on this patient also showed membranous glomerulonephritis. We presented a case with anti-LRP2 nephropathy/ABBA disease with concurrent CLL without evidence of CLL infiltration which is typical of poorly to immune responsive therapy and the prognosis of ABBA associated paraneoplastic syndrome with underlying CLL warrants future investigation.

**PO1507**

**Black Tar Heroin and AA Amyloidosis**

**Rama Kethineni, Monique E. Cho, Monica P. Revelo Penafiel, Olesya Ilkun, Janame J. Kottee, Niraj K. Yadav, Josephine Abraham. University of Utah Health, Salt Lake City, UT.**

**Introduction:** AA amyloidosis due to deposition of serum amyloid A protein occurs as a secondary reaction to chronic inflammatory disease, chronic infections, and familial period fever syndromes. We present a case of AA amyloidosis secondary to chronic black tar heroin use in the Intermountain West.

**Case Description:** A 61 yr. old Caucasian female with a history of Hepatitis C, IV Heroin use presented with bilateral leg pain, swelling, and abdominal distension. Examination was significant for ulceration in lower extremities with purulent discharges. Nebulized lab data include Hemoglobin of 8.2 g/dl, potassium of 10.6 mg/dl, BUN of 90 mg/dl, creatinine of 2.9 mg/dl, serum albumin of 2.1 g/dl, and ESR of 129 mm/hour. She had a urine protein to creatinine ratio of 12.3 g/g. Abdominal US revealed enlarged liver and normal renal echogenicity. The quantification of HCV RNA by polymerase chain reaction was negative, and her complement levels were within normal range. Cryoglobulin was also negative with a kappa/lambda light chain ratio of 1.33. Serum protein electrophoresis showed decreased albumin and immuno fixation electrophoresis showed a faint band in IgG kappa suggestive of a specific immune response. A TBM was obtained and showed non-AL amyloid deposition involving glomeruli, and arterries. Mass spectrometry performed at Mayo Clinic Laboratories confirmed renal involvement by Amyloidosis, AA (serum amyloid A)-type.

**Discussion:** “Black tar heroin” has increasingly been identified as a risk factor for AA Amyloidosis. Impurities in heroin promote vascular sclerosis and lead to the use of injection into muscle and skin. The suppurative infections that follow stimulate
the production of serum amyloid A protein with subsequent deposition in the kidney leading to nephritic syndrome and end stage kidney disease. Greater awareness of this complication may help prevention in areas with increased black tar heroin use. leading to nephrotic syndrome and end stage kidney disease. Greater awareness of this complication may help prevention in areas with increased black tar heroin use.

**Discussion:** Proteinuria is one of the lesser known side effects of statin therapy. It was not well described in the clinical development programme for Rosuvastatin, where it was found that the 80 mg dose caused proteinuria in 12% of patients. Furthermore, a comprehensive review of the renal effects of rosuvastatin, found that 1.2% of patients taking 40 mg of rosuvastatin developed 2+ proteinuria, and 0.3% developed 2+ proteinuria and 1+ hematuria. Our case highlights a rare manifestation of Rosuvastatin induced urinary abnormalities, which improve after stopping the drug. This should be kept in mind for patients on Rosuvastatin with negative workup for proteinuria and hematuria, before a renal biopsy is pursued.

**PO1510**

Rituximab for Membranous Nephropathy in a Patient with Sjögren Syndrome and Mixed-Connective Tissue Disease

**Joshua D. Pollock,** Maurice I. Khayat. Madigan Army Medical Center, Tacoma, WA.

**Introduction:** Membranous nephropathy (MN), a cause of nephrotic syndrome, is characterized by the deposition of immune complexes in the glomerular basement membrane with resultant subepithelial “spikes” visualized under light microscopy. Although often a primary disease process, several secondary etiologies exist, including Sjögren’s syndrome (SS) and mixed-connective tissue disease (MCTD). Treatment typically targets the underlying condition. Despite rituximab’s demonstrated efficacy in MN, MCTD and SS, case reports for specific treatment of MN secondary to these conditions have primarily described regimens of systemic corticosteroids with or without cyclophamide.

**Case Description:** A 54-year-old male was diagnosed with MN on renal biopsy in 2001. Multiple features suggested a secondary etiology (tubulointerstitial, mild to moderate proteinuria, negative ANCA, and circulating cryoglobulins). Rituximab 1000 mg on day 1 and 0 was administered, with partial remission noted 4 months following therapy. Complete remission was achieved 8 months following therapy and has been sustained for 13 months. His extrarenal symptoms of MCTD and SS have also resolved.

**Discussion:** Rituximab is a well-described treatment for primary MN, MCTD and SS. However, there is a paucity of literature evaluating its use in MN as the specific renal manifestation of MCTD and SS. This case illustrates the potential role for rituximab as an effective treatment for membranous nephropathy secondary to SS and MCTD when deciding on immunomodulatory therapy. The views expressed in this abstract are those of the authors and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense (DoD), or the U.S. Government.

**PO1511**

A Rare Case of Concurrent Glomerulonephritis and Autoimmunity


**Introduction:** We report a rare case of necrotizing and crescentic glomerulonephritis in the setting of Streptococcus mitis bacteremia.

**Case Description:** A sixty-one year old man with a history of hypertension, hyperlipidemia, and non-insulin-dependent diabetes presented to the emergency room with progressive lower extremity edema and dyspnea with tea-colored frothy urine. Hyperlipidemia, and non-insulin-dependent diabetes presented to the emergency room with progressive lower extremity edema and dyspnea with tea-colored frothy urine. Initial workup revealed bilateral pulmonary edema and acute kidney injury with a serum creatinine of 1.84 mg/dL (0.8 mg/dL 6 months prior) with 9.18 grams proteinuria and an active urine sediment. He was initially diuresed for decompensated heart failure but further workup revealed hypocomplementemia and positive ANCA/antineutrophil cytoplasmic antibody (PANCA/ANCA). A kidney biopsy revealed membranous glomerulonephritis (MGN) with focal endocapillary proliferative features and focal crescents with fibrinoid necrosis with positive PLAX2 immunostaining and serum PLAX2 IgG antibody testing revealing a titer of 1:2560. An echocardiogram revealed reduced left ventricular ejection fraction with a new aortic valve vegetation. Blood cultures obtained on admission ultimately grew Streptococcus mitis and he underwent aortic valve repair. Despite completion of a full antibiotic course, his creatinine remained impaired with nephrotic-range proteinuria and elevated serum PLAX2 titers. Repeat renal biopsy revealed membranous glomerulonephritis and he was started on immunosuppression with treatment of PLAX2-associated MGN.

**Discussion:** Peri-infectious PLAX2-associated MGN and ANCA-associated glomerulonephritis appears to be a rare. While its pluriactive ANCA-mediated glomerulonephritis was likely related to the infectious endocarditis, the relationship to the PLAX2-positive MGN remains unclear. We hypothesize that host immune response to infectious agents lead to an autoimmune process resulting in glomerulonephritis. It is possible that in addition to a genetic predisposition (“first hit”), a “second hit” which begins with activation of the innate immune response by an infectious agent leading to autoimmunity through various mechanisms including defective immune regulation, molecular mimicry, epitope spreading, and autoantigen complementarity.

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Introduction: Deficiencies in the classical complement pathway have been associated with the development of systemic lupus erythematosus (SLE) and lupus-like disease in 10-20% of affected patients. In fact, SLE patients deficient in classical complement present at an earlier age, with severe manifestations and a worse prognosis. Several mechanisms have been described to explain these immune phenomena including impaired clearance of immune complexes, impaired handling of apoptotic cells, or changes in regulation of cytokines. Here, we present a case of a young female with ANA-negative lupus presenting with dyspnea and acute renal failure responsive to immunosuppressive therapy found to have C2 Complement deficiency.

Case Description: A 44-year-old female with sickle cell trait, ANA-negative SLE, ESRD due to biopsy-proven class IV lupus nephritis briefly requiring HD, pulmonary HTN, presented with signs of fluid overload, acute on chronic renal failure in the setting of malignant hypertension. Labs revealed thrombocytopenia of 52 with a creatinine of 2.66 (prior 1.61), hypocoomplementemia and undetectable CH50 levels concerning for acute flare of SLE and an underlying functional complement deficiency. Low C3 and C4 were confirmed. Peripheral smear with schistocytes raised concerns for microangiopathy. Hospital course was complicated by encephalopathy and possible CNS involvement of lupus. Renal biopsy confirmed chronic sclerosing immune complex glomerulonephritis with minimal activity. The patient responded well to high dose corticosteroids, plasma exchange and mycophenolate mofetil. Final serology confirmed persistent C2 complement deficiency.

Discussion: There is a well-studied link between immune-complex mediated disease and complement deficiency. Of these, C2 deficiency is the most common. In our case, a C2 deficiency was found in the setting of ANA-negative SLE with severe clinical manifestations. Our case raises the question of whether testing to exclude underlying complement deficiency is particularly indicated in patients with ANA-negative SLE. It also remains to be seen whether clinical manifestations of microangiopathy are prevalent in these patients, and whether therapeutics targeting complement may be effective in their treatment.

PO1515

Hydralazine-Induced ANCA Vasculitis and Lupus Nephritis

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Introduction: Hydralazine is a common antihypertensive drug, but drug induced glomerulonephritis (DI-GN) is observed in 5-10% of the population on hydralazine after three years of therapy. We present a case of rapidly progressive glomerulonephritis due to hydralazine.

Case Description: 65-year-old female with a history of hypertension, diabetes mellitus, and chronic kidney disease presented for altered mental status. Her serum creatinine (SCr) three months and two years prior were 2.3 mg/dL and 0.9 mg/dL respectively. On presentation, her SCr was 12.7 mg/dL, and she was started on hemodialysis. During her hospitalization, she had persistent hemoptysis with worsening dyspnea, skin rash, HTN, and acute renal failure. Kidney biopsies were performed, which revealed lupus nephritis, low complement levels, negative histone antibody and ANCA titers, and negative double stranded DNA antibody (Table 1). Skin biopsy showed small and medium vessel vasculitis. Kidney biopsy revealed class 5 lupus nephritis with full house immunofluorescence staining and active cellular crescents (Fig 3). Review of her medications included hydralazine 25 mg three times a day for three years, and she was diagnosed with hydralazine induced glomerulonephritis and systemic vasculitis. She was given pulse steroids and cyclophosphamide with improvement in extrarenal manifestations, but no renal recovery.

PO1514

Postinfectious Glomerulonephritis Complicated by Complement-Positive Coombs Autoimmune Hemolytic Anemia

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Introduction: Postinfectious glomerulonephritis (PIGN) is the most common cause of GN in children. Mild normocytic anemia is often noted during the acute illness and is usually thought to be secondary to hemolysis from fluid overload and/or depressed erythrocyte production. Here, we describe a case of PIGN and autoimmune hemolytic anemia in a pediatric patient.

Case Description: A 3-year-old girl presented with 5 days of gross hematuria, fatigue, and decreased urination. Laboratory evaluation revealed elevated potassium at 5.4 mmol/L (normal range 3.6-5.2 mmol/L), creatinine 3.04 mg/dL (0.19-0.49 mg/dL), and blood urea nitrogen 98 mg/dL (7-20 mg/dL), low hemoglobin (Hb) 8.4 g/dL (11.4-14.3 g/dL) and normal platelet count. Urinalysis showed numerous red blood cells (RBCs) and nphoretic range proteinuria. Bilirubin, lactic dehydrogenase, and haptoglobin were normal. Direct antiglobulin test (DAT) was positive for monospecific C3, and negative for IgG. Peripheral blood smear revealed mild RBC polychromasia and occasional hemolysis and Poikilocytosis. Several hours after admission, her Hb dropped acutely to 6.3 g/dL requiring blood transfusion. Complement proteins C3 and C4 were low at <6 mg/dL (75-175 mg/dL) and 5 mg/dL (14.40 mg/dL), respectively. DNase-B Antibody was normal and dsDNA antibody was negative. A kidney biopsy revealed findings consistent with PIGN (Image 1). She received acute hemodialysis for the first 48 hours after admission for worsening hyperkalemia, uremia, anemia, and edema. Her Hb remained stable and did not require additional blood transfusions.

Discussion: Our case of concurrent PIGN and autoimmune hemolytic anemia is exceptionally rare. This unique association may explain the anemia that is often seen in PIGN. We suggest that PIGN cases with anemia should have a DAT performed.
PO1516

Chicken or the Egg Causality Dilemma: Primary ANCA Vasculitis Complicated by Infective Endocarditis (IE) vs. IE Leading to ANCA Vasculitis

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Introduction: As the cases of infective endocarditis increase in the United States it is important to recognize the associated complications. Glomerulonephritis is a well-recognized but not fully understood consequence. Immune complex deposition is the most common etiology but ANCA-mediated kidney injury is increasingly described and even less understood.

Case Description: A 65 year old male presented with acute onset dysarthria, left facial droop, left sided weakness, and dizziness. 5 months prior he was diagnosed with PR3+ ANCA vasculitis after presenting with 18 lbs weight loss, purpura, anemia, hematuria and sub nephrotic proteinuria. He was treated with methotrexate and a steroid taper, which finished one week prior to the current presentation. Admission vitals were: 145/74 mmHg, heart rate of 90 bpm, afibrile, and 100% oxygen saturation on room air. Lab work revealed: hemoglobin of 10.7 K/uL, creatinine of 1.17 mg/dl (baseline 0.9), low C3: 81 mg/dL, positive PR3 (>8.0), negative c-ANCA (1:128), negative MPO and p-ANCA, and UA: 3+ blood, negative protein, and 11-20 WBC. MRIs of the brain and heart revealed numerous acute and subacute infarcts and severe mitral regurgitation respectively, concerning for small vessel vasculitis, and he was started on high dose steroids. Discovery of streptococcus mutans bacteremia was a surprise. Suspicion was raised that the ANCA vasculitis may have been a consequence of underlying sub-acute endocarditis rather than a primary disease hence a kidney biopsy was planned and he was discharged on steroids and IV antibiotics. Kidney biopsy confirmed the diagnosis of ANCA-mediated endocarditis-associated glomerulonephritis with the presence of glomerulosclerosis with fibrocellular/fibrous crescents, segmental fibrinoid necrosis but no obvious immune deposits on light microscopy. Granular deposits in the mesangial and capillary wall stained for C3, IgM, IgA, kappa and lambda. He underwent 6 weeks of ceftriaxone and mitral valve replacement. His renal function is mildly impaired; he is recovering neurologically.

Discussion: Endocarditis-associated GN typically requires treatment of the underlying infection without immunosuppression, but when the injury is primarily ANCA-mediated, this presents a unique challenge in that end-organ damage from vasculitis may not improve without immunosuppression.

PO1517

Crescentic Glomerulonephritis in Sjögren Syndrome

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Introduction: Sjögren’s syndrome (SS) is an inflammatory autoimmune disorder involving the parotid, lacrimal and salivary glands causing sicca syndrome. Kidney involvement is variable and most often results in tubulointerstitial nephritis. Glomerular disease is infrequent with MPGN and membranous nephropathy being most prevalent pathologically.

Case Description: Patient is a 21 year old female with SS, hypothyroidism and asthma who was being evaluated for fever and fatigue. Lab evaluation revealed acute kidney injury (AKI) with creatinine rising from 1.0 to 1.8 mg/dL over several weeks. Echocardiogram was concerning for mobile echodensity at the tricuspid valve, but transesophageal echo showed no abnormalities and evaluation for infection was negative. CT showed extensive prominent lymph nodes in the chest, abdomen, and pelvis but lymph node biopsy showed benign reactive hyperplasia without neoplasm. Renal ultrasound showed normal sized kidneys. Urima persuasive for the presence of granulomatous inflammation and sediment revealed dysmorphic RBCs. She was started on high dose prednisone and hydroxychloroquine for possible lupus nephritis but due to diagnostic uncertainty and unresolved AKI, kidney biopsy was performed.

Discussion: Kidney biopsy demonstrated plasma rich interstitial nephritis with severe tubulitis consistent with SS. Interestingly, the biopsy showed 3 active cellular crescents out of 21 glomeruli with focal crescentic GN. Tubulointerstitial nephritis is the most common renal pathology in primary SS leading to renal tubular acidosis, impaired concentrating ability and proximal tubule defects. GN in SS is rare but has been associated with membranoproliferative GN, membranous nephropathy and cryoglobulinemic GN. Crescentic GN was unexpected and the treatment plan was adapted to taper the prednisone, start on Mycophenolate Mofetil and trial on Rituximab.

Light microscopy for renal biopsy of Sjogren’s case depicting interstitial nephritis and crescentic glomeruli
**PO1519**

**Unmasking a Case of Membranous-Like Glomerulopathy with Masked IgG-κ Deposits**
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**Introduction:** Membranous-like glomerulopathy with masked IgG-κ deposits (MGMID) is a recently described, exceedingly uncommon entity of glomerular immune-complex deposition requiring antigen retrieval on formalin-fixed paraffin-embedded tissue. We report a rare case of MGMID in a young female with newly diagnosed APLA.

**Case Description:** An 18 year old female with no medical history presented with left leg swelling. Vital signs were normal and an enlarged, discolored left lower extremity was appreciated on exam. Initial laboratory results were remarkable for Cr 0.78 mg/dL, albumin 2.3 g/dL, platelets 128,000/µL, PTT 87.1 s, INR 1.02, and hematuria and foamy urine. Spot urine protein:creatinine ratio was 10 and albumin was 1.6 mg/dL. The creatinine had slowly risen over several months from 0.9 mg/dL to a plateau of 1.8. Serologic work-up was unrevealing; PLA2r, complements, hepatitis serologies, ANA, ANCA, A1C, SPEP, immunofixation, and free light chains were all normal. Renal biopsy demonstrated amorphous deposits throughout the glomeruli which stained positive for serum amyloid A (SAA) (figure 1). We found no systemic causes to explain secondary amyloidosis. This case demonstrates a possible association of secondary amyloidosis with HIV.

**Discussion:** Only a few case reports have described an association of secondary amyloidosis with HIV. SAA renal amyloidosis has been described in a patient who acquired HIV via intravenous drug use. It was unclear if it was related to the HIV disease or to chronic inflammation from skin infections due to needle use. Renal amyloidosis has also been occasionally described in South African patients with HIV and in non-human primates with HIV-like disease. Elevated levels of amyloid A protein have been found in AIDS patients, suggesting a possible pathogenetic linkage. More studies are needed in this area to determine if there is a causal relationship between the two disorders and what is the best approach for management.

**Figure 1: Pathology**

Positive SAA staining

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**PO1520**

**A Case of Secondary Renal Amyloidosis Associated with HIV**

**Introduction:** Secondary amyloidosis is known to be associated with multiple chronic infections and inflammatory conditions including rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, and tuberculosis. HIV has not yet been established as a known association. We present a case of secondary amyloidosis associated with well-controlled HIV with no history of other potential etiologies.

**Case Description:** A 71-year-old man with hypertension and well-controlled HIV for 40 years (viral load undetectable and last CD4 917) was referred to the renal clinic for acute kidney injury and heavy proteinuria. He had complained of leg swelling and foamy urine. Spot urine protein:creatinine ratio was 10 and albumin was 1.6 mg/dL. The creatinine had slowly risen over several months from 0.9 mg/dL to a plateau of 1.8. Serologic work-up was unrevealing; PLA2r, complements, hepatitis serologies, ANA, ANCA, A1C, SPEP, immunofixation, and free light chains were all normal. Renal biopsy demonstrated amorphous deposits throughout the glomeruli which stained positive for serum amyloid A (SAA) (figure 1). We found no systemic causes to explain secondary amyloidosis. This case demonstrates a possible association of secondary amyloidosis with HIV.

**Discussion:** Only a few case reports have described an association of secondary amyloidosis with HIV. SAA renal amyloidosis has been described in a patient who acquired HIV via intravenous drug use. It was unclear if it was related to the HIV disease or to chronic inflammation from skin infections due to needle use. Renal amyloidosis has also been occasionally described in South African patients with HIV and in non-human primates with HIV-like disease. Elevated levels of amyloid A protein have been found in AIDS patients, suggesting a possible pathogenetic linkage. More studies are needed in this area to determine if there is a causal relationship between the two disorders and what is the best approach for management.

**Figure 1: Pathology**

Positive SAA staining
PO1521
Renal Cell Carcinoma Presenting as Henoch-Schönlein Purpura with AKI and Leukocytoclastic Vasculitis in Adults
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Introduction: Henoch-Schönlein purpura (HSP) is a small vessel vasculitis characterized by IgA tissue deposition. HSP presenting in adults is often the result of an underlying malignancy.

Case Description: A 60-year-old man with history of HTN, CVA, DMII, recent COVID-19 infection, presented for 2 week history of petechiae on bilateral upper and lower extremities. Skin biopsy findings were compatible with leukocytoclastic vasculitis (LCV). Patient on admission was also found to have AKI with creatinine 2.1 mg/dl, microscopic hematuria, and sub-nephrotic range proteinuria with urine protein/creatinine ratio of 2.66 g/g. Kidney biopsy findings were consistent with IgA dominant glomerulonephritis. Given multi-system involvement, patient was diagnosed with Henoch-Schönlein Purpura. Given unusual presentation with extreme of age, there was concern for malignancy. CT scan chest abdomen pelvis was performed which revealed a solid and septated 8.3 cm exophytic mass on the superior pole of left kidney. A partial left nephrectomy was performed with pathology report consistent with clear cell renal carcinoma. Patient’s hematuria, proteinuria and skin rash resolved with surgical intervention. Creatinine remained stable in the 1.6-1.8 mg/dl range on discharge.

Discussion: Henoch-Schönlein purpura (HSP) is generally seen in the first decade of life. There have been a few cases of HSP presenting in adults due to underlying solid organ malignancies including renal cell carcinoma (RCC). Our case illustrates the importance of evaluating adults presenting with clinical findings of HSP for underlying malignancy. Treatment of underlying malignancy will improve vasculitis symptoms including renal parameters.

Exophytic and septated mass within superior pole of left kidney (Figure 1).

PO1522
A Case of Necrotizing Crescentic Glomerulonephritis due to ANCA Vasculitis and Fibrillary Glomerulonephritis
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Introduction: Fibrillary Glomerulonephritis is a rare disorder thought to be idiopathic in nature. Cases of fibrillary GN have been associated with malignancy, monoclonal gammopathy, autoimmune disease, or infection. We present a unique case of fibrillary GN with pauc-immune crescentic GN due to Myeloperoxidase antibody (MPO) vasculitis.

Case Description: A 77 year old lady with history of well controlled diabetes, hypertension, congenital deafness, presented with weakness, fatigue & weight loss for four weeks. She was noted to have severe anemia with Hemoglobin of 6.6 g/dl, and presumed acute kidney injury. Her labs on admission were remarkable for creatinine 2.5mg/dl (unclear baseline creatinine), eGFR 25ml/min, potassium 5.3, Bicarbonate 16, Sodium 128. Urinalysis showed large blood and 1+ protein. The serological workup was positive for P ANCA 1:640, C ANCA 1:640, MPO ab and negative for PR-3 ANA, SRFP. Free light chain ratio, HIV, Hepatitis panel. Endoscopy and Colonoscopy was negative for any obvious bleeding. Patient underwent renal biopsy which showed 7 out of 15 glomeruli with early fibrocellular crescents with fibrinoid necrosis, along with healing phase of necrotizing arteritis. Immunofluorescence didn’t show any preferential staining for immunoglobulin, kappa or lambda. Electron microscopy showed mesangial mild non branching randomly arrayed thick fibrils with no immune complex type deposits. EM findings were confirmed by positive DNAJ/B9 stain. Patient received treatment with pulse dose steroids, two doses of rituximab 1 gm 14 days apart and continued on prednisone for slow taper with good renal response. Due to the findings of Fibrillar GN addition workup for lymphoproliferative disorder was done Whole body CT scan was negative but flow cytometry testing still pending.

Discussion: We present a unique case of fibrillary GN and pauci-immune crescentic GN with positive MPO antibodies. The significance of fibrillary deposits in this setting is unclear and usually not seen with pauci-immune crescentic GN. Fibrillary GN is a very rare diagnosis mostly thought to be idiopathic in nature. This unique presentation of fibrillary GN with ANCA vasculitis questions the current pathogenesis fibrillary GN and overall renal prognosis in association with glomerular pathologies like ANCA vasculitis.

PO1523
An Unexpected Clue in the Urinary Space: The Overlap Between IgA Predominant Staphylococcus aureus-Associated Glomerulonephritis and IgA Nephropathy: A Case Report
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Introduction: There is significant histological overlap between IgA nephropathy (IgANP) and IgA predominant Staphylococcus-aureus associated glomerulonephritis (IgAASAAGN). [1] [1] Satoskar et al., “Staphylococcus Infection-Associated Glomerulonephritis Mimicking IgA Nephropathy,” November 2006.

Case Description: Kidney biopsy was performed in a 60 yo male for an unexpected decline in kidney function. IgAASAAGN was diagnosed on histology and foreign particles that were consistent with staphylococci were noted in the urinary space on electron microscopy. The patient was found to have methicillin-sensitive staphylococcus aureus (MSSA) pneumonia. Two months later, after a second decline in kidney function, IgANP was diagnosed on repeat kidney biopsy.

Discussion: This patient is diagnosed with two distinct conditions on pathology samples that show very similar histological findings. The presence of SA in the urinary space is a previously unreported finding. SA infection is known as the initiating factor for the development of IgAASAAGN. Recent studies have also suggested SA cell envelope antigens as a new candidate for the induction of IgANP and antigens have been colocalized with IgA deposits in the glomeruli of affected patients. [2] SA infection and IgA deposition seem to play an essential role in the pathogenesis of both conditions, and the consideration that they may be two extremes of a disease spectrum could be considered. If the role of SA in the development of IgA nephropathy is confirmed, it may be of interest to explore the role of anti-staphylococcal antibiotics in the treatment regimen of IgANP. [2] Koyama et al., “Staphylococcus Aureus Cell Envelope Antigen Is A New Candidate for the Induction of IgA Nephropathy.”
Diagnostic Dilemma: Glomerular IgG Deposit with Negative Anti-GBM Antibody
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Introduction: Linear deposition of IgG along glomerular basement membrane (GBM) is hallmark of anti GBM glomerulonephritis. Subclass IgG 3 deposition is seen predominantly in these cases. Rare atypical anti-GBM cases have been described in literature as rare, indolent, no pulmonary involvement and undetectable antibodies. We describe a case of atypical anti GBM, four days after mRNA COVID vaccine.

Case Description: A 77-year-old male with history of hypertension presented with hypertensive emergency and acute kidney injury 4 days after first COVID vaccine (mRNA). Workup revealed sCr 2.6 mg/dl (1.5 mg/dl 1 month back), 3+ blood and 3+ protein by UA, normal C3, C4, ANA 1: 160, spot urine protein: creatinine- 2.2, serum albumin- 4g/dl, ANCA and anti-GBM antibody was negative so was Hepatitis panel and HIV. Serum electrochemistry was negative for monoclonal protein. He did not have any pulmonary symptoms and CXR was negative for acute pathology. Renal biopsy was performed. LM: mild to moderate nodular mesangial expansion, mildly increased mesangial cellularity and focal segmental nodular mesangial sclerosis. IF showed positive linear global capillary loop staining with IgG (2+), with kappa (1+) and lambda (2+) co-staining. Trace mesangial IgM and granular C3 (trace1+) are also noted in the peripheral capillary loops. EM showed diffuse foot process effacement. Few subepithelial, intramembranous and mesangial electron dense deposits were seen. Additional IgG subclasses IF showed positive linear glomerular staining for IgG1 (3+), IgG2 (1+), IgG4 (1+), negative for IgG3.

Discussion: Although no definitive active glomerular crescents or necrotizing lesions were seen, positive linear IgG staining in the glomerular capillary loops was concerning for atypical anti-GBM disease in setting of negative antibody and negative IgG3A study looking at 20 atypical anti-GBM patients found that 1 year patient and renal survival was 93% and 85% respectively. A few patients in this study had biopsy findings of DFPE and sub-epithelial deposits like ours. There have been few reports of COVID vaccine unmasking glomerulonephritis. However, it needs further investigation.

PO1526
Rapidly Progressive Glomerulonephritis due to Crescentic IgA Nephropathy in the Setting of HIV

Introduction: In patients with HIV-related kidney diseases, the most widely recognized histological abnormality is focal segmental glomerulosclerosis (FSGS). Less commonly found is IgA nephropathy in HIV patients, which tends to have a chronic stable course. We report a case of crescentic IgA nephropathy and FSGS in a patient with rapidly progressive glomerulonephritis and newly diagnosed HIV.

Case Description: A 54-year-old transgender woman with a history of alcohol use disorder presented with a petechial rash and lower extremity edema for 1 week, and was found to have a new diagnosis of HIV with an elevated creatinine. CD4 count was 143 and viral load was 103,774, and she was started on renally-dosed dolutegravir, abacavir and emtricitabine. Creatinine on admission was 1.27 mg/dL (baseline 0.7), and increased over the next several days to 5.3. Urine microscopy revealed dysmorphic RBCs and granular casts, which may help determine the optimal therapy for IgA nephropathy and IgA-induced FSGS.

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Underline represents presenting author.
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Features and Outcomes of Patients with C1q Nephropathy in the NEPTUNE and CureGN Cohorts: Comparisons to Minimal Change Disease and Focal Segmental Glomerulosclerosis

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Background: Predominant immunostaining for C1q distinguishes a subset of patients with primary glomerular disease. C1q nephropathy (C1qN) has been proposed but not universally accepted as a distinct glomerular disease. This study describes clinical characteristics and short-term outcomes of patients meeting the provisional CureGN definition of C1qN, including comparisons to patients with minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) without C1qN.

Methods: MCD and FSGS patients with C1qN were identified from the Cure Glomerulonephropathy Network (CureGN) and NEPTUNE cohorts. Comparisons were made to MCD and FSGS patients without C1qN, based on age, disease, and time since kidney biopsy, using 5-to-1 matching. We performed cross-sectional analyses of clinical and treatment data at enrollment and a longitudinal analysis of disease course.

Results: A total of 42 patients met the provisional CureGN definition for C1qN (16 adults >18yo, 11 teens 12-18yo, and 15 children <12yo), including 15 with MCD and 27 with FSGS. Those with C1qN were more commonly female (60 vs 49%, p=0.2) and black (34 vs 27%, p=0.4). At enrollment, those with and without C1qN had comparable kidney function (eGFR 90 vs 88 mL/min/1.73m², p=0.8). Individuals with C1qN were equally likely to have been treated with steroids or other immunosuppressive therapy (76 vs 81%, p=0.4) and to have ever achieved complete remission of proteinuria (defined as uPCR <0.3) (54 vs 65%, p=0.2). Median time to last follow-up was 3.1 yrs (IQR 1.9, 4.4) from enrollment and 4.8 yrs (IQR 3.3, 6.5) from biopsy date. While proportions with kidney failure were higher for FSGS compared to MCD (14 vs 1%, p=0.01), they were similar between patients with and without C1qN (7 vs 10%, p=0.6). There was a trend towards steeper GFR slope in C1qN patients (4.8 vs -0.2 mL/min/yr, p=0.06).

Conclusions: FSGS and MCD patients with and without C1qN have comparable demographics and short-term outcomes in CureGN and NEPTUNE. Outcomes do not appear to be biased by differences in immunosuppressive therapies. Further interrogation of genetic and molecular profiles between patients with and without C1q immunostaining on biopsy may be more informative.

Funding: Private Foundation Support

Morphologic Descriptors Most Predictive of Clinical Outcomes in Minimal Change Disease and FSGS

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Background: Previous studies applying the NEPTUNE Digital Pathology Scoring System (NDPSS) uncovered the value of kidney tissue features for clinically relevant patient subcategorization. This study aims to identify biomarkers in ultrastuctural descriptors most predictive of clinical outcomes in NEPTUNE patients.

Methods: 39 glomerular, 9 tubulointerstitial, 2 vascular, and 20 ultrastructural descriptors were quantified using the NDPSS on 39 MCD, 61 MCD-like, and 124 FSGS NEPTUNE digital kidney biopsies. Outcomes included time from biopsy to disease progression (kidney failure or a ≥40% eGFR decline with eGFR <90) and first complete remission (CR) of proteinuria (uPCR <0.3). Relative importance of descriptors for prediction of outcomes was obtained from random forest models, without adjusting for clinical features.

Results: The mean age, eGFR and UPCR at biopsy for the total 224 participants was 28.8, 85.2, and 5.4, respectively. Model performance was excellent (predictive discrimination 0.902 for disease progression and 0.853 for CR). Most predictive descriptors included conventional (e.g., global sclerosis or segmental sclerosis, and interstitial fibrosis/tubular atrophy) and unconventional features [Fig]. Top 10 predictors included inflammation, podocyte abnormalities, and acute tubular injury for both outcomes; deflation, interstitial foam cells, and collapse for disease progression; and endothelial cell abnormalities, hyalinosis, and periglomerular fibrosis for CR.

Conclusions: Most predictive descriptors of proteinuric glomerulopathies reflected structural changes in various renal compartments. Reporting these descriptors should be standardized to guide the subcategorization of proteinuric glomerular diseases and improve targeted clinical care.

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Natural History of Focal Segmental Glomerulosclerosis (FSGS): The UK National RadAr Idiopathic Nephrotic Syndrome Cohort

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Background: Idiopathic FSGS is an important cause of proteinuric renal disease leading to ESKD. Here we describe the natural history of FSGS using the UK National Registry of Rare Kidney Diseases Idiopathic Nephrotic Syndrome (RadAr-INS) Cohort, including retrospective and prospective data from 3007 patients with nephrotic syndrome (NS) not attributable to glomerulonephritis or systemic disorders recruited from 107 adult and paediatric kidney units across the UK since 2010.

Methods: Participants included those with biopsy-proven or monogenic FSGS and ≥12 mo. observation from baseline. Patients with ESKD (CKD stage 5 or on renal replacement therapy) at or prior to baseline were excluded. Baseline date was defined as first database occurrence of renal biopsy, primary renal diagnosis, NS symptoms, PCR ≥1 g/L, or initiation of immunosuppression. Renal survival was defined as absence of ESKD or death with survival time calculated from baseline to last follow-up.

Results: Of 786 FSGS patients meeting eligibility, median baseline age was 28 yrs (IQR 9-49) with paediatric patients representing 38% of the study population. Median proteinuria at baseline was 5.9 g/L (IQR 3.3-11.0; n=140), while mean eGFR was 163 mL/min/1.73m² (SD 47; n=69) and 71 mL/min/1.73m² (SD 32; n=103) for children and adults, respectively. Median follow-up duration was 9.7 yrs (IQR 5.7-16.1) with ESKD/death events occurring in 46% of patients (1% death). Kaplan-Meier survival curves of children and adults show 50% renal survival probability of 16 years & 12 years, respectively (Figure 1).

Conclusions: The RadAr-INS Cohort represents a large study population with lengthy follow-up data. These analyses indicate rapid progression and poor outcomes, highlighting a need for effective treatments for patients with FSGS.

Funding: Commercial Support - Traveque Therapeutics
Funding: Commercial Support - Traveere Therapeutics

Conclusions: Non-White patients are more frequently diagnosed with FSGS at later CKD stages with advanced GS. Strategies to improve earlier awareness and detection of FSGS are needed to allow effective intervention before severe kidney damage has occurred.

Funding: Commercial Support - Traveere Therapeutics

PO1531

Clinicopathological Characteristics of Adult Patients in the United States with Focal Segmental Glomerulosclerosis (FSGS)

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Background: Focal segmental glomerulosclerosis (FSGS) is a common histopathologic lesion of glomerular injury in patients with nephrotic syndrome. These analyses characterize clinical and histological features of FSGS in adults at time of kidney biopsy.

Methods: A retrospective study was performed using data from the Arkana Biopsy Database (January 1, 2016 to May 31, 2020) in patients that met study criteria, which included: ≥18 yrs, ≥1 FSGS positive kidney biopsy, and no prior kidney transplant, and available data on race/ethnicity. Outcomes included clinical and histologic characteristics.

eGFR was calculated using CKD-EPI-creatinine equation without race modifier.

Results: Of 64,105 adult kidney biopsies performed during the study period, 2,665 (3.2%) FSGS positive cases were identified and 1,482 pts (71.8%) evaluated met study criteria. Demographic characteristics included: 56.2% male, 55.1% White, 32.1% African American (AA), 7.7% Hispanic and 3.4% Asian. Overall mean (SD) age at biopsy was 49.0 (17.2) years. Outcomes included clinical and histological characteristics. Outcomes included clinical and histological characteristics. Among all FSGS types, “not otherwise specified” (27.2%) was most frequent across all race/ethnicity groups. Asians (17.7%) or Whites (14.7%). Of all FSGS types, “not otherwise specified” was most common across all race/ethnicity groups (range 64.2–75.4%). Among other FSGS types, tip lesion was most frequent in Whites (14.6%) and lowest in Hispanics (12.5%). The highest rates of severe foot process effacement (≥80%), while interstitial fibrosis and tubular atrophy ≥50% was most common in AAs (34.6%) compared to Hispanics (27.2%), Asians (17.7%) or Whites (14.7%). Of all FSGS types, “not otherwise specified” was most common across all race/ethnicity groups (range 64.2–75.4%). Among other FSGS types, tip lesion was most frequent in Whites (21.5%) and collapsing was most frequent in AA patients (12.4%).

Conclusions: Non-White patients are more frequently diagnosed with FSGS at later CKD stages with advanced GS. Strategies to improve earlier awareness and detection of FSGS are needed to allow effective intervention before severe kidney damage has occurred.

Funding: Commercial Support - Traveere Therapeutics

PO1532

Long-Term Outcomes of Patients with Focal and Segmental Glomerulosclerosis Treated with Tacrolimus

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Background: Tacrolimus (TAC) is used to treat Focal and Segmental Glomerulosclerosis (FSGS). Prolonged treatment is often required and there is little data on long-term outcomes.

Methods: This is a retrospective study of 29 patients who received TAC as first line immunosuppression for nephrotic syndrome (NS) secondary to FSGS from December 2007- January 2020 at our institution.

Results: Mean follow up was 59.6 months (12–144). The mean age at diagnosis was 42 years (range 18-85). 52% were Male. 59% were White, 10% Black, 21% Asian, 3% Chinese, 7% Other. Baseline mean eGFR was 64 ml/min (18-90). 23/29 (79%) obtained complete (CR) or partial remission (PR) of NS, at a mean time of 5.09 months (range 1-31 months). 6/29 (21%) did not enter remission with TAC. 2/6 subsequently achieved

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
remission with CyP and prednisolone/rituximab. 7/23 (30%) patients who achieved remission with TAC had at least one relapse, 4/7 after stopping TAC, 1/7 during TAC wean and 2/7 with therapeutic TAC levels. 4/7 were treated by restarting or increasing TAC, 1/7 also had steroids added, 1/7 received rituximab (achieving remission) and 1/7 was not further treated with immunosuppression. 4/4 restated with TAC monotherapy reached remission. 16/23 (70%) patients did not relapse and 7 of these remain off TAC and in remission (mean follow up of 92.6 months). At 1 year, the mean eGFR was 67.4 ml/minute (21-90). 1/29 patient developed end-stage kidney disease (ESKD) at 2 months. This patient did not responded to TAC. 16 patients have 5-year-follow up. The mean eGFR was 66.5 ml/minute (11-90). 1 further patient developed ESKD (this patient had not responded to TAC nor subsequent immunosuppression). 4 patients have 10-year follow-up. The mean eGFR was 80.8 ml/minute (67-90). 3 further patients developed ESKD. 1/3 had achieved PR, 1/3 had achieved CR but had multiple relapses despite re-treatment and 1/3 had CR but defaulted from follow up, presenting with ESKD 6 years later.

Conclusions: The long-term data from this study suggests tacrolimus can be effective in both achieving and maintaining remission of NS in FSGS. CR is associated with good long-term outcomes in most patients although relapse can occur and long term careful follow up is required. Non-responders have a worse outcome, although some patients do respond to alternative immunosuppression.

PO1533
Collapsing FSGS in a Patient with Acute Myeloid Leukemia and Prior COVID-19 Infection
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Introduction: Collapsing focal segmental glomerulosclerosis (c-FSGS) has been independently associated with COVID-19 infection, acute myeloid leukemia (AML), and apolipoprotein L1 (APOL1) risk variants. We describe a patient with homozygous APOL1 G1 risk allele and AML who developed renal failure due to c-FSGS and acute tubular injury.

Case Description: A 25-year-old male with a history of mild asthma and COVID-19 infection 1 month prior presented with a 3-week history of severe fatigue, weight loss, persistent dyspnea, and fevers. He was found to have leukopenia, thrombocytopenia, an acute kidney injury, and nephrotic range proteinuria. The patient was diagnosed with AML by bone marrow biopsy (BMBx). At presentation, his serum creatinine was 2.8 mg/dL, which rapidly increased to 6.9 mg/dL over 2 weeks. Urine protein:creatinine ratio (UPCR) by bone marrow biopsy (BMBx). At presentation, his serum creatinine was 2.8 mg/dL, which rapidly increased to 6.9 mg/dL over 2 weeks. Urine protein:creatinine ratio (UPCR) of 11g/g. Renal biopsy demonstrated acute interstitial nephritis (AIN) on light microscopy. Electron microscopy revealed global podocyte activation and foot process effacement, consistent with MCD (Figure). He responded to alternative immunosuppression.

Discussion: COVID-19 is associated with immunologic alterations precipitating c-FSGS, especially in patients with APOL1 high risk alleles. Additionally, FSGS has been reported in AML, but the etiology behind glomerular pathologies in AML is unclear and likely multifactorial. Studies have indicated immunologic dysregulation related to leukemia, as well as viral-related etiologies. The trigger for c-FSGS in our patient is uncertain.

PO1534
Role of LDL-Apheresis in Management of Glucocorticoid-Resistant Minimal Change Disease
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Introduction: Minimal Change Disease (MCD) is described as diffuse podocyte foot process effacement on kidney biopsy, resulting in nephrotic proteinuria, ~3 grams/day. Glucocorticoids (GC) are the mainstay of therapy and most patients achieve complete remission in a few months. 7-12% patients, however, have GC-resistance and thus limited treatment options. Often, they are suspected of having focal segmental glomerulosclerosis (FSGS) due to biopsy sampling error. We present a challenging case of GC-resistant MCD, managed with immunosuppression, and ultimately lipid (LDL) apheresis.

Case Description: An otherwise healthy 20-year-old male presented for sudden onset lower extremity swelling and 10-pound weight gain. Work up including ANA, C3, C4, p-ANCA, c-ANCA, serum and urine immunofluorescence and renal ultrasound were unremarkable. Notably, LDL was 390 mg/dL, proteinuria of 9 grams/day and serum creatinine (Scr) of 0.96 mg/dL. Kidney biopsy revealed diffuse podocyte effacement, consistent with MCD. He was treated with oral prednisone 1 mg/kg/day and diuretics for several weeks with minimal symptomatic improvement and had worsening kidney function, Scr 1.5 mg/dL and proteinuria of 36 grams/day. Unfortunately, he also contracted COVID-19 disease prior to second kidney biopsy. Repeat kidney biopsy revealed acute tubular necrosis along with widespread podocyte effacement, without sclerotic lesions, ~10% interstitial fibrosis and tubular atrophy. He was empirically treated with tacrolimus for FSGS. However, proteinuria continued to worsen and peaked at 83 grams/day. Ultimately diagnosed as GC-resistant MCD, he was weaned off steroids, he was referred for LDL-apheresis therapy. He is maintained on tacrolimus and LDL apheresis with symptomatic improvement, still has significant proteinuria of 67 grams/day and advanced chronic kidney disease (CKD).

Discussion: The exact pathophysiology of nephrotic syndromes is unclear, mechanisms of T-cell dysfunction causing production of glomerular permeability factor and nephrotoxic hyperlipidemia have been described. In cases of GC-resistant diseases, immunosuppression has only been partially successful. LDL-apheresis has a role in the management of such nephrotic syndromes, thought to reduce circulating lipid induced disruption of podocyte integrity, and help prevent decline of kidney function and decrease proteinuria as seen in this patient.

PO1535
Infliximab-Associated Minimal Change Disease in an Adult with Ulcerative Colitis

Introduction: Tumor necrosis factor-alpha (TNF-α) inhibitors are increasingly utilized for the treatment of several autoimmune conditions. They have been associated, in rare cases, with renal complications. We report a patient who developed minimal change disease (MCD) and interstitial nephritis while being treated with infliximab (IFX) for ulcerative colitis (UC).

Case Description: A 48-year-old male with a history of primary sclerosing cholangitis, liver transplant 8 years prior, psoriasis, and UC well-controlled on monthly IFX presented with a one-week history of lower extremity swelling, dyspnea, and weight gain. He was found to have rapidly progressive renal failure and nephrotic syndrome. Laboratory data showed a serum creatinine of 11mg/dl up from 1mg/dl 3-weeks prior and urine protein:creatinine ratio (UPCR) of 11g/g. Renal biopsy demonstrated acute interstitial nephritis (AIN) on light microscopy. Electron microscopy revealed global podocyte activation and foot process effacement, consistent with MCD (Figure). He continued to become progressively oliguric despite escalating doses of diuretics and received two days of hemodialysis due to volume overload. After a total of 7 days of high dose steroids, his urine output increased and hemodialysis was stopped. IFX was discontinued due to the association of TNF-α inhibitors with MCD and AIN. After a month of prednisone, his creatine improved to 1.6 mg/dl and UPCR improved to 0.3g/g.

Discussion: This is the first report of IFX associated MCD. Although IFX has been associated with lGA nephropathy, crescentic glomerulonephritis, renal artery occlusion, membranous glomerulopathy, and AIN in patients with spondylarthritides spectrum diseases, no reports exist in the literature regarding MCD. In our patient, infliximab was associated with AIN. Although IFX was not associated with HLA, we could not rule out a role of TNF-α inhibitors in our patient. The mechanism of infliximab associated MCD is unclear, but IFX may exacerbate or induce MCD in patients with inflammatory bowel disease.
PO1536

Anti-Phospholipase A2 Receptor Antibody Levels in Asian Patients with Membranous Nephropathy: A Territory-Wide Study

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Background: Different cut-offs of values of anti-phospholipase A2 receptor (anti-PLA2R) antibody for determining between primary membranous nephropathy (PMN) and secondary membranous nephropathy have been reported. The optimal anti-PLA2R levels to reflect disease activity states in Asian patients with PMN remain undefined.

Methods: We conducted a territory-wide study in Hong Kong to investigate the serum anti-PLA2R levels in Chinese patients with PMN during 2017-2020. Anti-PLA2R levels were measured by commercial ELISA kits (Euroimmun, Germany) in serum samples collected from biopsy-confirmed PMN patients during active disease or remission, and their predictive values for active PMN were evaluated.

Results: Forty and six serum samples from 320 PMN patients were analysed. 319 samples were obtained during active disease and 87 during disease remission. Anti-PLA2R titres during active diseases were significantly higher than that during remission (95.1±235.0 RU/mL vs. 19.3±9.3 RU/mL respectively, p<0.001). Using 20 RU/mL as cut-off, the sensitivity (SN) and specificity (SP) for predicting active disease were 39% and 98% respectively [AUC 0.68, p<0.001; positive predictive value (PPV) and negative predictive value (NPV) were 98% and 30% respectively]. Using 10 RU/mL as cut-off, the SN and SP for diagnosing active PMN were 46% and 95% respectively [AUC<0.71, p<0.001; PPV and NPV were 97% and 32% respectively]. Anti-PLA2R titres correlated with urine protein-to-creatinine ratio and 24-hr urine protein levels (r=0.32 and 0.37 respectively, p<0.001).

Conclusions: Anti-PLA2R showed good SP and PPV prediction for active PMN in Chinese patients, and correlated with severity of proteinuria. A lower threshold (10 RU/mL) may show improved SN for predicting active PMN in Asian patients.

PO1537

Qualitative and Quantitative Dosage of the Anti M-Type Phospholipase A2 Receptor Autoantibody: One-Year Experience in Quebec's Reference Center

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Background: Dosage of the M-type phospholipase A2 receptor antibody (anti-PLA2R) is now an essential tool for diagnosis and management of primary membranous nephropathy (MN). Since October 2018, Hôpital Maisonneuve-Rosemont (HMR) has been designated as Quebec’s reference center for serum anti-PLA2R antibody testing by the Institut National d’Excellence en Santé et Services Sociaux (INESSS), the regulatory body on drugs and tests usage in Quebec.

Methods: All patients who had a serum anti-PLA2R antibody testing performed at HMR from October 1st, 2018 to October 1st, 2019 were included in the study. Serum anti-PLA2R antibodies were screened by a qualitative test, followed by a quantitative test if the results were undetermined or positive. We calculated sensitivity, specificity, predictive value, and likelihood ratio for both tests, using kidney biopsy findings as the gold standard.

Results: In the province of Quebec, a total of 1690 tests were performed among 1025 patients during the study year. A small proportion of these patients (8%) were followed at HMR. Patients tested at HMR and in the rest of Quebec had similar characteristics. Test validity was only characterized for patients tested at HMR. Sensitivity and specificity were respectively, 59% and 100% for the qualitative test, and 71% and 100% for the quantitative test. The combined net sensitivity was 42% and the net specificity, 100%. The net positive and negative predictive value were 100% and 84% respectively, whereas the net negative likelihood ratio was 0.58.

Conclusions: Serum anti-PLA2R antibody testing was widely used in Quebec during its first year of availability. In one of the biggest real life cohort described, the test performed as previously described in the literature. Moreover, the two-step approach that was used at HMR, using a qualitative test before a quantitative test if needed, appeared to be an efficient way to avoid quantitative testing in negative patients and to better characterize undetermined results on immunofluorescence.

Funding: Government Support - Non-U.S.

PO1538

Clinical Relevance of NELL1 Antibodies in Patients with Membranous Nephropathy

Linda Reinhard, Benedikt Krümpelmann, Thorsten Wiech, Rolf A. Stahl, Elian Hoxa.

Background: NELL1 was identified as a potential novel target antigen in membranous nephropathy (MN). Here, we studied the association of NELL1-antibody (ab) with treatment response and prognosis in a large cohort of MN patients.

Methods: Circulating NELL1-antibodies were detected by Western blot in a prospective cohort of 87 PLA-R- and THSD7A-ab negative MN patients, 130 PLA-R- or THSD7A-ab positive MN patients and 116 control patients with a biopsy-proven GN other than MN. Clinical follow-up included treatment, remission or relapse of proteinuria and development of kidney function.

Results: NELL1-ab were identified in 18 (21%) patients with PLA-R- and THSD7A-ab negative MN but none of the control cohorts’ patients. We identified NELL1-specific IgG1, IgG2, IgG3 and IgG4 subclasses in the serum of 12 (67%), 7 (39%), 11 (61%) and 15 (83%) NELL1-ab positive patients, respectively. NELL1-ab positive patients were significantly (p<0.05) older compared to PLA-R-ab positive patients or MN patients without NELL1-ab (age: 70 vs 58 years). During 6 months of MN diagnosis, a malignant tumor was identified in 2 (11%) NELL1-ab positive, 7 (6%) PLA-R-ab positive, 3 (50%) THSD7A-ab positive and 7 (10%) MN patients without known target antigen. 14 NELL1-ab positive patients were observed over a median follow-up of 75 months. One patient presented with eGFR < 30 ml/min due to severe hypertensive and diabetic kidney damage and developed ESKD after 69 months. All other 13 patients had a remission of proteinuria. 12 (92%) patients had a complete remission, although only 4 patients received an immunosuppressive therapy. Remarkably, of the 9 untreated patients with complete remission of proteinuria, 4 patients had persisting NELL1-ab in the circulation over the whole observation period and 2 patients reached complete remission of proteinuria before NELL1-ab disappeared. Renal function was stable in NELL1-ab positive patients but showed a more pronounced decline in NELL1- ab negative patients.

Conclusions: NELL1-ab positive MN patients had slightly more often a malignant tumor, but also were significantly older compared to PLA-R-ab positive patients. Overall, NELL1-ab positive patients had a good prognosis. The presence of NELL1-ab in the serum did not show a close association with disease outcome.

Funding: Government Support - Non-U.S.

PO1539

Non-Pathogenic THSD7A Antibodies in a Patient with No Membranous Nephropathy

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Background: PLA-R- and THSD7A-ab (anti-PLA2R) antibodies (ab) are considered to be specific for the diagnosis of membranous nephropathy (MN). There is a controversial discussion whether the detection of circulating PLA-R- or THSD7A-ab is sufficient to diagnose MN, without the need of a kidney biopsy.

Methods: Circulating THSD7A-ab were detected and their specificity evaluated by an indirect immunofluorescence test (IFT), reducing, non-reducing and native Western blot analyses as well as a live cell assay. The kidney biopsy was investigated by immunohistochemistry and electron microscopy.

Results: A patient presented with high level proteinuria and was tested positive for THSD7A-ab using IFT. Except for the diagnosis of diabetes mellitus, the medical history of the patient was unremarkable. Because of persistent proteinuria and a decline of kidney function, a kidney biopsy was performed, showing the diagnosis of diabetic nephropathy and excluding MN. A detailed biochemical characterization of the THSD7A-ab was performed to clarify these discrepancies between the serological and histomorphological findings. The circulating THSD7A-ab from the serum of the patient bound to recombinant THSD7A in the IIFT, co-localizing with THSD7A in co-immunofluorescence staining experiments and reacted with purified THSD7A in reducing WB analyses. However, these antibodies did not bind THSD7A derived from human glomerular tissue in any of the tested conditions. Since the kidney biopsy revealed a diagnosis of type 2 diabetes mellitus, the circulating THSD7A-ab did not recognize recombinant THSD7A under native conditions in the native Western blot or live cell assay. In contrast, THSD7A-ab from MN patients recognized native THSD7A in all experiments.

Conclusions: In the first time the existence of non-pathogenic THSD7A-ab, which are not able to bind THSD7A in vivo and can hence not induce MN. Nevertheless, their presence can be detected by different assays, leading to false-positive results for pathogenic circulating THSD7A-ab. In cases of low THSD7A-ab positivity in IFT, findings from different diagnostic tests such as kidney biopsy, Western blot analyses and live cell assays should be integrated in making a safe diagnosis of THSD7A-ab positive MN.

Funding: Commercial Support - Euroimmun AG, Lübeck, Germany, Government Support - Non-U.S.

PO1540

Urinary NPHS2-mRNA in Relation to Glomerular and Tubular Damage Markers in Patients with Membranous Nephropathy

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Background: Measurement of podocyte-specific mRNA in patients’ urine samples has been proposed as a novel tool to monitor podocyte loss in glomerular disease, and may have prognostic value. In our hospital, we routinely measure timed urinary excretion of high- and low-molecular weight proteins as prognostic markers in patients with membranous nephropathy (MN). Here, we investigated the relationship between NPHS2-mRNA and high- and low-molecular weight proteins in patients with MN.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Urine Biomarkers Predict Treatment Response in the MENTOR Study

PO1541

Urine Biomarkers Predict Treatment Response in the MENTOR Study

Methods: We included 35 patients with MN (80% male, median age 67, median eGFR 63). NPHS2-mRNA was measured in urine pellets as described by Wickman et al. (JASN 2013). Normal values of urinary NPHS2-mRNA were obtained in spot urine samples of 19 healthy controls.

Results: Clinical characteristics and results of urinary measurement are shown in Table 1. Mean urinary NPHS2-mRNA/creatinine ratio (UpodCR) was 64 fold higher in patients with MN versus healthy controls. UpodCR showed weak but significant correlations with urinary IgG excretion and proteinuria selectivity index (Figure 1), but not with total proteinuria or gFR (Table 1).

Conclusions: Urinary expression of NPHS2-mRNA correlated significantly with protein markers of glomerular damage in patients with MN. However, correlations were weak. Prospective studies are needed to evaluate if urinary NPHS2-mRNA excretion holds independent prognostic value.

Table 1. Characteristics of patients with membranous nephropathy (N=35)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CR/PR</th>
<th>NPHS2-mRNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>9.4</td>
<td>15.2</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>5.9</td>
<td>4.3</td>
</tr>
<tr>
<td>UPCR (g/mg Cr)</td>
<td>2.0</td>
<td>0.8</td>
</tr>
<tr>
<td>UCon (g/mg Cr)</td>
<td>1.8</td>
<td>0.9</td>
</tr>
<tr>
<td>UpodCR (mg/mg Cr)</td>
<td>14.2</td>
<td>5.7</td>
</tr>
<tr>
<td>UUDP (g/mg Cr)</td>
<td>4.7</td>
<td>2.8</td>
</tr>
<tr>
<td>UAlb (g/mg Cr)</td>
<td>1.9</td>
<td>1.4</td>
</tr>
<tr>
<td>UPod (mg/mg Cr)</td>
<td>1.0</td>
<td>0.4</td>
</tr>
<tr>
<td>UCon (g/mg Cr)</td>
<td>1.8</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Continuous variables are expressed as Median (interquartile range). Correlations are expressed in Spearman’s R2 (p-value). UAlb = Urinary albumin, UPod = Urinary NPHS2 mRNA.

Figure 1. UpodCR correlations with protein markers of glomerular injury.

PO1542

Use of Urinary Proteins as Predictors of Response to Immunosuppressive Treatment in Membranous Nephropathy

PO1543

APOL1 High-Risk Genotype Is Associated with Worse Renal Outcomes in Black Patients with Membranous Nephropathy

Methods: We measured the abundance of 55 urinary cytokines, metalloproteases and urinary excretion of NPHS2 mRNA. The primary outcome of interest was achievement of CR/PR at 12 months despite IS with rituximab or cyclosporine. The treatment outcome was defined as patients achieving either complete (CR; <0.3g/24 hours) or partial remission (PR; >0.3-<3.5g/24 hours) of proteinuria at 12 months.

Results: In both cyclosporin and rituximab arm, all urinary proteins exhibited a decline from baseline to 12 months post treatment. However, none of the baseline urinary proteins were found to be significantly associated with treatment response at 12 months (p>0.05 for all). Results were similar when restricted to patients with positive anti-PLA2R at baseline.

Conclusions: Baseline measures of the urinary albumin, uIgM, uIgG, and uα1m are not predictors of patients going into CR or PR at 12 months after treatment with rituximab or cyclosporine.
White patients from CureGN were included for comparison. Data from CureGN or chart abstraction for GDCN patients were used to determine demographics, diagnosis, disease onset, and ESKD (dialysis initiation or transplantation). Fisher’s exact, Wilcoxon rank, and Kaplan-Meier curves with log rank tests were used to evaluate differences between high risk (2 variants) and low risk (0/1 variant) and white population. 

Results: There were 106 African American patients with diagnosis of MN in our study. Of these, 15 patients (14%) were high risk (two risk alleles of APOL1) and the remaining 91 patients (86%) were low risk (0/1 risk alleles of APOL1). Data were available for 493 white patients. Hazard ratio for composite outcome of ESKD/death was 4.21 (95% CI 1.54,11.51) among African Americans (high risk vs. low risk) and 6.37 (95% CI 2.74, 14.80) compared to white population. Time to endpoint was significantly faster in those with high risk APOL1 genotype (Figure), p<0.0001. 

Conclusions: High-risk APOL1 genotype in African Americans is associated with faster time to ESKD/death compared to low-risk AA or white patients with MN.

Funding: NIDDK Support

PO1544
Treatment-Resistant Membranous Nephropathy in a Patient with NPHS2 Mutation
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Introduction: Membranous nephropathy (MN) is one of the most frequent causes of nephrotic syndrome (NS) in adults. NPHS2 gene encodes podocin, a protein of the slit diaphragm that is essential for recruitment of nephrin into the lipid rafts and for maintaining the glomerular filtration barrier. Recessively transmitted mutations in NPHS2 cause familial forms of steroid-resistant NS that progress to end-stage renal disease (ESRD).

Description: A 37-year-old male was referred to our clinic with NS and hypertension. Admission labs showed creatinine of 3 mg/dl, serum albumin of 3 g/dl, proteinuria of 2 g/dl and microscopic hematuria (30 cells/hpf). Immunological testing – ANA, ANCA, anti-C1q, anti-GBM – was negative, C3 and C4 were normal. Kidneys appeared normal on ultrasound examination. A renal biopsy was performed. Light microscopy revealed 19/23 glomeruli with global sclerosis and 4/23 glomeruli with thickening of GBM, podocyte hypertrophy and segmental sclerosis; there was also diffuse tubular atrophy, interstitial fibrosis and arteriolar hyalinization. Electron microscopy showed subepithelial electron dense deposits with spike formation, with granular capillary loop staining for IgG4 in immunofluorescence. The histopathological diagnosis was stage II MN associated with diffuse glomerulosclerosis secondary to hypertension. In the meantime, the anti-PLA2R antibodies returned positive (titre 1:320). Therapy was started with Rituximab 1000 mg; a second dose was administered after 14 days. Despite treatment, NS persisted and kidney function worsened; hemodialysis was initiated 6 months after the diagnosis. One year later, the patient’s 16-year-old son was diagnosed with NS, resistant to steroids. Genetic testing identified NPHS2 c.947C>T p.(Pro316Leu), c.3447dup, p.(Val1150Cysfs*39) in KANK1, inherited from the mother.

Discussion: Recent data suggest an important role of genes in the pathogenesis of MN. NPHS1 polymorphisms are associated with low remission rate after treatment and high disease progression. Our patient has a heterozygous mutation in NPHS2, resulting in abnormal signaling through the nephrin-podocin complex and podocyte dysfunction. Therefore, it is very probable that in this case of primary MN genetics played a major role in treatment resistance and progression to ESRD.

PO1545
Primary Membranous Nephropathy Flare After COVID-19 Vaccination
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Introduction: Primary membranous nephropathy (MN) is most commonly due to phospholipase A2 receptor antibodies (PLA2R Ab). It is unclear whether the COVID-19 vaccine can trigger flares of glomerular diseases such as primary MN. We present a patient with MN and metastatic breast cancer who developed nephrotic syndrome after receiving her second mRNA-1273 COVID-19 vaccine with positive PLA2R Ab by ELISA suggesting MN flare.

Case Description: A 62 year old female with history of Stage IIIIB T3N3M1 ER/PR positive HER-2 negative metastatic left breast invasive ductal carcinoma, hypertension, breast cancer, and primary MN with histology confirmed with histology confirmed with histopathology and proteinuria 2 weeks after COVID-19 vaccination. She had previous proteinuria of 7029 mg/24hr in August 2018 with PLA2R Ab 128 RU/mL in October 2018. She underwent modified radical mastectomy in September 2018 followed by adjuvant chemotherapy in December 2018, after which PLA2R Ab decreased to <2 RU/mL. In February 2019 and urine protein/creatinine ratio (UPCR) decreased to 1094 mg/g Cr in April 2019. She was diagnosed with metastatic breast cancer and started anastrozole transiently. She received mRNA-1273 COVID-19 vaccines in late January and February 2021. In March 2021, she presented with bilateral leg edema, dyspnea, and bilateral pleural effusions. Urinalysis had >1000 protein, 24hr urine protein 11.2 g, Cr 1.6 mg/dl, and PLA2R Ab 787 RU/mL. Renal biopsy showed immune complex-mediated glomerulopathy with positive PLA2R, consistent with primary MN stage II-H. Glomerular basement membrane deposits were strongly positive for IgG4. Electron microscopy showed numerous subepithelial and occasional intramembranous electron-dense immune-type deposits. She was treated with lisinopril and furosemide followed by rituximab in May 2021. Prior to rituximab PLA2R Ab was 342 RU/mL and UPCR was 8671 mg/g Cr.

Discussion: There is insufficient data on the risk of flare after COVID-19 vaccine in glomerular diseases. There have been few cases reports of primary MN and minimal change disease after COVID-19 vaccine as well as MN after influenza vaccine. Our case of primary MN flare after COVID-19 vaccine adds support to a potential association between SARS-CoV-2 variants and antigen loss to the PLA2R antigen. Close follow-up of patients with primary MN and other glomerular diseases after COVID-19 vaccination is warranted.

PO1546
Primary Membranous Nephropathy Concurrent with ANCA-Positive Crescentic Glomerulopathy in a Hispanic Man
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Introduction: Primary membranous nephropathy (MN) is a common cause of glomerular disease in adults usually presenting with nephrotic syndrome. Crescents are an unusual finding in MN; its presence suggests a concomitant disease process, such as pauci-immune anti-neutrophil cytoplasmic antibody-related (ANCA) glomerulonephritis (GN).

Case Description: A 36-year-old Hispanic man presented with a 1-week history of fatigue, weight loss, and lethargy. Examinations revealed an obese Hispanic man with rales on lung auscultation and lower-extremity edema. Laboratory results showed a serum creatinine (sCr) 8.8 mg/dl, BUN of 54 mg/dl. Urinalysis revealed 4+ protein, 25-50 red blood cells per hpf. Spot urine protein creatinine ratio (UPCR) was 19 g/g, p-ANCA titer 1:640. Urine toxicology screen was positive for cocaine. Other serologies and imaging were unremarkable. Renal biopsy showed MN with PLA2R positive staining as well as necrotizing and crescentic glomerulonephritis. Interstitial fibrosis and tubular atrophy were seen only in 10% of the sample. Management was initiated with a pulse of steroids followed by a taper, and renally dosed oral cyclophosphamide. The patient was initiated on hemodialysis due to uremic symptoms and volume overload. Three months after initiation of therapy, urine output significantly improved. Laboratory data showed: a 24 hours urine creatinine clearance of 31 ml/min, sCr 2.9 mg/dl, and UPCR 5.3 g/l. Patient was euolemic. Hemodialysis was discontinued. MN and ANCA GN are distinct manifestations of renal injury with different clinical, laboratory, and pathology findings. Our case highlights an individual with both entities. We hypothesize that the patient’s renal findings of p-ANCA and crescentic GN were likely associated with levamisole adulterated cocaine in the background of primary MN. The patient discontinued cocaine use after our discussions. We decided to treat the patient’s MN with immunosuppressive therapy. Fortunately, the patient has responded favorably to our management with significant improvement in renal function.

PO1547
Clinical-Pathological Features of Podocyte Infolding Glomerulopathy
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Background: Podocyte infolding glomerulopathy (PIG) is characterized by presence of microstructural aggregates originated from cytoplasmic infoldings of podocytes in the glomerular basement membrane (GBM). Few PIG cases have been reported and the significance of this morphology is still unclear. This study aims to elucidate the incidence, clinical-pathological features and prognosis of PIG.

Methods: Renal biopsies with PIG features from January 2018 to December 2020 in Kingmed Diagnostic Laboratory were reviewed. Patients were divided into three groups according to their clinical and pathological findings.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
PO1548
Baseline Characteristics of Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits in the International Kidney Registry Consortium (K-REG)

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Background: Proliferative glomerulonephritis with monoclonal Ig deposits (PGNMID) is a monoclonal gammopathy of renal significance-associated lesion unique for low rates of paraprotein and clone detection. Prognosis is poor with 30% of patients progressing to ESKD, but recent data suggest improved outcomes with clone-directed therapy regardless of clone-detection status. Here, we present the baseline kidney and hematologic characteristics of patients with PGNMID from the International Kidney Registry Consortium (K-REG).

Methods: PGNMID cases were identified retrospectively by K-REG sites. Baseline demographic, clinical, kidney biopsy, hematologic and treatment data were analyzed and stratified by presence or absence of clone detected, as well conservative vs. non-specific immunosuppression vs. clone-directed therapy prescribed.

Results: 134 patients from 15 sites in 3 countries with PGNMID were included, 13% of which had been included in previously published studies. The mean age was 57 (SD 17) years, of whom were female and 72% Caucasian. The median baseline eGFR was 35 (IQR 21-52) ml/min/1.73m2 and median proteinuria 3.9 (IQR 1.5-7.2) g/day. IgG kappa was the most common involved paraprotein (61%). 30% of patients had a detectable circulating paraprotein by SPEP or sIFE and 11% by UPEP or uIFE. 75% of patients underwent a bone marrow biopsy. Overall, a clone was detected in 19% of patients. There were no significant differences in age, sex, race, baseline eGFR, or proteinuria based on clone or paraprotein-detection status. Clone-directed therapy was prescribed in 55% of patients, non-specific immunosuppression to 15% of patients and conservative therapy in 40% of patients. Clone-directed therapy was prescribed in 82% of patients with a detectable clone vs. 52% of patients without a detectable clone (p = 0.011).

Conclusions: In this large series of PGNMID, a minority of patients had detectable clone. Baseline demographic and clinical characteristics were not different based on clone detection status but treatment varied significantly depending on clone-detection status. Additional analyses of the K-REG cohort will provide insight into renal and hematologic responses.

PO1549
Kidney Outcomes in Biopsy-Proven Thrombotic Microangiopathy with Eculizumab Therapy

Mohammad A. Sohail,1 John R. Sedor,2 Susana Arrigian,1 Jesse D. Schold,2 Leaf C. Herlitz,2 Ali Mehdi,1 Cleveland Clinic, Cleveland, OH; ‘Cleveland Clinic Glickman Urological and Kidney Institute, Cleveland, OH.

Background: There are limited long-term data on kidney outcomes in ecuizumab-treated patients with biopsy-proven thrombotic microangiopathy (TMA). We report our experience of using eculizumab in patients with primary (genetic/antibody mediated) TMA, secondary TMA syndromes associated with antiphospholipid syndrome (APS) or systemic lupus erythematosus (SLE), as well as TMA of undetermined etiology.

Methods: We reviewed adult patients with kidney biopsy-proven TMA treated with eculizumab between 2014-2019. Transplant recipients, pregnant patients and those with scleroderma, shiga-toxin related hemolytic uremic syndrome or thrombotic thrombocytopenic purpura were excluded. Kidney response to eculizumab at 26 weeks for patients not on kidney replacement therapy (KRT) and for those requiring KRT at the time of or within 1 week of initiation of eculizumab, was defined as an increase of 15 ml/min/1.73m2 and liberation from KRT respectively.

Results: We collected data on 16 patients (primary TMA [n=3]; secondary TMA including SLE [n=3] and APS [n=4]; TMA of undetermined etiology [n=6]). The median time from biopsy diagnosis to treatment initiation was 3.0 days (IQR: 1.0-10.0) and the median duration of therapy was 303 days (IQR:160,604). 13 patients (81%) required KRT at the time of initiation of eculizumab. 4 patients died during follow up, 2 of whom died within 26 weeks. 6 (37.5%) patients were off KRT at 26 weeks. 2/3 patients who required KRT when therapy was started. 2 of 3 patients who did not need KRT initially eventually progressed to end-stage kidney disease after 1 and 5.5 years from initiation treatment. 3/6 patients (50%) and 3/8 patients (37.5%) with mild and moderate interstitial fibrosis and tubular atrophy (IFTA) (IFTA) on biopsy respectively responded to therapy, whilst those with severe IFTA (n=2) showed no response.

Conclusions: Although eculizumab use has been expanding rapidly for primary and secondary TMA syndromes, our data depicts a suboptimal kidney response, which appears independent of the need for KRT at treatment initiation. Severity of IFTA may be a predictor of kidney response to eculizumab. We suggest that more data is needed on long-term kidney outcomes with eculizumab across TMA syndromes before universally adopting this expensive therapeutic strategy.

PO1550
Recurrence of Atypical Hemolytic Uremic Syndrome After Kidney Transplantation: A Prospective Cohort Study

Caroline Duineved, Romy N. Bouwmeester, Keea L. Wijnssma, Nicole Van De Kar, Jack F. Wetzels. CUREiHUS study group Radboudumc, Nijmegen, Netherlands.

Background: Since 2016, aHUS patients in the Netherlands are treated with a restrictive treatment protocol. Withdrawal of eculizumab is considered after a treatment period of three months. Furthermore, kidney transplantations in aHUS patients are performed without eculizumab prophylaxis, with initiation of eculizumab in case of post-transplant recurrence. This restrictive treatment protocol is monitored in the CUREiHUS study. Here, we present the CUREiHUS study results for kidney transplant patients.

Methods: All kidney transplant patients who received eculizumab therapy for a suspected aHUS recurrence, and who were included in the CUREiHUS study (after informed consent), were evaluated.

Results: In the period from January 2016 until October 2020 we included 15 (F 12, M 3; median age 42y, range 24-66) patients with suspected aHUS recurrence after kidney transplantation. Patients were classified as high (N=8) or moderate (N=7) recurrence risk. The time-interval to recurrence showed a bimodal distribution. Seven patients presented early after transplantation (median 3 m, range 0.3-8.8), with typical aHUS features: rapid GFR loss and laboratory signs of TMA. Eight patients presented late (median 46m, range 18-69) after transplantation. Of these, 3 patients showed typical aHUS features, while in 5 patients no laboratory evidence of TMA was seen, and only a gradual eGFR loss. Treatment with eculizumab resulted in disappearance of TMA and improvement/ stabilization of eGFR in 14 patients. Withdrawal of eculizumab was thus far proposed in 10 patients, and successful in only 5. Median follow-up after recurrence is 29 months (range 3-53 months). At last follow-up median eGFR was 32.0 (ml/min/1.73m2) (range 7-80), considerably less than eGFR before recurrence (54.3 ml/min/1.73m2, range 22-103).

Conclusions: Patients with aHUS who develop recurrence after kidney transplantation do not fully recover kidney function. The major cause is treatment delay due to late recognition of disease recurrence in patients who present with a “creeping creatinine”. Discontinuation of eculizumab is often unsuccessful.

PO1551
A Case of Thrombotic Microangiopathy from an Intra-Abdominal Abscess


Introduction: Infection mediated thrombotic microangiopathy (TMA) has a high mortality with many patients requiring kidney replacement therapy. Recognition of TMA can only occur in the setting where clinical abnormalities can be identified. A rare case of TMA from complicated diverticulitis and polymicrobial intra-abdominal abscess.
Early Recurrence of C3 Glomerulopathy (C3G) in the Allograft

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Background: C3 glomerulopathy (C3G) has been classified as a glomerular complement mediated disease with predominant C3 deposits for decades. Data regarding clinical course, treatment options and long term prognosis in children and adolescents is still scarce. The aim of the study was to retrospectively describe a single tertiary center’s experience with C3G in the pediatric population, and correlate presentation, pathology, complement findings, response to treatment and disease course.

Methods: A retrospective cohort study. Patients presented with C3G by the age of 18 years comprised the study group. All cases underwent kidney biopsy at presentation. Repeated kidney biopsy was performed on a need basis, in native or transplanted kidneys.

Definition of C3G was based on the 2013 consensus guidelines. Patients underwent complement workup and genetic tests. Treatment regimen was not uniform.

Results: 17 patients were diagnosed with C3 glomerulopathy. Features of Dense deposit disease (DDD) were found in 8 patients, C3 glomerulonephritis in 6 patients. For 1 patient EM was not available. Mean age at diagnosis was 12.7 years (range 1.9 – 17.3). 6 girls and 11 boys. Median follow up 4.4 years (range 1.1-20.9). Treatment modalities ranged from ACE inhibitors and Angiotensin receptor blockers to corticosteroids, rashes (4) (23%) patients reached end stage renal failure and had kidney transplantation. All of them had disease recurrence in the transplanted kidney. Complement workup was positive for C3Nef in 6 patients, C4Nef in 2 patients, C5Nef in 2 patients, factor H antibodies in 2 patients. Genetic testing was positive in one patient. Elevated creatinine at presentation, severe proteinuria, DDD in kidney biopsy– were correlated with worse prognosis.

Conclusions: Understanding the pathophysiology of C3G as a complement mediated disease has progressed during the past years. Still no guidelines exist regarding treatment and prognosis in the pediatric population. Our cohort presented a wide variability in disease course and presentation. Further understanding of the correlation between exact complement abnormality and C3G prognosis is warranted, especially now when new complement system blockers may become available.
PO1555

Utilizing Pharmacokinetic Studies to Optimize Therapy in a Child with C3 Glomerulonephritis and Nephrotic Syndrome: A Precision Medicine Approach
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Introduction: C3 glomerulonephritis (C3GN) is caused by complement alternative pathway dysregulation, has no definitive treatment and is characterized by progression to ESRD. Terminal complement blockade has successfully been used especially in patients with elevated C5b-9 levels.

Case Description: We describe a 6 year old boy with C3GN, who presented with nephrotic syndrome, severe hypertension (4 anti-hypertensive medications) and acute kidney injury. Complement C3 level was 0.12 g/L (normal 0.8-1.5) with pos C3NeF and elevated C5b-9 levels (2135, normal <239 ng/ml). Despite 6 months of treatment with steroid and MMF, he had ongoing nephrotic syndrome and worsening kidney function. He commenced on standard Eculizumab dosing. Despite 6 months of therapy, he had persistent severe hypertension, nephrotic syndrome requiring weekly albumin/levo-furosemide infusions and worsening kidney function. Complement C3 levels remained low with elevated C5b-9 levels, suggesting sub-optimal terminal complement inhibition due to urinary loss. We confirmed sub-therapeutic plasma concentrations of eculizumab as free plasma eculizumab levels were low on day 7 (9, normal >99 ug/ml) and undetectable on days 10 and 14 post-infusion. Eculizumab frequency was subsequently increased to weekly with MPA-AUC guided adjustment of MMF dosing. Since then, his kidney function, C5b-9 levels (279 ng/ml) and nephrotic syndrome improved significantly, leading to discontinuation of albumin/levo-furosemide and anti-hypertensive medications.

Discussion: Use of pharmacokinetic studies can aid in individualized eculizumab treatment in C3GN patients with ongoing proteinuria and who failed to respond to standard dosing.

PO1556

Remission of C3 Glomerulonephritis with Rituximab
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Introduction: C3 glomerulonephritis (C3GN) is rare form of glomerulonephritis. It is diagnosed primarily by kidney biopsy with immunofluorescence showing deposits of C3 along the basement membranes. It differs from dense deposit disease with absence of the pathognomonic deposits on electron microscopy (1). There are no randomized trials to guide therapeutic decisions. Spontaneous and treatment-associated complete remissions are rare.

Case Description: 69-year-old female with history of well controlled hypertension on amldipine was sent to hospital with elevated creatinine of 2.52 (unknown baseline) with positive ANA - 1:320 titer. Patient was asymptomatic with negative family history of kidney disease. She denied taking NSAIDs. Serum creatinine on admission was 3.05 mg/dL. Urinalysis showed numerous RBCs with 2 g of proteinuria in the 24-hour urine collection. P-ANCA was positive. All other pertinent serologies were negative including complements, C-ANCA, MPO, PR3. Renal ultrasound revealed medical renal disease. Renal biopsy was performed and preliminary reports showed crescentic glomerulonephritis. Pulse dose steroids was started followed by oral prednisone. In addition, Rituximab was started weekly. Final biopsy confirmed C3GN. Patient did not require dialysis and renal function significantly improved after 4 doses of rituximab to serum creatinine of 1.5 mg/dL.

Discussion: In C3GN with rapidly progressive glomerulonephritis (crescents on biopsy), treatment is not well established. Most patients are treated with steroids in combination with either cyclophosphamide or Mycophenolate mofetil (2). Rituximab was used in some case reports (3). In our patient, since P-ANCA was positive and preliminary biopsy showed crescents, Rituximab was started immediately after pulse dose steroids. Patient did not require dialysis, due to good response and remission. Rituximab is a promising treatment option for C3GN. Reference Smith, R.J.H., et al C3 glomerulopathy — understanding a rare complement-driven renal disease. Nat Rev Nephrol 15 (2019). Fernando Caravaca-Fontán et al. Mycophenolate Mofetil in C3 Glomerulopathy and Pathogenic Drivers of the Disease. Clin J Am Soc Nephrol. September 2020, 15 (9) 1287-1298. Giaine P et al. Remission of C3 glomerulopathy with rituximab as only immunosuppressive therapy. Clin Nephrol. 2015 Jan;83(1):57-60.

PO1557

Myeloperoxidase Immunohistochemical Staining and Response to Eculizumab in a Pediatric Patient with Dense Deposit Disease

Introduction: Previous studies have demonstrated residual complement mediated deposits in repeat renal biopsies of patients with C3 glomerulopathies (Dense deposit disease (DDD) and C3 glomerulonephritis) following eculizumab treatment despite clinical improvement. With the residual complement deposition, it is often difficult to determine whether there is a reduced complement mediated endothelial cell injury. Herein, we report the use of myeloperoxidase (MPO) immunohistochemical staining to show decreased glomerular endothelial cell injury in a pediatric patient with DDD on chronic eculizumab therapy.

Case Description: Our patient was diagnosed with DDD by renal biopsy when he was 5 years old after presenting with a serum creatinine of 5.2 mg/dL, a urine protein to creatinine ratio of 2.5, and a complement C3 level of 50 mg/dL. Functional complement testing showed the presence of C3 and C5 nephritic factors. He was treated with eculizumab (600 mg every 2 weeks) and azathioprine, and over the course of 6 months, his serum creatinine, proteinuria, and complement C3 levels returned to normal. After weaning the frequency of his eculizumab infusions, he experienced a flare of DDD 15 months after initial presentation with a serum creatinine of 3.6 mg/dL, urine protein to creatinine ratio of 7, and complement C3 level of 76 mg/dL. He was re-dosed with eculizumab (600 mg every 2 weeks) with a rapid response to treatment. He had normalization of his serum creatinine to pre-flare levels within 6 months. Since then he has been maintained on eculizumab infusions (600 mg every 4 weeks) along with mycophenolate mofetil. A second kidney biopsy was performed after 3 years of treatment with eculizumab to evaluate response to treatment. The biopsy showed some residual features of dense deposit disease including C3 complement deposition. To evaluate if eculizumab blocked complement mediated injury on glomerular endothelial cells, MPO staining of his initial and repeat biopsy was performed: his initial biopsy revealed diffuse endothelial staining for MPO along glomerular endothelium and the repeat biopsy showed either no MPO staining or weak MPO staining in the glomerular endothelium.

Discussion: In this case, we find that MPO immunohistochemical staining may be useful for monitoring the response to complement blockade in patients with DDD.
PO1558

Pregnancy-Associated Membranoproliferative Glomerulonephritis (MPGN)
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Introduction: Nephrotic syndrome (NS) in pregnancy is rare due to MPGN. We present a case of MPGN in pregnancy for which no other cause was found.

Case Description: A 33-year-old G1P0 woman develops hypertension and proteinuria at 12 weeks gestation followed at 21 weeks by NS (75g/24h proteinuria, albumin 1.1 g/dL). AKI with creatinine (Cr) 1.1 mg/dL (up from 0.6), hematuria, and mildly elevated AST and ALT. C4 is low (5.9 mg/dL). SLEP and UPEP detect monoclonal IgG kappa with serum light chain ratio 5.1. ANA, anti-dDNA, cryoglobulins, C3 nephritic factor, and serologies for hepatitis B and C, T. pallidum, and HIV are negative. Renal biopsy reveals MPGN. After counseling, she opts to end the pregnancy. Cr, AST, ALT, and hematuria rapidly normalize, but the proteinuria at first persists. Immunosuppression is offered, but she declines. The proteinuria slowly falls to <0.1 g/dL Cr with supportive care and telmisartan over a year. Apart from low C4, an atypical hemolytic uremic syndrome (aHUS) panel is negative. Genetic testing for aHUS is also negative (heterozygous mutation in DGKE and heterozygous deletion in CFH R1-CFH R3). HLA analysis shows B35 and B51 alleles. C4d staining later performed on the biopsy is strongly positive.

Discussion: As in this case, in NS pregnancy is associated with an increased risk of complications such as superimposed preeclampsia. The etiology of this MPGN case is unknown, with no clear infectious or autoimmune cause. The C4d deposition and negative aHUS testing suggest a defect in the classic complement pathway. The paraprotein may or may not be involved as, though the immune complex deposition was polyclonal, monoclonal IgG-kappa has been rarely reported to activate complement in other autoimmune disorders. Regardless of mechanism, we speculate this MPGN case was triggered by pregnancy as it improved after the pregnancy with supportive care alone.

PO1559

Comparing and Contrasting Glomerular Disease Patients: A Real-World Analysis Showing Demographic, Clinical, and Treatment Differences Across More Than 1,000 Patients

Background: One-half of nephrologists selected glomerular diseases as their leading area of interest in nephrology in 2020. These rare and often-idiopathic disorders are seen as particularly challenging to manage, but an influx of promising pipeline drugs may offer new treatment options in the not-so-distant future.

Methods: 1,112 glomerular disease patient records were collected in collaboration with 290 US nephrologists via HIPAA-compliant, online chart review tool between December 20, 2020 – February 16, 2021.

Results: Chart audits reveal ~8% of nephrologists’ patient populations have a glomerular disorder. Of that group, 26% have IgAN, 26% have FSGS, and 3% have Alport’s Syndrome, among other conditions. IgAN patients are typically middle-aged, white males, in the middle-to-upper class and often present with hypertension, hyperlipidemia, and/or obesity. FSGS patients are mostly middle-aged, black males, in the lower-to-middle class and often present with hypertension, hyperlipidemia, obesity, and/or edema. Alport Syndrome patients tend to be younger (18-49), white males, in the lower-to-middle class and present with hypertension, hearing loss, and sometimes ocular abnormalities. Of the three conditions, FSGS patients are most heavily prescribed steroids and advanced therapeutics like MMs, cyclophosphamide, and Achar Gel and are least likely to be deemed “optimally managed” by their nephrologist. Alport patients are much less likely to receive steroids and are most likely to be seen as optimally managed. Interestingly, despite the value of ACEI/ARB therapy, 42% of IgAN patients were not on therapy at referral, with FSGS and Alport close behind. Nephrologists are trialing SOLITZIs across conditions, with up to one-in-ten patients currently on the drug. A diagnosis for Alport Syndrome may take several months or even years after referral to determine (unlike IgAN and FSGS where it usually takes under four months). Alport is also the least likely of the three diseases to be diagnosed via kidney biopsy. Patient referrals are often deemed “late” by nephrologists, but particularly with the faster-progressive FSGS and IgAN.

Conclusions: Deeper understanding of key comparative differences among rare glomerular diseases may aid physicians in developing strategies for diagnosis and treatment.

PO1560

Glomerular Diseases in Flanders: Overview of the FCGG Biopsy Registry
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Background: High-quality population-based registries on glomerular diseases are required for epidemiological study and new trial design. The FCGG (Flemish Collaborative Glomerulonephritis Group) database is a population-based registry that has been including data on all native kidney biopsies performed in Flanders since 2017 (Northern part of Belgium) covering a population of approximately 6.5 million inhabitants.

Methods: Clinical data and nephrological diagnosis according to the ERA-EDTA Coding system for Primary Renal Disease are collected together with pathological data including primary and secondary pathological diagnoses according to the Mayo Clinic/ Renal Pathology Society Consensus Guideline 2016. Here, we describe the main results of the first three years of the registry.

Results: From 2017 until 2019, 2,178 biopsies were included, of which 5.7% were performed in the pediatric population. Median age (IQR) was 59 years (42-71). Biopsy incidence proportion was 130 biopsies p.m.p. per year in the adult population. Glomerular disease was present in 54% of the adult biopsies (Fig. 1A). IgA-nephropathy (IgAN) was the most frequently diagnosed disease in adults (17.3% of total, 30.2% of glomerular subcategory). The etiologies of the nephrotic syndrome differed across age categories, with membranous nephropathy (MN) being most frequently diagnosed in the total group of adult nephrotic patients (Fig. 1B). IgAN and pauci-immune glomerulonephritis (AAN) were the two most important causes of the nephritic syndrome in adults. A crescentic pattern of injury was most frequently diagnosed in adults with AAV, lupus nephritis (LN) and IgAN (Fig. 1C, crescents in 82%, 31% and 24% of biopsies, respectively).

Conclusions: The FCGG database is a valuable population-based registry that characterizes the epidemiology of glomerular disease in Flanders. These results are relevant to the clinician, will enable disease subgroup analyses and are useful to set up observational or interventional trials in patients with glomerular disease.
Results: Our analysis indicates specific and unique protein/molecular signatures among patients with GN, MCD, FSGS and LN with respect to disease status and pathological diagnosis. Univariate analysis indicated that at least 62 proteins were significantly different in complete remission vs. proteinuric patients across all pathologies. Multivariate analysis showed significant contributions by several proteins to identify disease state and pathological status of identified protein signatures that are differentially abundant across the 3 distinct glomerulopathies.

Conclusions: Pediatric glomerular disease and disease activity are associated with unique urine proteomes and if confirmed will lead to further identification of important biomarkers. We are currently performing validation of a subset of proteins as biomarkers to determine if they are diagnostic and predictive of treatment response.

Funding: NIDDK Support

PO1562
The Thromboembolism Among Hospitalized Patients with Different Types of Chronic Glomerulonephritis: A Retrospective Study Spanning 18 Years from a Single Tertiary Hospital

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Background: Chronic kidney disease is associated with hypercoagulability and platelet dysfunction. However, data on thromboembolism associating different types of chronic glomerulonephritis (CGN) are less.

Methods: We conducted a retrospective analysis using the database of hospitalization with CGN in Peking Union Medical College Hospital (PUMCH), China from 2000 to 2017. The tenth revision from the International Classification of Diseases (ICD-10) codes of discharge diagnosis was used to identify types of thromboembolism and etiology of glomerulonephritis (GN), systemic vasculitis (AAV), Henoch-Schönlein purpura nephritis (HSPN), IgA nephritis (IgAN), idiopathic membranous nephropathy (IMN), minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS). Cochran-Armitage trend test and Logistic regression were used for analysis.

Results: Between 2000 and 2017, there were 15,714 hospitalizations with the aforementioned CGN. Their mean age was 51.7 ± 19.8 years and 39.4% were males. The annual prevalence of overall thromboembolism increased steadily from 1.6% in 2000 to 6.6% in 2017 in a dose-response manner (p for trend <0.001). Among all thromboembolism cases, 49.8% had venous thromboembolism and 31.7% had a pulmonary embolism. The prevalence of thromboembolism in IgAN, FSGS, MCD, IMN, HSPN, LN, and AAV were 0.6%, 2.4%, 2.6%, 5.89%, 2.2%, 4.4%, and 5.3%, respectively. The patients with thromboembolism had 2.30-fold increased risk of death (95% CI 1.53-3.46) after adjustment for age and gender. In multivariate analyses adjusted for multiple confounders such as gender, hypertension, diabetes, cardiovascular disease, cerebrovascular disease, heart failure, chronic obstructive pulmonary disease, infection, LN (OR 8.15; 95% CI 5.25-12.65), IMN (OR 6.93; 95% CI 4.39-10.92), AAV (OR 4.53; 95% CI 2.66-7.61), MCD (OR 4.42; 95% CI 2.56-7.61), HSPN (OR 4.05; 95% CI 2.33-7.03), and FSGS (OR 3.18; 95% CI 1.56-6.49) were significantly associated with the increased risk of thromboembolism compared with IgAN.

Conclusions: In the present study, chronic glomerulonephritis, particularly lupus nephritis, idiopathic membranephropathy, and systemic vasculitis were independently associated with an increased risk of thromboembolism.

PO1563
Identification and Validation of Infection-Related Acute Care Events in Patients with Glomerular Disease

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Background: Infections are an important contributor to morbidity and mortality in glomerular disease (GD). Accurate identification of infections using real world clinical data would support the conduct of observational studies examining infection risk, but standard approaches are labor-intensive. We sought to derive and test the validity of diagnosis-code based algorithms to identify infection-related acute care events (ACEs) within a large cohort of children and adults with GD.

Methods: CureGN is a prospective multi-center cohort study of patients with minimal change disease, focal segmental glomerulosclerosis, membranous nephropathy, or IgA Nephropathy. We describe the sensitivity, specificity, and positive and negative predictive values (PPV/NPV) of four infection diagnosis code lists using manually curated infectious and non-infectious ACEs (hospitalization or emergency department visit) as the gold standard. We then validate the best performing code list within a more contemporary CureGN cohort, using multi-site adjudication of medical records.

Results: In the development phase, the optimal performing combination of diagnosis code lists were used by CureGN coordinators combined with those described by Sahli et al. (PPV 78%, 95% CI 73-83%) (Table 1). Using this code list, 265 infections and 1231 non-infectious ACEs were identified among 2599 CureGN participants in the validation phase (labeled 124 were randomly selected and adjudicated). The PPV and NPV for the final code set were 87% (95% CI 75-90%) and 83% (95% CI 72-93%) respectively.

Conclusions: Diagnosis codes can be used to accurately identify infection-related ACEs among patients with GD. Future studies should validate our findings in other GD cohorts and for specific infection types of high-severity or burden.

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

Risk Factors for TB in GN

PO1564
Patients with Glomerular Disease Are at Very High Risk of TB Infection Compared to the General Population

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Background: Advanced kidney disease is a known risk factor for active TB disease; however this risk has not been studied in patients with glomerular disease (GN). We sought to determine the incidence of TB disease in patients with GN and to explore the risk factors associated with immunosuppressed (treatment) and non-immunosuppressed (treatment susceptible) patients with GN.

Methods: A population-level cohort was created using a centralized kidney biopsy registry (2000-2012) of all GN cases in British Columbia, Canada. IgA nephropathy (IgAN) n=857, focal segmental glomerulosclerosis (FSGS) n=564, ANCA-GN n=404, lupus nephritis (LN) n=366, membranous nephropathy (MN) n=398, minimal change disease (MCD) n=191, and other GN (n=305). TB disease was ascertained by linkage to administrative databases. High TB incidence was defined as >30/100,000 person years (PY) consistent with the definition used in first-world countries. Incidence rates were standardized to the general population to generate standardized incidence ratios (SIR, 95% CI). Hazard ratios were calculated using Cox proportional hazards regression.

Results: During a median follow-up 6.2 years, there were 41 cases of TB disease. TB incident rate was 197.4/100,000PY, and was higher in patients with LN vs. other types of GN (403.0/100,000PY, p<0.05). TB incidence in patients with GN was 23-fold higher than the general population (SIR 23.4, 16.8-31.7), and was high in both Canadian and foreign-born patients (range 124.1-579.6/100,000PY). TB incidence was higher during periods of IS use (282.4 vs. 147.8 per 100,000PY, p<0.05), and most cases (80.5%) had IS exposure prior to TB diagnosis. Time from IS to TB disease was highly variable, with median 3.9 years but 24% of TB cases occurred within 1 year. Reduced kidney function and higher proteinuria were also associated with increased TB risk (Table).

Conclusions: Patients with GN have a high risk of TB disease, irrespective of GN type or country of origin. TB disease can occur within months of starting IS, suggesting that all GN patients should be screened for latent TB early in their disease course.

Risk Factors for TB in GN

Poster
The Impact of Obesity on Glomerulonephritis: A Multicenter Cohort Study of Kidney Biopsy over 40 Years

Jennifer Young

Common form of GN. Obesity had significant risks for progression of ESKD in patients with DMN, and HT-N are significantly higher in obese patients although IgAN is the most common form of obesity at time of diagnosis associated with proteinuria in glomerulonephritis (GN) in obese patients.

Methods: A total of 14,833 adult patients who underwent kidney biopsy and had body mass index (BMI) ≥ 30 kg/m² were identified in 18 tertiary hospitals during 1979-2018. Obesity was defined as BMI ≥ 30 kg/m². We analyzed the prevalence of specific forms of glomerulonephritis in obese patients and effect of obesity on mortality and end stage kidney disease (ESKD).

Results: Obese patients in glomerular disease have increased about 12.8-fold over 40 years between 1979-1988 (0.6%) and 2009-2018 (7.7%). In GN patients with obesity, prevalence of IgA nephropathy (IgAN) is the most common (33.7%) followed by FSGS (13.3%), minimal change disease (MCD) (10.8%), membranoproliferative (MN) (6.0%), lupus nephritis (LN) (2.7%), and hypertensive nephropathy (HT-N) (2.6%). The prevalence of FSGS (HR 1.60, 95% CI 1.24-2.06), DMN (HR 1.46, 95% CI 1.01-2.12) and HT-N (HR 2.14, 95% CI 1.29-3.54) were significant higher in obese patients compared than non-obese patients. Obesity had a 1.39-fold increased risk for ESKD progression during 93.8±0.8 months follow up in total patients (95% CI 1.11-1.73). Obesity had higher risks for progression of ESKD in MCD (HR 2.48, 95% CI 1.02-6.04) and LN (HR, 3.28, 95% CI 1.30-8.31). In patients with FSGS, DMN, and HT-N, obesity was not associated with ESKD. Obesity was not associated with mortality in GN patients although obesity was related to mortality only in MCD patients (HR 2.48, 95% CI 1.02-6.04).

Conclusions: Obesity rates are increasing in GN patients. The prevalence of FSGS, DMN, and HT-N are significantly higher in obese patients although IgAN is the most common form of GN. Obesity had significant risks for progression of ESKD in patients with GN, especially MCD and LN patients.

PO1566

Obesity at Time of Diagnosis Associated with Proteinuria in Glomerular Disease

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Background: Obesity is an established risk factor for chronic kidney disease (CKD).

Methods: We evaluated a cohort of adult patients with biopsy-proven IgA nephropathy, focal segmental glomerulosclerosis (FSGS), ANCA-associated vasculitis (ANCA), or membranoproliferative (MN) between January 2014 and June 2020, to follow up through April 2021. We categorized body mass index (BMI) at time of biopsy as <25 kg/m², 25 kg/m² ≥ 30 kg/m² or ≥ 30 kg/m². We used Fisher's exact and Kruskal-Wallis tests to compare baseline characteristics between groups and a proportional hazards model to evaluate factors associated with CKD progression to kidney replacement therapy (KRT). We used the sign rank test to compare Kaplan-Meier curves of KRT-free survival.

Results: The cohort included 153 patients: 77 (50%) male with median age 50 (IQR 38-65) years and median BMI 28 (IQR 24-34) kg/m². Compared to patients with lower BMIs, patients with BMI ≥ 25 kg/m² had higher median urine protein to creatinine ratios (uPCR) (p = 0.02, Table 1). In univariate analyses, factors associated with progression to KRT were: blood pressure (p = 0.01), uPCR (<p = 0.01), and lower eGFR (<p = 0.001). BMI at biopsy was not associated with CKD progression, adjusted HRs (95% CIs): BMI ≥ 25 kg/m²-1.09 (0.42-2.83); BMI ≥ 30 kg/m²-1.54 (0.68-3.52). Logrank test for differences (data not shown).

Conclusions: Among glomerular disease patients, BMI was associated with proteinuria, but not with progression to KRT.

Funding: NIDDK Support
The Significance of Hematuria in Primary Proteinuric Glomerular Disease

PO1569

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Background: Urinary casts identified through microscopic examination of the urinary sediment (MicrExUrSed) constitute clinically useful elements for the diagnosis of acute and chronic kidney pathologies. Granular, waxy and cellular casts are well characterized. However, a unique type of casts containing non-polarizable lipid-like granules immersed within a lightly granular cast matrix is occasionally found. These casts have been labelled as vacuolated denatured casts (VDC). The clinical significance of VDC is not known.

Methods: A total of 1,022-kidney biopsies was performed. The median follow-up time was 67 (IQR 45, 92) months. Age for GN patients was 43.9 ± 16.7 years and 44.8 ± males. The total and average YLL of all GN were 4741.9 years and 4.64 years, respectively. The average YLL for secondary GN (n = 391) was higher than primary GN (n = 469) being 7.31 ± 2.23 years (p = 0.05). DN (n = 97) had average YLL at 9.76 years followed by LN (n = 243) at 7.1 years. The average YLL (years) for primary GN were: FSGS (n=125), 2.52 years; MGN (n=106), 2.32; IgAN (n=164), 2.26; and MCD (n=74) 1.57. P < 0.05.

Conclusions: The relation between the primary cause of GN and the clinical and histological presentations of GN is not clear. The present study provides useful information on the impact of GN for prioritization of public health policies intervention.

Methods: In this retrospective study, we estimated the average YLL in each glomerular disease. The YLL is the difference between age at death and the standard life expectancy of an individual at the same age. To calculate YLL, we retrieved data from Ramathibodi Hospital Glomerular Registry during January 2011 to December 2020 and national data of standard life expectancy 2020. In both cases, deaths and date of death were recorded. Life table estimator (Newton-Cotes formula) was used to get the average YLL. The total patients in each GN type. GN were categorized into primary GN (IgA nephropathy (IgAN), focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MGN) and minimal change disease (MCD)), and secondary GN (tubulointerstitial, ANCA-GN, infection related GN (IGN) or MPGN, and diabetic nephropathy (DN)).

Results: A total of 1,022-kidney biopsies was performed. The median follow-up time was 67 (IQR 45, 92) months. Age for GN patients was 43.9 ± 16.7 years and 44.8 ± males. The total and average YLL of all GN were 4741.9 years and 4.64 years, respectively. The average YLL for secondary GN (n = 391) was higher than primary GN (n = 469) being 7.31 ± 2.23 years (p = 0.05). DN (n = 97) had average YLL at 9.76 years followed by LN (n = 243) at 7.1 years. The average YLL (years) for primary GN were: FSGS (n=125), 2.52 years; MGN (n=106), 2.32; IgAN (n=164), 2.26; and MCD (n=74) 1.57.

Conclusions: GN causes premature mortality with secondary GN being associated with higher premature mortality. The primary GN, DN and IIGN nephritis have the highest YLL. This study provides useful information on the impact of GN for prioritization of public health policies intervention.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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492
PO1572
Feasibility and Acceptability of Home Urinalysis Monitoring Using a Smartphone Application
Daniella Lev Fere,1,2 Hannah C. Derwick,3,4 Susan L. Furth,5 Lance S. Ballester,5
Jonah Mink,1,2 Stephanie Omumua,1 Michelle Denburg,1 ’The Children’s Hospital of Philadelphia, Philadelphia, PA; 2Schneider Children’s Medical Center of Israel, Petah Tikva, Israel; 3Helen IO, Tel Aviv, Israel; 4Ben Gurion University Faculty of Health Sciences, Beer Sheva, Israel.

Background: Monitoring proteinuria in patients with kidney disease is of crucial importance given its implications for long term disease progression and clinical management. As part of efforts to encourage test adherence, leveraging technology to provide a clinical grade urine analysis result from a home test can greatly enhance the clinical experience for patients, caregivers and providers.

Methods: Children and young adults (5-21 yrs old) at a single pediatric center participated. Caregivers or patients (>12yrs) completed a brief survey and then received a home urinalysis kit by mail. The Healthy.io smartphone app uses advanced computer vision to assess the urine analysis dipstick using the smartphone camera. Families downloaded the app through a text message link and performed a home urine test followed by a survey about their experience. Urine results immediately appeared in the app for patients and accessed by the study team through a secure portal. Patient satisfaction was compared between the new app and current practice (home albumusis or a urine sample brought to clinic) using Wilcoxon rank test with a p value <0.05. Free text responses were analyzed to identify themes related to the app experience.

Results: 103 children, 63 (61%) male, median age 10.9 yrs. (IQR 7.8-14.2) were enrolled. Primary diagnosis included: 47 (46%) glomerular disease, 48 (47%) non-glomerular disease and 8 (8%) kidney transplant recipients. 103(98%) patients were satisfied with the smartphone app compared to 41(40%) patients who were satisfied with the current practice P<0.0001. (Table 1) Patients’ free text comments were divided into themes in table 2.

Conclusions: The Healthy.io home urine testing app received very high rates of satisfaction among patients and caregivers compared to current practice and holds great potential to enhance patient-centered care.

Funding: Commercial Support - Healthy IO Company

Table 1: Patient satisfaction with current practice and Healthy.io home urinalysis smartphone app

Table 2: Written comments regarding app use

PO1573
Proliferative Glomerulonephritis in a Patient with NK Cell Lymphocytosis
Hannah Angle, Jia Yi, Koyal Jain. University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC.

Introduction: Monoclonal gammapathy of renal significance (MGRS) occurs in patients with non-malignant lymphoproliferative disorders who present with kidney injury secondary to monoclonal immunoglobulin deposition.1 We present a rare case of proliferative glomerulonephritis (PGN) likely due to NK cell lymphocytosis.

Case Description: A 57-year-old male with NK lymphocytosis and HITN presented with progressively worsening oliguric renal failure (creatinine 1.1 to 6.2 mg/dL over 3 months) and elevated lambda free light chains (FLC) with a k/λ ratio of 0.06 (k=5.314, λ=52.58). Urine sediment showed numerous dysmorphic RBCs and granular casts. Renal biopsy (limited specimens) revealed PGN with polyclonal-IgG-dominant deposition and background of moderate interstitial fibrosis and tubular atrophy. Although obvious monoclonal lesions were absent and the PGN may have been coincidental, there was concern for a potential paraneoplastic GN induced by NK cell lymphocytosis or, less likely, MGRS. Thus, patient was treated with Cyclophosphamide-Bortezomib-Dexamethasone (CyBoD). However, due to worsening kidney function patient was started on hemodialysis, hoping for potential renal recovery. Despite significant hematologic response (plasma cell burden <1%), chemotherapy was discontinued after 7 months due to lack of renal improvement and worsening medication side effects.

PO1574
A Sporadic Case of Fibronection Glomerulopathy in Which Mass Spectrometry Was Indispensable for the Diagnosis
Rie Kunitomo, Takahisa Kawakami, Kiyotaka Nagahama, Satoru Hibuino, Kazuhiro Fukuoka, Yoshinori Komagata, Shinya Kaname. Kyorin University, Tokyo, Japan.

Introduction: Fibronection glomerulopathy (FG) is an autosomal-dominant hereditary disease, which is caused by deposition of mutated fibronection (FN). The immunostaining of FN is decisive for the diagnosis. We present a case of FG, in which FN was not detected with immunostaining and the detection of FN with mass spectrometry determined the diagnosis.

Case Description: A 60-year-old female with non-functional right kidney with calcui, 5-year history of proteinuria and 2-year history of hypertension presented with proteinuria and nephrocalcinosis. There was no family history of kidney diseases. Physical examination was significant for blood pressure of 176/98 mmHg and the edema. Laboratory test showed serum creatinine of 2.53 mg/dL, serum albumin of 2.3 g/dL, urinary protein 5.8 g/day, and slight urinary granular RBCs. Anti-nuclear antibody, monoclonal protein, cryoglobulin, HCV, or hypercomplementemia was not detected. Open biopsy was performed. Light microscopy showed lobular glomeruli with mesangial expansion with PAS-positive material. Immunoglobulins, including k and λ, light chains, and complements were not detected. Electron microscopy showed massive mesangial deposits with fibrilary structure. However, Congo red staining and immunostaining of DNAJ9B and fibronection (IST-4 and IST-9) were all negative. Finally, the analysis of microdissected glomeruli with liquid chromatography/mass spectrometry (LC/MS) revealed abundance of FN, demonstrating the diagnosis of solitary FG.

Discussion: FG is caused by deposition of the soluble form of FN from serum, rather than the insoluble form produced by resident cells. Therefore, immunostaining with the monoclonal antibody IST-4, which can detect soluble FN, is usually positive in FG, while that with IST-9, which binds only to cellular FN, is negative. Although IST-4 staining was negative in the reported case, FN was detected with LC/MS. This might be due to a structural change of FN in the deposits, which hindered the binding of IST-4 antibody to FN. Furthermore, it was also confirmed that LC/MS is a powerful method to identify characteristics of unexplained glomerular deposits.

PO1575
To Treat or Not to Treat? Therapeutic Challenges in a Case of Advanced Renal Sarcoi
Catherine Lanned, John S. Thrulow, Maura A. Watson. Walter Reed National Military Medical Center, Bethesda, MD.

Introduction: Use of potentially toxic therapy in patients with low chance of renal recovery is clinically challenging. Kidney biopsy with significant interstitial fibrosis and tubular atrophy (IFTA) and reduced estimated glomerular filtration rate (eGFR) suggests unlikely recovery. We describe a patient with advanced IFTA who recovered substantial kidney function with treatment.

Case Description: A 55-year-old man was diagnosed with pulmonary and renal sarcoidosis. Renal biopsy at diagnosis showed granulomatous interstitial nephritis with non-caseating granulomas and 20% IFTA. Prednisone was discontinued but was continued by the patient for onerous side effects. Serum creatinine (Scr) stabilized at 1.5-1.8 mg/dL. He returned two years later with Scr=5.8 mg/dL (eGFR 12 ml/min/1.73m2). Urinalysis was bland. Serum calcium was 10 mg/dL, phosphorus 4.0 mg/dL and intact PTH 20 pg/mL. He lacked pulmonary or systemic symptoms to merit empiric treatment, and he was resistant to receive steroids due to prior side effects. Given new concurrent diagnosis of a monoclonal gammapathy and sclerotic bone lesions, repeat renal biopsy was performed which revealed agranulomatous interstitial nephritis and 50% IFTA consistent with sarcoid. Despite concern for lack of recoverable kidney function due to high chronicity and reduced eGFR, treatment with high-dose prednisone was started based on the unknown time course of recurrence in a relatively young active patient. Scr improved to 3.0-3.2 mg/dL (eGFR 17 ml/min/1.73m2) and dose of prednisone remained stable. The gammapathy was not renally significant and sclerotic bone lesions were attributed to sarcoidosis.

Discussion: In this patient with active sarcoidosis, presenting with eGFR 12 ml/min/1.73m2 and 50% IFTA on biopsy, it would be reasonable to presume limited benefit and defer steroid treatment, especially given patient reluctance. However, there was significant recovery with treatment. This should prompt reconsideration of the prognostic value of renal pathology in sarcoidosis, especially in view of known heterogeneous involvement. The data presented are those of the authors and do not reflect the official policy of the Department of the Army/Navy/air Force, the Department of Defense, or the United States government.
PO1576

Clinicopathological Characteristics of Adult IgA Nephropathy: A Retrospective Cohort Study

Dawn J. Caster,1 Clint Abner,2 Kerime Ararat,2 Patrick D. Walker,2 Amin Yakubu,2 Martin C. Bunke,1 University of Louisville, Louisville, KY; 1Arkana Laboratories, Little Rock, AR; 2Genesis Research, LLC, Hoboken, NJ; 3Traverse Therapeutics Inc, San Diego, CA.

Background: IgA nephropathy (IgAN) is the most common form of primary glomerular nephropathy and a leading cause of chronic kidney disease (CKD). These analyses characterize clinical and histological features of IgAN in adults at time of kidney biopsy.

Methods: A retrospective study of clinical and histologic characteristics was performed in patients (pts) ≥18 yrs of age with ≥1 IgAN positive kidney biopsy without prior kidney transplant reported from Arkana Laboratories (Jan 1, 2016-May 30, 2020). Estimated glomerular filtration rate (eGFR) was calculated using the CKD-Epi equation without race modifier. All results are at the time of biopsy.

Results: Of 47,262 kidney biopsies performed during the study period, 3,638 (6.5%) IgAN positive cases met the study criteria and were included, of which, 62.7% were male, 49.6% White, 5.1% African American, 5.3% Hispanic, 5.6% Asian and 34.4% Unknown/Other race/ethnicity. Mean (SD) age at biopsy was 47.7 (16.6) yrs. Urine protein to creatinine ratio/24-hour urine protein data were available for 52.4% of pts and the median (Q1-Q3) was 3.0 (1.0 – 5.0) g/g. Additionally, 65.2% of pts had hypertension, 63.1% had existing liver disease were excluded.

Conclusions: The large proportion of pts diagnosed at CKD stage ≥3 and high MEST-C scores for S and T suggest significant disease duration at the time of biopsy. Earlier intervention may be of value to prevent ESKD.

Funding: Commercial Support - Traverse Therapeutics

Table 1. Immunofluorescence microscopy characteristics of adults with biopsy-confirmed IgA nephropathy

<table>
<thead>
<tr>
<th>IgAN</th>
<th>n</th>
<th>%*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal/Trace</td>
<td>53</td>
<td>1.2%</td>
</tr>
<tr>
<td>+</td>
<td>3.1%</td>
<td>31.4%</td>
</tr>
<tr>
<td>++</td>
<td>2.9%</td>
<td>67.2%</td>
</tr>
<tr>
<td>-</td>
<td>4.0%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Via</td>
<td>1.1%</td>
<td>25.7%</td>
</tr>
<tr>
<td>++</td>
<td>1.0%</td>
<td>24.3%</td>
</tr>
<tr>
<td>+</td>
<td>1.1%</td>
<td>32.7%</td>
</tr>
<tr>
<td>Mesangial Hypercellularity</td>
<td>755</td>
<td>12.0%</td>
</tr>
<tr>
<td>No significant mesangial hypercellularity</td>
<td>2,130</td>
<td>52.7%</td>
</tr>
<tr>
<td>Mild to moderate mesangial hypercellularity</td>
<td>2,074</td>
<td>47.3%</td>
</tr>
<tr>
<td>Endocapillary hypercellularity</td>
<td>3,660</td>
<td>83.0%</td>
</tr>
<tr>
<td>No mesocapillary proliferation</td>
<td>744</td>
<td>17.0%</td>
</tr>
<tr>
<td>Segmental Sclerosis</td>
<td>1,132</td>
<td>25.7%</td>
</tr>
<tr>
<td>Absence of segmental sclerosis and/or adhesion of tuft to Bowman capsule</td>
<td>1,007</td>
<td>24.3%</td>
</tr>
<tr>
<td>Presence of segmental sclerosis and/or adhesion of tuft to Bowman capsule</td>
<td>1,455</td>
<td>32.7%</td>
</tr>
<tr>
<td>Tubular Atrophy or Interstitial Fibrosis</td>
<td>755</td>
<td>12.0%</td>
</tr>
<tr>
<td>Tubular atrophy or interstitial fibrosis</td>
<td>2,845</td>
<td>64.9%</td>
</tr>
<tr>
<td>Crescents</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>E0 (no crescents)</td>
<td>3,575</td>
<td>82.6%</td>
</tr>
<tr>
<td>C1 (present in 24% glomeruli)</td>
<td>662</td>
<td>15.3%</td>
</tr>
<tr>
<td>C2 (present in ≥25% glomeruli)</td>
<td>147</td>
<td>3.4%</td>
</tr>
</tbody>
</table>

*May not equal 100% due to unknown values

PO1577

Natural History of IgA Nephropathy: Analysis of a UK National RaDaR IgA Nephropathy Cohort

Jonathan Barratt,1,2 Moin Saleem,3,4 Fiona E. Bradlon,1 Kevin Carroll,1 Ping He,1 Bruce M. Hendry,1 Alex Mercer,12 David Pitcher,12 Retha D. Steenkamp,1,2 A. Neil Turner,1,2 Daniel P. Gale,1,2 1University of Leicester, Leicester, United Kingdom; 2Leicester General Hospital, Leicester, United Kingdom; 3University of Bristol, Bristol, United Kingdom; 4Bristol Royal Hospital for Children, Bristol, United Kingdom; 5UK Renal Registry, Bristol, United Kingdom; 6The Renal Association, Bristol, United Kingdom; 7Royal Free Hospital, London, United Kingdom; 8University College London, London, United Kingdom; 9Traverse Therapeutics Inc, San Diego, CA; 10University of Edinburgh, Edinburgh, United Kingdom; 11JAMCO Pharma Consulting, Stockholm, Sweden; 12KIC Statistics Ltd, Cheshire, United Kingdom.

Background: Primary IgA nephropathy (IgAN) is the most common form of glomerulonephritis and a major cause of renal failure. Here we describe the natural history of IgAN using the UK National Registry of Rare Kidney Diseases (RaDaR). Since 2013, patients with biopsy-proven IgAN and eGFR <60 mL/min/1.73m² or proteinuria >1g/24h have been enrolled into RaDaR from 107 adult and paediatric kidney units across the UK, including retrospective and prospective data. Patients with systemic vasculitis or pre-existing liver disease were excluded.

Methods: Baseline date was defined as first occurrence of renal biopsy, primary renal diagnosis or symptom presentation. Patients were grouped into those with ESKD (ESKD group) and those without ESKD at baseline with survival time calculated from baseline to last follow-up for all patients.

Results: In the ESKD group (n=326), median age at first dialysis (56% of patients) and kidney transplant (7%) was 38 yrs (IQR 29-50). In the CKD group (n=1838), median baseline age was 39 yrs (IQR 28-50) with paediatric onset of disease comprising 6%. Baseline median urine PCR was 1.5 g/g (IQR 0.6-3.2; n=356) and mean eGFR was 58 mL/min/1.73m² (SD 32; n=440). Median follow-up was 9.2 years (IQR 5.1-16.3) and ESKD/death occurred in 53% of patients (~1% death). Kaplan-Meier survival curves of paediatric and adult patients show 50% survival probability of 24 & 10 years, respectively (Figure 1).

Conclusions: RaDaR contains a large cohort with long follow up enabling detailed investigation of the natural history of IgAN. These results indicate associations between rapid disease progression and poor outcomes, highlighting a need for effective treatments for patients with IgAN with renal impairment or >1g/24h proteinuria.

Funding: Commercial Support - Traverse Therapeutics

PO1578

Symptom Burden Among Immunoglobulin A Nephropathy (IgAN) Patients in a US Real-World Setting

Robert M. Perkins,1 Carolina A. Aldworth,2 Raymond Przybysz,3 Jim P. Doherty,2 Stephen W. Olson,1 Aneshe T. George,3 Jaydeep Das,4 Rachel Studer,1 Novartis Pharmaceuticals Corporation, East Hanover, NJ; 2Novartis Pharmaceuticals Corporation, East Hanover, NJ; 3Novartis Healthcare Pvt. Ltd., Hyderabad, India; 4Novartis Pharmaceuticals Corporation, East Hanover, NJ.

Background: Immunoglobulin A nephropathy (IgAN) is the most prevalent chronic glomerulonephritis and 15-40% of patients will progress to end stage kidney disease (ESKD) within 10-20 years of diagnosis. The symptom burden by eGFR and proteinuria levels has not been well described in IgAN and is presented here.

Methods: This is a retrospective, stratified analysis of adult (≥18 years) patients in de-identified Optum® Electronic Health Records (2007-2019). Pre-processed physician notes were used to select patients with at least two IgAN records without any secondary or negative indication. Patients without a record of renal biopsy, valid eGFR and proteinuria

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
levels, or with a history of ESKD/kidney transplant were excluded. The demographic and clinical characteristics, including symptoms up to 12 months before and up to the 1st record of IgAN are presented here; these symptoms were stratified by eGFR and proteinuria levels.

Results: The final cohort consisted of 846 patients with a mean age of 48.5 years; 57.7% were male and 7.0% Asian. Proteinuria levels of ≥1 g/day were found in 35.7% of patients. The median eGFR was 39.0 ml/min/1.73m², median creatinine was 1.8 mg/dL, and 20.8% of patients had severe deterioration of kidney function (eGFR <15). Overall, more patients in higher chronic kidney disease (CKD) stages experienced any given symptom but this trend was inconsistent for higher proteinuria levels.

Conclusions: Our study found that a considerable proportion of patients experienced pain, fatigue and edema. Except in a few instances, all symptoms increased with lower eGFR levels but this trend was less apparent for proteinuria. Our overall findings suggest that a relatively large proportion of IgAN patients, even those with preserved kidney functions could be experiencing substantial symptomatic burden and this warrants further investigation.

Funding: Commercial Support - Novartis Pharmaceuticals Corporation

PO1579
Clinical Outcomes of Kidney Diseases Diagnosed in Active Duty Service Members
Trevor W. Tobin, John S. Thurlow, Robert Nee, Christina M. Yuan. Walter Reed National Military Medical Center, Bethesda, MD.

Background: There are no studies that have reported glomerular disease prevalence and looked at the overall healthcare outcomes following renal biopsies in active duty soldiers. We aimed to determine the prevalence of renal diseases amongst the soldiers biopsied at our hospital and determine the outcomes for these individuals as a result of their diagnoses.

Methods: In this retrospective study, we evaluated the results of all native renal biopsies performed at Walter Reed National Military Medical Center from 2005 to 2020. We used this data to determine the prevalence of patients who progressed to have ESKD (End Stage Kidney Disease), renal transplantation, creatinine doubling, proteinuria greater than 3.5 gms/day, medical evaluation board (MEB), and death. The AHTLA and JLV EMR systems were used to collect data on the patients who met our inclusion criteria.

After the data was collected, chi squared tests were performed and Kaplan Meier Curves were created for analysis.

Results: Among 169 patients (mean age =32 years old; 79% male; 48% white; 37% black; 7% Hispanic; 4% Asian; 3% pacific islander; 2% other), the most common indication for renal biopsy was for concomitant hematuria and proteinuria (31%) and the most common histologic diagnosis was IgA Nephropathy (23%). The mean time of follow up was 7.3 years. 11% progressed to ESKD, of whom 87% received a kidney transplant (10% overall). Approximately one third progressed to proteinuria greater than 5.3 gms per day and 5% died.

Conclusions: We identified IgA Nephropathy as the dominant histologic diagnosis in our patients undergoing renal biopsy between 2005 and 2020. Despite our patients being largely young and healthy individuals, renal biopsy identified severe disease with over 10% of patients progressing to ESKD and 5% mortality.

PO1580
Clinicopathological Features, Risk Factors, and Outcomes of Immuno-globulin A Nephropathy Associated with Hepatitis B Virus Infection
Jiachuan Xiong, Xinqiao Hospital, Chongqing, China.

Background: Hepatitis B virus (HBV) infections are associated with an increased risk of kidney diseases. However, the effects of HBV infection on the prognosis of immune-A nephropathy (IgAN) are unclear.

Methods: A total of 838 patients with biopsy-confirmed IgAN were enrolled in this retrospective cohort study. The patients were categorized into either affected by IgAN and HBV infection (HBsAg-IgAN) or by primary IgAN with no sign of HBV infection (P-IgAN). A 1:1 propensity-score matching was performed between the two groups, followed by a Kaplan-Meier survival analysis, to compare the diagnoses, and a Cox regression analysis, to identify factors influencing the HBsAg-IgAN outcomes.

Results: A total of 176 pairs of patients were successfully matched. A significant difference in the systolic blood pressure and ura, serum creatinine, uric acid, and 24-h urine protein levels was observed between the groups. A renal pathological analysis also revealed a significant difference in the mesangial hypercellularity between the groups. During a median follow-up period of 2.4 years, Kaplan-Meier analysis also revealed a significant difference in the renal survival between the groups. Furthermore, multivariate Cox analysis confirmed that HBV infection is an independent risk factor for IgAN progression (hazard ratio [HR] 2.096; 95% confidence interval [CI] 1.091-4.026).

Finally, the HBsAg-IgAN patients who received treatment with renin-angiotensin-aldosterone system inhibitors had a better overall prognosis than those who received immunosuppressive therapy and antiviral treatment.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.

PO1581
Factors Associated with ESKD in Mexican Patients with IgA Nephropathy: A Single-Centre Retrospective Cohort Study
Diana Xavier, Guadalupe Ramos De Jesus, Octavio R. Garcia-Flores, Bernardo Moguel. Instituto Nacional de Cardiologia Ignacio Chavez, Mexico, Mexico.

Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis in the world among patients undergoing renal biopsy. To standardize the histological findings, the Oxford Classification (OC) has allowed clarifying kidney lesions that confer potential risk of progression. The aims are describe the factors associated with ESKD and treatment implemented in Mexican patients with IgAN.

Methods: We conducted a single-center, retrospective cohort study in a tertiary hospital in Mexico City, patients with biopsy-proven IgAN and followed up for at least 2 years and examined the relationship between clinical parameters and OC to predict the risk of ESKD after biopsy. We used age and sex adjusted Cox proportional hazards models to study the association of the predictor variables (MEST-C, global glomerulosclerosis and proteinuria >1g/day) with the incidence of ESKD. The HRs were expressed with 95% confidence intervals (95% CI).

Results: 35 patients were included, mean age 37.2±15.2 years, 60% were female, mean eGFR and proteinuria at biopsy were 60.8±34.6 ml/min/1.73m² and 3.4±4.0 g/day respectively. ESKD or eGFR decline by ≥50% as compared to baseline occurred in 10 patients (28.6%) in a median follow-up of 2 years. The eGFR at 24 months post-biopsy 59.1±39.6 ml/min/1.73m². 18 patients received immunosuppressive treatment and 24 received prednisone. The distribution of MEST-C lesions were: M1-35(100%), E1-20(57.1%), S1-33(94.3%), T1-15(42.9%) and T2-2(7.3%), C1-1(31.4%) and podocytopathic features in 0 (0%) of the MEST-C components. only T2-2(7.3%) were significantly associated with ESKD (HR 4.66, 95% CI 0.8 to 27.1). After adjusting for confounding variables global glomerulosclerosis >50% (HR 1.92 [1.02-3.58], p=0.001) and New Oxford classification system (O-grade III (HR 2.79 [0.89-8.58], p=0.001) were independently associated with ESKD.

Conclusions: There are no reports in Mexico of clinical characteristics and outcomes of IgA nephropathy. This study demonstrates that IgA nephropathy was more common in young adults and women and that the progression to ESKD or the global glomerulosclerosis >50% is similar to the reported in the literature. IFTA >50%, and O-grade III were associated with the development of ESKD in Mexican population.

PO1582
External Validation of Two New IgA Risk-Prediction Tools in a Norwegian Cohort
Yngvar Lunde Haakso1, Njål Lura, Rune Bjorneklett, Lars S. Bostad, Thomas Knoop, Haakelund Universitetssjukehus, Bergen, Norway; Universitetet I Bergen, Bergen, Norway.

Background: Recently two prediction tools for IgA nephropathy (IgAN) have been developed combining clinical and histopathological parameters. Barbour and colleagues developed the International IgAN Prediction Tool, to predict the risk for 50 % decline in estimated glomerular filtration rate (eGFR) or end stage renal disease (ESRD) up to 80 months after diagnosis. Schena and colleagues developed the IgA Nephropathy Clinical Decision Support System (CDSS), using artificial neural networks (ANN) to estimate the risk for ESRD. In the present study we aim to externally validate both prediction tools using a Norwegian cohort with long-term follow-up.

Conclusions: Our results indicate that the clinicopathological features and outcomes of patients with IgAN differ significantly between those with and without HBV infection, and that HBV is an independent risk factor for IgAN progression.

Funding: Government Support - Non-U.S.

Poster
PO1583
International IgA Nephropathy Network (IIgANN) Risk Prediction and Longitudinal Outcomes in the First South-Asian Prospective IgA Nephropathy Cohort (GRACE-IgANI)
Suceena Alexander,1 Santosh Varughese,1 Athul Thomas,1 Jeethu J. Eappen,1 Elenjickal E. John,1 Anna T. Valson,1 Vinosi G. David,1 Mohamed R. Daha,2 George John,1,2 John Feehally,3 Jonathan Barratt,4 Christian Medical College Vellore, Vellore, India; 2Université Libre de Bruxelles; 3University of Leicester; 4University of Leicester, Leicester, United Kingdom; 5University of Leicester College of Life Sciences, Leicester, United Kingdom.

Background: The Glomerular Research And Clinical Experiments- IgA Nephropathy in Indians is a prospective longitudinal cohort registered with WHO trial id: ISRCTN36834159. The performance of the IIgANN risk prediction score (Barbour et al.) has not been assessed in South Asian IgAN.

Methods: 201 consenting adult IgAN patients were consecutively recruited post kidney biopsy. 195 patients (97%) completed 3 year longitudinal follow-up. Of these, 180 patients had complete Oxford MEST-C score at baseline. Composite outcome (CO) was defined as ≥50% fall in eGFR from baseline and/or eGFR <15ml/min/1.73m2 or RRT/death.

Results: The median predicted 3-year risk of a 50% decline in eGFR or ESKD using the IIgANN risk prediction tool was 18.1% (IQR 7.4–31.2) at baseline. The minimum risk was defined as ≥50% fall in eGFR from baseline and/or eGFR <15ml/min/1.73m2 or RRT/death. Concordance index was 0.85 for Barbour, and 0.82 for Schena (p=0.03).

Conclusions: Both prediction tools perform well and could become helpful tools for clinicians to identify patients at risk. Barbour’s tool seems to lose prognostic discriminative value at a faster rate than Schena’s over time.

PO1584
IgA Nephropathy Histopathology and Long-Term Renal Prognosis
Nora C. Maddy, Robert Nee, Sarah M. Gordon, Stephen W. Olson. Walter Reed National Military Medical Center, Bethesda, MD.

Background: The Oxford Classification established the mesangial hypercellularity (M), Endocapillary hypercellularity (E), segmental sclerosis (S), Tubulointerstitial fibrosis (T), and crescents (C) score as an important prognostic tool for IgA nephropathy (IgAN). However, these studies did not investigate the impact of complement 3 (C3) immunofluorescence (IF) staining or interstitial inflammation (iI) on long term renal outcomes, nor evaluate an ethnically diverse population which included African Americans.

Methods: We queried the military health system (MHS) by ICD-9/10 codes to identify potential IgA nephropathy cases. We then reviewed the electronic medical record to find those with biopsy-proven IgA nephropathy. Prespecified clinical data was collected to include MEST-C scores, iI, and C3 IF. Primary outcomes included >50% decline in estimated glomerular filtration rates (eGFR), chronic kidney disease (CKD) with eGFR <60ml/min/1.73m2, and end-stage kidney disease (ESKD).

Results: 172 patients were identified with a mean follow-up of 11 years. Mean age was 32 years; 77.9% male; 64.5% White, 9.9% Black, and 12.2% Asian/Pacific Islanders. C3 IF ≥2+ was significantly associated with ESKD (p=0.03) and >50% decline in eGFR (p=0.02). If ≥15% was significant for ESKD (p=0.003), CKD (p=0.01), and >50% decline in eGFR (p=0.01). T and C scores were significant for ESKD, CKD, and >50% decline in eGFR (all p<0.001). S score was significant for ESKD (p=0.02) and CKD (p<0.001). E score was significant for CKD (p<0.003). M score was not significant for any of the primary outcomes.

Conclusions: We present histopathology associated long term renal outcome data for the most ethnically diverse IgAN cohort with the longest follow up to date in such a population. Our data suggests that degree of C3 staining on IF and amount of interstitial inflammation could augment the prognostic accuracy of the MEST-C score. In addition, it supports the theory that IgA immune complexes activate the alternative complement pathway which drives significant interstitial inflammation ultimately resulting in tubular atrophy and interstitial fibrosis.

Disclaimer: The views expressed are those of the authors and do not reflect official policy of the Department of the Army/Navy/Air Force, Department of Defense, or United States government.
PO1585

Severity of Arterial and Arteriolar Sclerosis in IgA Nephropathy and Effects of Renin-Angiotensin System Inhibitors on Its Prognosis

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Background: IgA nephropathy (IgAN) patients often suffer from renal arterial intimal thickening (AIT) and arteriolar hyaline (AH) however, it is unclear whether these features are associated with a poor prognosis. This study aimed to analyze whether treatment with renin-angiotensin system inhibitors (RASI) improves those patients’ survival.

Methods: This retrospective cohort analysis included total 871 patients with IgAN, grouped according to the absence or presence of AIT (Study 1; AIT0: n=415, AIT1: n=268) or AH (Study 2; AH0: n=405, AH1: n=354). The clinical, laboratory, and histological backgrou nds of the patients were analyzed along with their 20-year renal progression. In the AIT1 and AH1 groups, the effect of renin-angiotensin system inhibitors (RASI) on renal progression after making adjustments for the background was analyzed and risk factors for progression were also analyzed.

Results: IgAN patients with AIT1 or AH1 had significantly higher age, blood pressure, body mass index, total cholesterol, uric acid levels, and proteinuria than patients with AIT0 or AH0. They also had more marked histodiagnostic findings, decreased renal function, and lower survival rates (AIT: 62.2% vs. 83.4%, P<0.0001; AH: 63.5% vs. 85.4%, P<0.0001). Multivariate Cox regression analysis considering with clinical and histological findings and treatments revealed AIT and AH as an independent factor for disease progression (AIT1: hazard ratio (HR), 1.98, 95% confidence interval (CI), 1.98-2.01; AH1: HR, 2.12, 95%CI, 2.04-2.19). The renal survival rate was significantly higher in IgAN patients with AIT0 or AH0 who were treated with RASI than in those who were not treated with RASI after background adjustments (AIT1: 71.1% vs. 50.4%, P=0.023; AH1: 76.4% vs. 39.5%, P=0.006). RASI was found to be an independent factor in the prevention of progression, by multivariate Cox regression analysis (AIT1: HR, 0.40, 95%CI, 0.14-0.84; AH1: HR, 0.42, 95%CI, 0.27-0.67).

Conclusions: AIT and AH are associated with serious clinical, laboratory and histological findings and a poor prognosis. RASI was found to improve renal progression of those patients.

PO1586

Intensity of Glomerular Galactose-Deficient IgA1 Deposition Can Be a Marker of Disease Activity in IgA Nephropathy

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Background: Galactose-deficient IgA1 (Gd-IgA1) plays a crucial role in the development of IgA nephropathy (IgAN). Recently, it was reported that Gd-IgA1 specifically deposit on glomeruli of primary IgAN using Gd-IgA1-specific monoclonal antibody (KM55 mAb). However, the association of intensity of Gd-IgA1 deposition and clinical parameters and histological severity are not clarified.

Methods: We performed immunostaining with KM55 mAb on paraffin sections of all 141 patients with primary IgAN, glomerular Gd-IgA1 deposition was quantified by Image-J software (low, middle, and high groups). The level of proteinuria in the positive. We divided patients into tertiles according to the amount of Gd-IgA1 deposition with creatinine, serum/urinary level of Gd-IgA1, and proteinuria.

Results: Intensity of glomerular Gd-IgA1 by Image-J software, and analyzed its association with histological findings. We also analyzed the association of intensity of glomerular Gd-IgA1 by Image-J software, and analyzed its association with clinical parameters and histological severity are not clarified.

Conclusions: The intensity of glomerular Gd-IgA1 deposition is associated with histological severity, especially acute lesions. Thus, galactose-deficient IgA1 staining may be a valuable index for therapeutic intervention.

PO1587

Segmental Necrotizing/Crescentic Glomerulonephritis (SGN) in IgA Nephropathy (IgAN): A Single-Center Experience

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Background: The presence of SNGN on renal biopsy generally portends a poor prognosis, similarly poor prognosis was seen with presentation and course of pts with IgAN to determine if the presence of SNGN portends a poorer prognosis in this pt population.

Methods: Biopsies done at Rush University Medical Center from 1992-2019, found IgAN in 75 pts in whom AIT and SNGN was seen in 21 (28%). Clinical, laboratory, histologic features at biopsy, treatment and outcome data (doubling of SCr and ESKD) were collected prospectively. Pts with and without SNGN were compared. Data is presented a means±SD and a P value of <0.05 was significant.

Results: At biopsy there was no difference in age (42±16 vs 43±17 yrs), gender (54% vs 46% male), race or Scr (1.7±1 vs 1.6±1 mg/dl) in pts with compared to those without SNGN. Pts with SNGN had higher systolic BPs (140±14 vs 131±17 mmHg, P=0.02) and higher UPro/Scr ratio (2.8±2.7 vs 1.7±1.7 g/g, P=0.04). All 15 SNGN pts tested were ANCA negative. The percent of glomeruli with global (GS)+segmental (SS) sclerosis (33±25% vs 38±28%) and interstitial fibrosis/tubular atrophy (IFTA) (22±20 vs 23±22%) was similar for those with vs without SNGN. In pts with SNGN, only 15% had lesions involving >25% of glomeruli. FU was similar on average (76± vs 87± yrs) in pts with and without SNGN and treatment with ACEi/ARBs was similar (88 vs 100%). A larger proportion of pts with SNGN were treated with immunosuppressive agents (69 vs 21%, P=0.003). At FU, doubling of SCr (25 vs 22%), ESKD (19 vs 21%) and renal survival at 10 yrs (80 vs 76%) were similar in pts with and without SNGN. In both groups, pts that progressed to ESKD had a higher proportion of glomeruli with GS+SS (IgAN: 63±16 vs 24±21%, P=0.002 and No SNGN: 64±27 vs 31±24%, P=0.002) and IFTA (IgAN: 47±19 vs 16±16%, P=0.006 and No SNGN: 41±27 vs 17±18%, P=0.01). In pts with SNGN, the proportion of glomeruli with SNGN was similar in those with and without ESKD (16±14 vs 18±17%).

Conclusions: In pts with IgAN, the presence of SNGN is frequently seen but does not alter prognosis. This may be the result of >25% involvement with SNGN lesions in the majority of our pts and more aggressive treatment in pts with SNGN. The presence of advanced GS+SS and IFTA at biopsy were most associated with progressive kidney disease rather than SNGN.

PO1588

Novel Scoring System Based on the Oxford Classification Indicating Steroid Therapy Use for IgA Nephropathy

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Background: The Oxford classification identifies predictors of the renal prognosis for IgA nephropathy (IgAN); however, it has been unclear about usefulness for deciding the management approach. We analyzed the clinical utility of this classification for indicating steroid therapy.

Methods: The effects of steroid therapy on the long-term prognosis for all 858 IgAN patients and patients divided with M0, M1, E0, E1, S0, S1, and C0 scores were analyzed using the Oxford classification (M, mesangial hypercellularity; E, endocapillary hypercellularity; S, segmental sclerosis; T, tubular atrophy/intertstitial fibrosis, and C, crescents) were examined using Kaplan-Meier analysis and Cox regression analysis. The steroid responder score (SRS) and steroid non-responder score (SNRS) were determined using the obtained results. The effects of steroid therapy on renal prognosis according to the combination of the total SRS and SNRS for IgAN were analyzed using Cox regression analysis.

Results: Steroid therapy improved the 20-year renal survival rates in all IgAN patients (steroid (+): 75.5% vs. steroid (-): 61.7%, P=0.025) and patients with M1, E1, S1, and T0 scores. We recognized the total score of M1, E1, S1, and C scores (0-4 points) as the SRS and that of T1 and T2 scores (0-2 points) as the SNRS. Multivariate Cox regression analysis revealed that steroid therapy improved the long-term renal prognosis in IgAN patients with higher SRS and lower SNRS (SRS4/SNRS0: hazard ratio [HR], 0.08 and P<0.008; SRS3/SNRS3: HR, 0.05 and P<0.025; SRS4/SNRS1: HR, 0.11 and P<0.007), but not in IgAN patients with lower SRS (0–3) SNRS1 and any SRS/SNRS2.

Conclusions: Patients with SRS4/SNRS1 or SRS3/SNRS3 who responded to steroid treatment; contrarily, those with T1 and T2 scores did not. A higher SRS was a useful indicator for steroid therapy. Nevertheless, prevention of progression in IgAN patients with SNSR was difficult with steroid therapy.
PO1589

Remission of Hematuria Is Associated with Favorable Prognosis in IgA Nephropathy

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Background: Recent studies have shown that remission of hematuria is associated with favorable clinical outcomes in patients with IgA nephropathy (IgAN). The current study was conducted to compare the long-term clinical outcomes between patients with remission of hematuria and those with persistent hematuria using the stricter but intuitive definition of “remission of hematuria” than that used in previous studies.

Methods: This retrospective, multicenter, observational study was conducted using a cohort of patients diagnosed with IgAN through kidney biopsy at three tertiary hospitals. A total of 403 patients who had been followed up for more than 3 years and who underwent regular check-ups at intervals of at least 6 months were enrolled. Hematuria remission was defined as the absence of hematuria for at least 3 months after biopsy for diagnosis but with no RBC per high-power field observed in the urine under the microscope for at least 2 years thereafter.

Results: The mean annual rate of eGFR decline was lower in the remission of hematuria group than in the persistent hematuria group (-1.51 ± 2.86 vs. -2.60 ± 3.18 mL/min/1.73 m²/yr, p = 0.002). In the remission of hematuria group, the mean annual rate of eGFR decline decreased after hematuria disappearance (from -1.28 ± 7.06 to 0.09 ± 0.29 mL/min/1.73 m²/yr; p = 0.016). Multivariable analysis revealed remission of hematuria as an independent predictor of a 50% reduction in kidney function (hazard ratio, 0.55; 95% CI, 0.33 to 0.99). Renal survival, defined as a 50% reduction in kidney function, was better in the remission of hematuria group than in the persistent hematuria group (p = 0.030). However, free of ESRD was not significantly different between the two groups (p = 0.079).

Conclusions: In this study, which used a more rigorous but intuitive definition of hematuria remission than that used in previous studies, patients with remission of hematuria showed favorable kidney prognosis. This new definition for remission of hematuria could be used as a prognostic marker in actual clinical practice.

Comparison of renal outcomes between the two groups

PO1590

Reduction of Urinary Levels of Lectin Pathway Complement Components in an IgA Vasculitis Patient After MASp-2 Inhibition with Narsoplimab

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Background: A young female suffering from IgA vasculitis was treated with 4 mg/kg weekly infusions of narsoplimab (a MASp-2 inhibitor) for 12 weeks. MASp-2 is considered the key activator of the lectin pathway (LP) by cleaving C4 and C2, after the binding of LP pattern recognition molecules to its ligands. Inhibition of MASp-2 is predicted to decrease complement activation in complement-mediated kidney diseases. In this exploratory study we measured the levels of different LP complement components to evaluate the influence of narsoplimab on complement activation.

Methods: Urine levels of complement activation markers (C4c, C3bc and soluble C5b-9) and urinary levels of ficolin-1, -2 and -3, MBL, CL-11, MASp-3, MAC-1 and PTX-3 were measured using sandwich-ELISAs. Urine samples were subjected to LC/MS/MS. Correlations between LC/MS/MS and sandwich-ELISA were conducted using simple linear regression and Spearman’s rank correlation coefficient. Significance: p value < 0.05. Urine proteins were adjusted for creatinine excretion and expressed as specific protein/creatinine ratio.

Results: C4c/creatinine ratio, ficolin-3/creatinine ratio and C3bc/creatinine ratio levels were decreased 75%, 58% and 29% respectively, from baseline to the end of the treatment; while levels of MBL and CL-11 remained stable during the treatment. C4c/creatinine ratio levels were significantly correlated to LC/MS/MS C4 data (R²: 0.5059; Spearman: r = 0.5824, p = 0.0402). Circulating levels of complement components in serum were unaltered during treatment. Soluble C5b-9, ficolin-1, -2, MASp-3 and MAC-1 were undetectable in urine and PTX-3 was undetectable in both urine and serum.

Conclusions: This is the first report describing the effect of narsoplimab on urinary complement levels in a complement-mediated kidney disease. Our data suggest a decrease in local complement activation with narsoplimab treatment. Further studies are ongoing to evaluate the use of urine as a non-invasive, inexpensive and readily accessible resource to monitor responses to complement-directed treatments.

Funding: Commercial Support - Omeros Corporation

PO1591

Identification of Urinary Diagnostic Biomarker for IgA Nephropathy by Lectin Microarray

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Background: IgA nephropathy (IgAN) is the most common form of glomerulonephritis and the pathogenic roles of aberrantly glycosylated IgA1 have been reported. The glycan abnormalities are mediated by the alterations of glycan processing enzymes, such as decreased activity of β-1,3-galactosyltransferase (CIGALT1). However, it is unknown whether the detection of urinary glycosylation changes contributes to the diagnosis of IgAN.

Methods: We measured the urinary glycan signals bound to 45 lectins on LeCChip in the 493 patients with renal biopsy-proven kidney diseases at Okayama University Hospital from December 2010 to September 2017. To evaluate the diagnostic performance, we added the urinary glycan signals to the diagnosis model with the reference standard, i.e., the presence of hematuria, 24 hr urinary protein excretion, and concentration of serum IgA.

Results: The inclusion of 6 lectins showed a significant improvement of the models: Amanthus Caudatus (ACA) with the difference of AUC 0.038 [95%Cl, 0.019 - 0.058, P < 0.001], Agaricus Bisporus (ABA) 0.035 [95%Cl, 0.015 - 0.055, P = 0.001], Mawia Amuresis (MAH) 0.035 [95%CI, 0.015 - 0.054, P < 0.001], Mawia Amurensis (MAH) 0.035 [95%CI, 0.015 - 0.054, P < 0.001], Macula Pomifera (MPA) 0.021 [95%CI, 0.000 - 0.047, P = 0.006], Jacalin 0.019 [95%CI, 0.004 - 0.034, P = 0.012], and Lycopersicon Esculentum (LEL) 0.016 [95%CI, 0.0 - 0.032, P = 0.045]. All 6 lectins demonstrated reduced signals in IgAN patients and 3 lectins (ACA, BABA, MAH) showed false discovery rate (FDR) below 0.05. In 3 lectins, each signal plus reference standard showed good model fitting associated with the improvement of AUC. By decision curve analysis, there was a 3.45% net benefit by adding urinary glycan signals to ACA at the pre-defined threshold probability of 40%.

Conclusions: The reduction of Galβ1-3GalNAc (T-antigen), Sia(2-6)Galβ1-3 GalNAc (Sialyl T) and Sia(2-3)Gal(α1-3) GalNAc (disialyl-T) was suggested by binding specificities of 3 lectins. CIGALT1 and COSMC were responsible for the biosynthesis of these glycans, and they were known to be downregulated in IgAN. The urinary glycan profile may be useful for the identification of diagnostic marker for IgA nephropathy.

Funding: Private Foundation Support, Government Support - Non-U.S.

PO1592

Urinary Transferin and IgG Are Significant and Early Markers of Tubulo-interstitial Lesions in Patients with IgA Nephropathy

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Background: IgA nephropathy (IgAN) is the most common form of primary glomerulonephritis and is a frequent cause of end-stage renal disease. There is a pressing need to identify suitable noninvasive biomarkers in IgAN, to aid with diagnosis, treatment decisions, prediction of the histological lesions and disease progression. Our aim was to assess diagnostic value of urinary transferrin and IgG excretions in prediction of morphological lesions in patients with IgAN.

Methods: 37 patients [19 female, age Me 33 (25; 48) years] with biopsy proven IgAN and without acute kidney injury, infectious diseases, severe heart failure, respiratory insufficiency, cancer were included in the study. 24-hour urinary excretions of transferrin (uTr), IgG (uIgG) were measured by immunoturbidimetric method. Tubulo-interstitial fibrosis (TIF), tubular atrophy (TA) were assessed semi-quantitatively (0-lesions absent; 1-mild focal tubular and interstitial lesions; 2-moderate tubular and interstitial lesions; 3-diffuse tubular and interstitial lesions). All patients consistently were separated into two groups according to the degree of each morphological lesion (TIF or TA): “mild” (TIF or TA grade 0 or 1) and “severe” (TIF/TA grade 2-3).

Results: uTr, uIgG positively correlated (p<0.05) with TIF (r=0.38, r=0.43) and TA (r=0.38, r=0.43), respectively. We did not find correlations between uTr, uIgG and glomerulosclerosis. Using ROC-analysis all patients were separated in two groups using uTr or uIgG according to the degree of morphological lesions (“mild” or “severe”) (Figure 1). We also found that all cut-off values of uTr, uIgG corresponded to the level of urinary protein excretion not more than 1.25 g/24hour.

Conclusions: Our data shows that uTr and uIgG can be used as markers of early tubulo-interstitial lesions in patients with IgA nephropathy with mild protein excretion (<1,25 g/24hour).

Funding: Government Support - Non-U.S.
GWAS methods. The results were tested for Hardy-Weinberg equilibrium (control group; ± ± ± ± patients (mean age 42,9 ± 14,22 y.; 14 ♂), 39 sex- and age-matched and 35 unmatched.

**Background:** IgA nephropathy (IgAN) is the most common glomerular nephropathy globally, with up to 40% of patients at risk of progressing to ESKD. Endothelin (ET) A receptor activation results in mesangial cell (MC) activation, proteinuria, inflammation, and fibrosis, all considered hallmarks of IgAN progression, suggesting the potential for therapeutic benefit of ETA antagonists. The aim of our study was to identify intrarenal transcriptional signatures of ET-activation to stratify patients at high risk of IgAN progression.

**Methods:** We used two approaches to establish a transcriptional signature of ET-activation. First, using a targeted approach, an ET-activation network was generated using three publicly available datasets, produced a gene set of 60 transcripts to create an activity score which was assessed in kidney biopsy profiles in patients with IgAN (n = 25) from the European Renal CNDA Bank (ERCDB). In addition, an ET-activation signature was also generated via RNASeq profiling of primary human MCs stimulated with ET1 (4nM) +/- the selective ETA antagonist atrasentan (1nM, 25nM, n=3/group). Pairwise differential gene expression and gene set enrichment analysis (GSEA) was performed.

**Results:** The targeted analysis showed that the ET-activity score correlated with increased proteinuria (r=0.42, p<0.05) and decreased eGFR (r=-0.47, p=0.02) in patients with IgAN. The transcript network showed enrichment in endothelial and fibrotic clusters in renal single cell RNASeq profiles. Differential expression analysis identified three publicly available datasets, produced a geneset of 60 transcripts to create an activity score which was assessed in kidney biopsy profiles in patients with IgAN (n = 25) from the European Renal CNDA Bank (ERCDB). In addition, an ET-activation signature was also generated via RNASeq profiling of primary human MCs stimulated with ET1 (4nM) +/- the selective ETA antagonist atrasentan (1nM, 25nM, n=3/group). Pairwise differential gene expression and gene set enrichment analysis (GSEA) was performed.

**Conclusions:** The targeted analysis showed that the ET-activity score correlated with increased proteinuria (r=0.42, p<0.05) and decreased eGFR (r=-0.47, p=0.02) in patients with IgAN. The transcript network showed enrichment in endothelial and mesangial cell clusters in renal single cell RNASeq profiles. Differential expression analysis identified the ET gene network was reversed by atrasentan in MCs (25nM, n=7-8 genes, q<0.05). GSEA in MCs revealed up-regulation of cell proliferation, inflammation and fibrotic networks, with ET1 treatment, which were blocked by atrasentan.

PO1595

**NR3C1 Polymorphisms in Membranous and IgA Nephropathies**

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**Background:** In other diseases (ex. asthma and pemphigus vulgaris) NR3C1 single nucleotide polymorphisms (SNPs) were associated with glucocorticoid (GC) treatment outcomes. The aim of the study was evaluation of the frequency of NR3C1 (SNPs) in adult membranous (MN) and IgA (IgAN) nephropathies biopsy proven patients.

**Methods:** We analyzed NR3C1 SNPs rs6198, rs14123247 and rs17209237 in 39 MN patients (mean age 42,9±14,22 y.; 14 ♂, 39 sex- and age-matched and 35 unmatched IgAN patients (mean age 33,5±12,3 y.; 34 ♂ and 39 sex- and age-matched and 136-unmatched healthy controls (mean age 48,7±17,9 years; 89 ♂) using RT-PCR and GWAS methods. The results were tested for Hardy-Weinberg equilibrium (genotypes p<0,05) and compared between MN, IgAN and controls within MN and IgAN between GC-resistant and -sensitive and GC-dependent and -independent groups using the χ² with Yates’s correction test.

**Results:** The frequency of the minor C allele of rs6198 SNP was significantly increased in MN (p=0,05) and IgAN (p=0,05) compared to controls; and in GC-resistant MN (p=0,05), GC-resistant (p=0,05) and GC-dependent (p=0,05) IgAN. The rs14198 SNP genotypes were unequally distributed among GC-resistant MN and IgAN (p=0,05) and GC-dependent (p=0,05) IgAN. The frequency of the major A allele of rs17209237 was significantly increased in GC-sensitive (p<0,05) and -independent (p<0,05) IgAN. There was a disequilibrium in rs17209237 SNP distribution among GC-sensitive MN (p<0,05). The minor C allele was significantly more frequent among MN (p<0,05) and IgAN (p<0,05) relapse patients and there was rs6198 genotypes distribution inequality for these both groups (p<0,05, p<0,05).

**Conclusions:** Rs6198 and rs17209237 alleles and genotypes have different values between MN and IgAN and controls; and between patients differently responding to the GC treatment. Results indicate that they predict GC treatment outcomes and therefore should be further investigated for their potential prognostic value.

PO1596

**A Rare Case of Paraneoplastic IgA Nephropathy in the Setting of Renal Cell Carcinoma**

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**Introduction:** Paraneoplastic nephropathy can present in patients with malignancy. Renal cell carcinoma (RCC) is the most common urologic malignancy; there is a paucity of reported paraneoplastic nephropathies associated with this condition. As such, we present an intriguingly unique case of nephrotic range proteinuria in the setting of recurrent, metastatic renal cell carcinoma.

**Case Description:** An 81-year-old male with history of recurrent metastatic RCC, solitary kidney after a nephrectomy, with stage III chronic kidney disease (CKD) presents with newly worsening renal function. In a 3-month span, his creatinine (Cr) rose from 1.35 mg/dL to 4.6 mg/dL, which prompted further investigation. He had reported taking daily nonsteroidal anti-inflammatory drugs along with his ACE-inhibitor. Urinalysis showed microscopic hematuria with random urine protein/creatinine ratio resulted 16 g/g and renal ultrasound was unremarkable. Other serologic tests at the time were notable for C3 134 mg/dL, C4 32 mg/dL, negative ANA, negative C-ANCA. Of note, he had suffered an E. coli and MRSA UTI, clostridium difficile infection, and was treated for pneumonia with microbials. A renal biopsy was obtained with pathology significant for IgA-dominant mesangial and capillary wall immune complex deposition with only segmental and weak C3 (Oxford score was reported as M1, E1, S1, T0, C9). Because of the weak C3, in spite of the patient’s history of recent infections, a secondary para-neoplastic IgA nephropathy was favored. He was treated with Nivolumab plus Ipilimumab with improvement in serum Cr improved to 2.23 mg/dL in the following 3 months after starting immunotherapy and remained stable in one-year follow up.

**Discussion:** Acutely worsening renal function and nephrotic range proteinuria in the setting of malignancy prompts investigation into a paraneoplastic nephropathy. As in this case, secondary IgA mesangial nephropathy can rarely present with RCC. This association is scarce and furthermore there is a lack of understanding of the development of this glomerulopathy. Treatment of the underlying malignancy has shown to improve and preserve renal function. Further investigation into the immune-pathophysiology can help drive the development of further treatment strategies.

PO1597

**Circulating and Depositing Glomerular Antibodies: A Concordance or Coexistence**

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**Introduction:** Anti-GBM disease is a systemic autoimmune disorder characterized by circulating IgG antibodies (rarely IgA and IgM), may coexist with pauci-immune membranoproliferative glomerulonephritis and membranous glomerulopathy. The concurrent or sequential presentation of anti-GBM disease with IgA nephropathy has been rarely described.

**Case Description:** We herein report a case of 31-year-old female who had presented with sudden onset of breathlessness, pedal oedema for 15 days and oliguria for 5 days with 1 episode of haematuria. There were no arthralgias, oral ulcers, alopecia, skin rash, sore throat and diarrhoea. Her marital life was of five years with no history of conception or abortions. On examination she had mild pedal edema and her BP was 180/130 mm Hg. Blood investigations revealed haemoglobin 9.5 g/dl, urea 209 mg/dl, serum creatinine of 26 mg/dl, thrombocytopenia, and anemia. She was treated with high dose prednisolone and his ACE-inhibitor. Urinalysis showed 5+ proteinuria and white blood cell casts. Her creatinine improved to 2.23 mg/dL in the following 3 months after starting immunotherapy and remained stable in one-year follow up.

**Discussion:** Acutely worsening renal function and nephrotic range proteinuria in the setting of malignancy prompts investigation into a paraneoplastic nephropathy. As in this case, secondary IgA mesangial nephropathy can rarely present with RCC. This association is scarce and furthermore there is a lack of understanding of the development of this glomerulopathy. Treatment of the underlying malignancy has shown to improve and preserve renal function. Further investigation into the immune-pathophysiology can help drive the development of further treatment strategies.
Discussion: Presentation of IgAN along with anti GBM without linear deposition on renal biopsy but with positive anti GBM titers makes this case interesting. The association of anti GBM disease with IgAN nephropathy could be a coexistence as IgAN is most common glomerular disease or these IgA mesangial deposits might have role in the pathogenesis of triggering GBM antigens and formation of antibodies in this case.

PO1597
Early Predictors for Stable Kidney Function in Lupus Nephritis
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Background: Early prediction of outcomes in LN is essential to adjust LN treatment. The aim of this study was to evaluate the early course of laboratory parameters and their association with long-term stability of kidney function.

Methods: We studied 433 patients from our local LN cohort recruited between 2008 and 2017. All patients had >36 months follow-up and complete evaluation at LN flare, 3-, 6- and 12-months of follow up with hemoglobin, creatinine, 24h-proteinuria, albumin, anti-dsDNA-Ab, complement C3 and C4 fragments. The main outcome was stable kidney function defined as eGFR within 25% of the best eGFR attained in the first 12 months of treatment. Each variable was evaluated individually by ROC curves and in association with other variables. The change in area under the curve (AUC) was analyzed with De Long’s test.

Results: Median follow up was 73 months (IQR 51-101). Kidney survival was 90% and 81% at 3- and 5-years, respectively. Stability of kidney function was 77% and 65% at 3- and 5-years, respectively. The predictive performance of each parameter varied with the timepoint where evaluated (Table). Serum albumin and hemoglobin AUCs improved from baseline to the 3- and 6-month timepoint. Proteinuria and eGFR AUCs improved at each timepoint up to the 12-month timepoint. C3, C4, and anti-dsDNA-Ab level did not improve at any timepoint vs. baseline. The best predictor of 36-month eGFR stability was proteinuria <1g/g by 12 months. The sum of proteinuria plus eGFR provided the best combined AUC at each timepoint (Figure 1).

Conclusions: Early course of albumin, hemoglobin, and serological parameters does not improve prediction for stable kidney function in LN. The predictive performance of each biomarker improves over time. The combination of proteinuria and eGFR remains the best predictor of kidney outcomes.

Table 1. Area under the curve (AUC) of the evaluated parameters to predict stable kidney function by 36 months.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUC (95% CI)</th>
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<tbody>
<tr>
<td>Proteinuria</td>
<td>0.70 (0.63-0.77)</td>
</tr>
<tr>
<td>eGFR</td>
<td>0.67 (0.60-0.74)</td>
</tr>
<tr>
<td>Sum of proteinuria plus eGFR</td>
<td>0.73 (0.66-0.79)</td>
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Figure 1. ROC curves of proteinuria (A), eGFR (B), and the sum of proteinuria plus eGFR (C) to predict stable kidney function by 36 months.

PO1598
Long-Term Outcomes of Lupus Nephritis in a Single Tertiary Care Center in South India
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Background: Lupus nephritis (LN) is a frequent and severe manifestation of SLE, a risk factor for chronic kidney injury and end-stage renal disease in SLE we evaluated the clinical presentation and outcome with various treatment regimens in patients with lupus nephritis

Methods: A retrospective study in 50 patients with biopsy proven LN [class III (12), class IV(11), class V(4), class III+V(10), class III+V(7), class IV+V(6)] treated with NMP for 3 days followed by monthly CYC for 6 months and oral corticosteroids 0.5-1mg/kg with tapering to 10mg/day at the end of 6th month as induction protocol. AZA or MMF as maintenance regimen based on clinician discretion. Clinical presentation, histopathological (LM+IP) features, treatment regimen, treatment response and renal relapse and outcome were evaluated.

Results: Patients had a mean follow up of 3.6 years, clinical presentation nephrotic N.S (36%), nephritic Nes (24%), RPGN (16%), nephritic-nephrotic NS-NeN (12%), AKI (12%) patients who had RPGN and AKI presentation had crescentic GN and high chronicity index, 46% attained complete remission(CR), 28% attained partial remission, 26% did not respond to treatment(NR) at the end of induction.15 and 8 patients out of 23 who attained complete remission were initiated on MMF and AZA as maintenance regimen respectively, 13/15 in MMF group and 7/8 in azathioprine.patients continued to have CR or NR at the end of 2 years. In patients who attained partial remission 5 on MMF and 5 on AZA, 4 on quarterly pulse doses of cyclophosphamide, 3/5 patients on MMF had C.R, 2/5 on AZA had C.R, 2/4 on quarterly pulse doses of CYC had C.R. 6 out of 12 patients maintained renal remission progressed to CKD at the end of 6 months. 4/7 patients who did not respond to CYC as induction were treated with MMF, 2 patient were treated with rituximab and one with triple immunosuppression(tacrolimus+MMF+corticosteroids),1 patient who treated with MMF and 1 patient who treated with rituximab attained partial remission, no patient attained complete remission at the end of 2 years.

Conclusions: Induction regimen with cyclophosphamide is non inferior when compared to various other induction regimen in LN. Quarterly pulse dose of CYC has no better outcome when compared to AZA and MMF as maintenance. Non responders at the end of 6 months of induction does not have better outcome at the end of 2 years.

PO1599
The Relationship Between Renal Flares and Continuity of Medical Care in Patients with Lupus Nephritis
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Background: African American and Hispanic patients with lupus nephritis (LN) are known to have worse clinical outcomes compared to those of white patients, with higher prevalence of severe inflammatory nephritis, higher rates of doubling creatinine, End Stage Kidney Disease (ESKD) and death. In this study, we characterized the frequency and severity of renal flares of patients treated in our lupus nephritis clinic.

Methods: Patient demographics are presented as mean ±SD; student t-tests were used when appropriate; Chi-square tests were used to determine differences in the number of renal flares and the number of missed appointments (dischotomized into 0 vs. >1).

Results: Between 2005–2019, a total of 116 patients with Lupus Nephritis treated at the multidisciplinary lupus clinic in a safety net hospital in Boston, MA were enrolled in our study. 23.3% of patients (n=27) self-identified as white and Asian and non-Hispanic (group 1); 76.7% of patients (n=89) self-identified as Black, African American and/ or Hispanic (group 2). Patients’ demographics and disease characteristics were similar between the two groups. Over the duration of the study, 59.5% of patients (n=69) did not experience any flare, and 40.5% of patients (n=47) experienced a flares. Of the patients that experienced ≥1 flares, 89% (n=42) missed one or more appointments over the course of the study. The rate of missed appointments in group 2 was significantly higher than the one observed in group 1 (85.4% vs. 48.1% respectively, p<0.001).

Conclusions: This study represents one of the largest cohorts of patients with lupus nephritis with consistent, longitudinal, long term follow up. We found that in our black, African American and/ or Hispanic population, there is a significant difference in frequency and number of missed appointments between renal flares and missed appointments. In our safety net hospital setting, missed appointments frequently represents patients’ inability to access care due to various challenges including lack of sick days at work, transportation challenges, access to certain technologies and language barriers. When looking to reduce racial and ethnic health care disparities, we should design interventions that are aimed at removing key barrier to health care access.

PO1600
Collapsing Glomerulopathy Can Worsen Prognosis in Lupus Nephritis

Background: Collapsing glomerulopathy (CG) conveys a poor renal prognosis and is characterized by podocyte atrophy with segmental or global collapse of the capillary walls. While it can be idiopathic, it is often seen in association with other viral, drug, and autoimmune conditions including lupus nephritis (LN). This retrospective study describes features and clinical outcomes of 16 patients with SLE and biopsy proven CG.

Methods: Using our Glomerular Disease Collaborative Network registry, we performed retrospective chart review on patients with systemic lupus erythematosus and CG on kidney biopsy with or without an LN lesion from 2000 - 2021. Patients with multiple biopsies, the first biopsy with GC was identified as the incident biopsy. We defined poor renal outcome as reaching a renal endpoint of serum creatinine doubling, chronic dialysis initiation, or renal transplantation. Patients were characterized by baseline demographics, laboratory results, interstitial fibrosis, and medications.

Results: We identified 16 patients with mean age of 33 years at incident biopsy. Most were female (87.5%) and black (87.5%). Mean serum creatinine (S Cr) was 3.1mg/dL and mean proteinuria by 24-hour urine collection or spot urine protein:creatinine ratio was 7.12g. Excluding 2 patients with limited follow-up, 11 of 14 (78.6%) patients had poor renal outcomes. These patients were similar in age (mean 33 years) and were also majority female (90.1%) and black (90.1%). In this group, mean S Cr was 5.35mg/dL and proteinuria was 3.69g. This group had significant interstitial fibrosis and tubular atrophy with 71% grade severe and 28.6% grade moderate. 43% of patients were on IFTA. The renal endpoint was reached in 4.5 years (average). Of 3 patients who did not have a renal end point, mean S Cr was 1.83 mg/dL with less IFTA noted on biopsy. Treatment options varied with most receiving mycophenolate or cyclophosphamide.

Conclusions: This descriptive project confirmed that CG was associated with poor renal prognosis in LN; the majority of the patients required dialysis, proceeded to transplantation, or had doubling of serum creatinine during follow up. Despite treatment with standard of care agents, outcomes remained poor. Patients who had worse S Cr at presentation or severe IFTA had worse outcomes.
PO1601
SEROLOGICAL ACTIVITY IN PURE MEMBRANOUS LUPUS NEPHRITIS IN A PREDOMINANTLY BLACK POPULATION
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Background: Clinically significant kidney disease is estimated to occur in nearly 60% of patients with systemic lupus erythematosus (SLE). A majority of these patients develop proliferative disease, however 10-15% develop a non-proliferative form of disease known as membranous lupus nephritis (LN) (Class V lupus nephritis). These patients typically present with significant proteinuria. Austin et al. reported 7% of patients with low complement levels and 21% with elevated anti-dsDNA levels. In this study we assess serological activity (C3, C4, anti-dsDNA) of pure membranous LN in a predominantly black patient population.

Methods: Kidney biopsy log from 2010-2017, and a retrospective chart review was completed. We excluded any patients with proliferative disease (active or chronic). We analyzed serological activity (C3 level, C4 level & anti-dsDNA) at time of renal biopsy and again at 24 weeks. Results: Of the total 101 patients with pure membranous LN, we had 54 patients with sufficient follow-up data. 52 of the 54 were female with an average age of 35.5; 92.5% (50 of 54) were black. At time of kidney biopsy, low C3 and low C4 was found in 54% and 41% of patients respectively. Whereas an elevated anti-dsDNA was identified in 39% with 20% having the classic triad of low C3, low C4 and elevated anti-dsDNA. When compared to 24 weeks (roughly end of induction therapy) low C3 and low C4 was found in 37% and 24% of patients respectively. Whereas an elevated anti-dsDNA was identified in 31% with 13% have the combination of low C3, low C4 and elevated anti-dsDNA

Conclusions: In this predominantly black population of pure membranous LN the majority of patients did not have the classic triad of low complements and elevated anti-dsDNA (20% at time of diagnosis/biopsy). Compared to others looking at pure membranous we did find higher rates of low complements and elevated anti-dsDNA at time of diagnosis (54% with low C3 initially). Possibly due to our unique urban patient population which is >90 percent black, i.e. more severe SLE. Despite the majority of patients not having the classic triad of low C3, low C4, and elevated anti-dsDNA, clinical providers must be diligent in assessing the need for kidney biopsy in SLE; and non-SLE patients as serological activity does not correlate with biopsy findings. Earlier treatment correlates with improved prognosis.

PO1602
Role of Kidney Biopsies in Lupus Erythematosus Patients: Clinico-pathological Correlation
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Background: Lupus nephritis (LN) affects >50% of the patients with systemic lupus erythematosus (SLE) and is a major cause for morbidity and mortality. The diagnosis of LN as well as the extent and severity of renal involvement are assessed via kidney biopsy. However, appropriate clinical indications for a kidney biopsy are not well defined in adults, nor is the predictability of the clinical presentation. Therefore, a clinico-pathological correlation of patients with SLE and presumed SLE who underwent a kidney biopsy is conducted.

Methods: We evaluated a total of 134 biopsy samples from 123 patients with either SLE or presumed SLE at the time of biopsy that were obtained during a 10-year period at a major medical center in New York City. 11 patients underwent a biopsy twice during that period. Laboratory, and clinical data were also collected retrospectively via chart review.

Results: 86% of the patients were female, 31% African American, 21% White, and 11% Asian. The mean age at the time of the biopsy was 36.2±12.6 years, the mean serum-creatinine 1.4±1±28 mg/dL, and the mean urinary protein excretion 3.8±3.43 g/dL. 97% of the biopsy samples had evidence of LN, with the majority showing either Class IV-V (29%) or Class V (33%). About 13% had findings other than LN, such as TMA, focal collapsing features of the glomeruli, diabetic nephropathy, or possible ANCA vasculitis, with or without evidence of LN. Additionally, in patients of 65% of the biopsy samples, eGFR was <60 mL/min/1.73 m², and 29% (38/132) had a negative urine dipstick for blood. Complement levels were low in 88/128 instances, and anti-dsDNA was positive in 57% of the instances (n=127). When comparing all proliferative forms of LN (n=74) with Class V lupus nephritis, there were significantly higher creatinine, higher proportion of hematuria, anti-dsDNA positivity, low complements, as well as a proteinuria level ≥1 g/d.

Conclusions: We conclude that normal serum-creatinine values may not preclude significant kidney pathology in SLE patients and those with proliferative forms of LN may have a negative urine dipstick for blood (14%), normal complement levels (14%), and/or a negative anti-dsDNA test (29%) around the time of the biopsy. Furthermore, patients with SLE may have other morphologic findings correlating with clinical renal presentation, instead of LN.

PO1603
RITUXIMAB FOR SEVERE RECURRENT PROLIFERATIVE LUPUS NEPHRITIS AFTER KIDNEY TRANSPLANTATION: PONDERING A RARE CASE
Rui Song, Mingyue He, Ilay Rakham, Serban Constantinescu, Iris J. Lee. Lewis Katz School of Medicine at Temple University, Philadelphia, PA.

Introduction: Severe histologic recurrence of lupus nephritis (LN) post-kidney transplant (KTX) is extremely rare on standard transplant immunosuppression. Severe recurrence shortens allograft survival, yet treatment guidelines post-KTX are lacking.

Case Description: A 52-year-old African American (AA) man with ESRD secondary to LN underwent a second KTX from a deceased donor. He had a prior living-unrelated KTX with graft failure due to mixed rejection without LN recurrence. For the second KTX, he received Thymoglobulin induction and maintenance immunosuppressive regimens including re-coated mycophenolate sodium (EC-MPS), Tacrolimus, Prednisone, with immediate graft function (nadir creatinine 1.4mg/dL). He developed leukopenia requiring a reduction of EC-MPS to 360mg twice daily. He developed nephrotic range proteinuria 6 months post-KTX but had stable allograft function, bland urine sediment, normal complements, and negative anti-dsDNA antibodies. Despite inactive serologies, allograft biopsy revealed diffuse proliferative sclerosing and crescentic LN (ISN/RPS class IV). Due to persistent leukopenia, Rituximab was chosen over commonly-used Cyclophosphamide (CYC) for therapy. He received intravenous Methylprednisolone (3000 mg) and Rituximab 800mg (375 mg/m²) for 4 doses. Complete B-cell depletion was maintained for 3 months. His proteinuria decreased from 6.9 g/day to 1.2 g/day, and renal allograft function remained stable.

Discussion: Severe recurrent LN post-kidney transplant is rare and can present a diagnostic and therapeutic challenge. Despite rituximab’s efficacy in LN recurrence, the first KTX did not rule out LN recurrence on the second kidney allograft. In our case, the only presence of persistent progressive proteinuria warranted allograft biopsy. AA ethnicity and reduction of EC-MPS were risk factors, which highlights the significance of LN pathogenesis. Rituximab targets CD20+ B cells and has been successfully utilized for refractory LN. It has a more favorable toxicity profile compared to CYC which has been the conventional treatment for clinically significant LN post-KTX. We propose Rituximab as a better treatment option for severe recurrence of LN post-KTX.

PO1604
INFLUENZA VACCINATION IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE): EFFECTIVENESS, EFFICACY, SAFETY, UTILIZATION, AND BARRIERS
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Background: Influenza infections increase morbidity and mortality among immunocompromised individuals with SLE and lupus nephritis. Yet, they are highly preventable through vaccination. We aimed to describe the effectiveness, efficacy, safety, utilization and barriers to influenza vaccination in SLE so that targeted strategies can be implemented to improve vaccination rates.

Methods: We conducted a systematic review and meta-analysis of all published and unpublished studies up to 19 May 2021 via PubMed, Embase, Cochrane, WHO Clinical Trials, and ClinicalTrials.gov, which reported on our desired outcomes relating to influenza vaccination in SLE and lupus nephritis.

Results: Of 726 articles screened, 44 studies (14779 patients) were included. 9 studies reported on effectiveness, 20 studies on efficacy, 24 studies on safety, 12 studies on utilization, and 4 studies on barriers to influenza vaccination. Influenza involvement or lupus nephritis was present in 20%. The majority were female (90.8%). The mean age was 41.3 years (95% CI 36.8-45.7), mean disease duration was 10.91 years (95% CI 7.10-14.72), and mean SLEDAI score was 4.15 (95% CI 3.18-5.12). Individuals who received influenza vaccination were less likely to develop pneumonia (relative risk, RR 0.38, 95% CI 0.08-1.86, p=0.23), acute bronchitis (RR 0.21, 95% CI 0.09-0.48, p=0.0002), and viral respiratory infections (RR 0.36, 95% CI 0.21-0.64, p<0.0005). Pooled seroconversion and seroprotection rates were 56.6% and 68.2% for H1N1, 56.7% and 73.7% for H3N2, and 46.8% and 69.9% for B influenza strains. Mean SLEDAI scores did not change significantly after vaccination. Flares occurred in 20.3%, while local and systemic adverse events occurred in 20.5% and 26.6%, respectively. Only 39.1% of SLE patients were currently vaccinated against influenza. Meta-regression showed that vaccination rates were significantly associated with increasing GDP of the country (p=0.002) and increasing mean years of disease duration (p=0.02). The most common barriers to vaccination were concerns over the safety or efficacy of the vaccine (37.2%), lack of doctor recommend (23%), and having experienced side effects of other vaccines previously (13%).

Conclusions: Influenza vaccination is effective and safe in SLE and lupus nephritis. Targeted strategies are required to overcome barriers to improve influenza vaccination uptake.

PO1605
LUPUS NEPHRITIS IN A PATIENT WITH AUTOIMMUNE HEPATITIS: A CASE REPORT
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Introduction: Overlapping autoimmune hepatitis (AIH) and lupus nephritis (LN) is a rare entity, only occurring in 1-2.6% of AIH cases, and is difficult to diagnose due to the overlap of diagnostic criteria. Over 100 cases have been reported in the literature.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Delayed Clinical Manifestation of Biopsy-Proven Thrombotic Microangiopathy in a Patient with Lupus Nephritis: A Case Report

Najia Idrees,1 Madeline A. Dilorenzo,1 Joshua S. Huddert,2 Jean M. Francis,1 Hann Menni-Joseph.1 1Boston Medical Center, Boston, MA; 2South Shore Hospital, Weymouth, MA.

Introduction: Complement-mediated thrombotic microangiopathy (c-TMA) involves unregulated complement activation due to inherited or acquired mutations in complement regulatory proteins. Immune complex formation, an important component of lupus nephritis (LN) pathogenesis, can over activate the complement system leading to c-TMA in the kidneys. Findings of c-TMA in LN patients have been associated with end-stage kidney disease (ESKD) or death in up to 50% of patients.

Case Description: 32-year-old female, with a history of lupus and ISN/RPS class III LN since 2017 and recent stroke, was evaluated at our lupus clinic for LN flare and baseline eGFR (mean ± SD) at baseline and 6 months follow up were 20.8 ± 13.7. Almost all patients (59/60, 98.3%) presented with hematuria and 17/60 (28.3%) had nephrotic-range proteinuria. Extra renal involvement most commonly pulmonary was seen in 35/60 (58.3%) patients. 44/60 (73.0%) had crescents and nearly all had interstitial fibrosis and tubular atrophy (IFTA) (median, IQR 30%, 56%). Most patients were induced with cyclophosphamide (49/60, 81.7%) and 16/60 (26.7%) received plasma exchange. eGFR (meanSD) at baseline and 6 months follow up were 20.8±19.4 and 43.5±23.0 respectively. 15/60 (25%) patients progressed to ESKD. On multivariate linear regression analysis, age (B = -0.5), IFTA (B = -0.7) and baseline eGFR (B = 0.3) predicted eGFR at 6 months and IFTA (OR, 95% CI, 11.5, 1.1-11907.7) and eGFR at 6 months (OR 0.9, 95% CI 0.8-1.0) were associated with ESKD (P < 0.05) on multivariate logistic regression analysis. Ethnicity, ANCA type or titer, crescents on biopsy and treatment received did not predict ESKD at 6 months.
PO1609

Long-Term Outcome in Patients with ANCA-Associated Vasculitis (AAV): The Monocentric Experience of Brescia

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Background: Glomerular Diseases: Clinicopathological Features and Outcomes in IgAN, Lupus Nephritis, and Vasculitis

PO1610

Glomerular Diseases: Clinicopathological Features and Outcomes in IgAN, Lupus Nephritis, and Vasculitis

PO1611

ANCA-Associated Crescentic Glomerulonephritis (AAV-GN) in Patients with Chronic Lymphocytic Leukemia (CLL): A Case Series


Background: Previous case reports have identified an association between CLL and AAV-GN. However, information on the clinical and pathologic characteristics and long-term outcomes of AAV in these patients is limited.

Methods: We queried medical records and research databases of CLL and AAV subjects seen at our institution to identify patients with diagnoses of CLL and AAV-GN from 1990-2020. We analyzed patient demographics, AAV-GN, CLL specific characteristics, treatments, and outcomes. Kidney biopsies were also reviewed.

Results: We identified 12 patients with AAV-GN and CLL. The mean age at diagnosis was 65 years (48, 80) for CLL and 68 years (57, 80) for AAV-GN. 5 patients were diagnosed with CLL prior to AAV-GN, 4 the same month, and 2 developed CLL >3 years after diagnosis of AAV-GN. At the time of first AAV-GN diagnosis, all had acute kidney injury, with a median serum creatinine (SCr) of 1.9 mg/dL (SD 3.2). Other organs involved included lungs (n=3), skin (n=1), and eyes/encephalitis (n=1). 9 patients p-ANCA-MPO and 2 had c-ANCA-PR3 and one with an indeterminate ANCA but had PR3. On light microscopy, all had crescents, no vasculitis of the arteries, but 9 patients had focal lymphoid infiltrates without a formal diagnosis of CLL in the kidneys. On immunofluorescence 6/12 had trace to 1+ of IgA, 5/12 with IgG and 4/12 with C3. 5/12 of the biopsies had mesangial deposits and majority (1 with diffuse and 7 with moderate) had foot process effacement. All patients received treatment for AAV (9 with rituximab, and 3 with cytotoxic drugs). Renal outcomes were favorable with 11 patients showing an improvement or stabilization in Scr. One patient (p-ANCA MPO antibodies) developed end stage kidney disease, and 3 patients died, two from CLL and the other from heart failure.

Conclusions: In this cohort of outcomes, kidney biopsies were informative. AAV and CLL, the vast majority had p-ANCA MPO, suggesting that the two conditions have either a common underlying lymphocyte dysfunction or that CLL is a predisposing factor to the development of AAV. Anti-CD20 monoclonal antibody therapy was most commonly used, and it led to remission of AAV-GN.

PO1609

Predicting Outcomes in ANCA-Associated Vasculitis Using a Complete National Cohort

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Background: Outcomes in ANCA vasculitis remain difficult to predict & therapeutic decision-making can be challenging. We aimed to establish if a renal risk score (RRS) could predict outcomes.

Methods: The Scottish Renal Biopsy Registry is a complete national dataset of all biopsies performed in Scotland. Those who had a first renal biopsy between 2014 & 2017 with evidence of ANCA vasculitis were included. Demographic data & outcomes were recorded. A new risk score was calculated. Each patient was categorised according to % of normal glomeruli, % of tubular atrophy/interstitial fibrosis & eGFR (CKD-EPI) at time of biopsy. Individual scores were summated & patients defined as low, medium or high risk. Cox proportional hazard models were created for survival to ESKD, relapse & death, stratified for risk group.

Results: Two-hundred & sixty-nine patients with biopsy proven ANCA vasculitis were identified. Fifty percent (n=123), 46% (n=112) & 5% (n=11) were stratified as low, medium & high risk respectively. Fifty-two percent (n=129) were male & mean age at biopsy was 67.7±12.2 years. Mean eGFR was lower in the high-risk category (8.6±1.8) vs. ‘v’ Low risk 45.7±26.0 ml/min/1.73 m2, p<0.001) & proteinuria was higher (405 (170-767) vs. ‘v’ Low risk 81 (QI 41-155) mg/mmol, p<0.001). Thirty-seven percent (n=91) were PR3 antigen positive. Eighteen (7%) patients experienced pulmonary haemorrhage; representation similar across all risk groups. Those categorised as medium or high risk were more likely to receive plasma exchange & haemodialysis at presentation (p<0.001) compared with the low risk category. Overall, 16% (n=40) of patients relapsed with a trend to higher risk of relapse in the low risk group (27% of these patients, p<0.05). Thirty seven (15%) patients developed ESKD. Cox proportional hazard model for development of ESKD shows that those in high risk category were more likely to reach ESKD (adj HR 78.4, 95% CI 14-438.4, p<0.001).

Conclusions: A simple RRS, using routinely reported data, in patients with renal biopsy proven ANCA vasculitis can help to predict development of ESKD. It may also be predictive of future relapse in those with a lower RRS. The RRS could inform monitoring & treatment decisions. A unique strength of this data is that it is based on a complete national dataset making it less susceptible to bias from regional variations in practice.

PO1612

Kidney Biopsy Chronicity Grading in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis

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Background: Kidney biopsy is valuable for prognostic assessment of renal outcomes in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) with glomerulonephritis (AAV-GN) but the impact of chronic changes is not determined.

Methods: A retrospective cohort study of MPO- or PR3-ANCA positive patients with AAV and active renal disease. We applied the Mayo Clinic Chronicity Score (MCCS), validated and evaluated its implications on outcome prediction in AAV-GN.

Results: We analyzed 329 patients with kidney biopsies available to score. The extent of chronicity was graded by MCCS as (i) minimal – 102 (31.0%), (ii) mild – 106 (32.2%), (iii) moderate – 86 (26.1%), and (iv) severe – 35 (10.6%). The MCCS grades correlated with the degree of renal function impairment at presentation (mean eGFR of 48.3 vs. 29.2 vs. 23.7 vs. 18.5 mL/min/1.73 m2, p<0.0001). Higher degrees of the individual components of the MCCS (glomerulosclerosis, interstitial fibrosis, tubular atrophy and arteriosclerosis) were associated with lower median eGFR (p<0.0001) and decreased event free (kidney failure (KF) and death) survival (p=0.002, p<0.001, p<0.001 and p<0.0001 respectively). Patients with a high MCCS grade showed decreased renal function more frequently (p<0.0001). Increasing MCCS grades were associated with decreased renal recovery (p<0.001), more frequent events and shorter time to KF (p=0.0001), KF and death (p<0.0001), and death (p=0.0001) in our cohort. Clinical presentation and treatment used (CYC or RTX). The MCCS stratified renal outcomes for each MCCS grade and can be used in clinical practice as a cut-off for KF prediction (MCC/Sa4).

Conclusions: Chronic changes on kidney histology independently predict renal function, outcomes and response to treatment in AAV-GN.

PO1613

The Effect of Cumulative UVB Dose on ANCA-Associated Vasculitis

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Background: ANCA-associated vasculitis (AAV) has a relapsing-remitting course but the precise triggers of onset and relapse are unknown. The potential effect of ultraviolet B (UVB) radiation on disease phenotype and activity, mediated by vitamin D (vit D), has been proposed, given the marked incidence variation of AAV phenotypes and serotypes with latitude. Using a well-validated vit D proxy (cumulative-weighted

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UVB dose (CW-D-UVB) at wavelengths that induce vitD synthesis, we hypothesized that prolonged periods of low ambient UVB are associated with an increased risk of GPA phenotype and AAV relapse in this subgroup.

Methods: The UKIVAS (n=1994) and Irish Rare Kidney Disease (RKD) (n=439) registries were used (total n=2433). Inclusion criteria: i) definite AAV diagnosis, ii) positive proteinase-3 (PR3) or myeloperoxidase (MPO) serology and/or positive histopathology. Logistic regression was used to investigate the relationship between latitude, CW-D-UVB and AAV phenotype/serotype in the entire cohort. A multi-level model was then applied to examine their effect on AAV relapse risk in the RKD subgroup.

Results: CW-D-UVB varied across seasons and latitudes. There was no relationship between latitude/CW-D-UVB at disease onset and AAV phenotype/serotype. MPA, MPO-ANCA, older age and rituximab maintenance were protective against relapse. There was no association between CW-D-UVB and relapse risk, even when examining phenotype specific risk (table 1).

Conclusions: We found no association between cumulative UVB, a validated vitD proxy, and AAV phenotype, ANCA serotype nor AAV disease activity in a genetically homogeneous cohort. These findings cast doubt on the role of vitD in AAV disease activity.

PO1614
A Severe Presentation of Systemic Lupus Erythematosus (SLE) and ANCA-Associated Vasculitis (AAV) Overlap Syndrome
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Introduction: An increasingly recognized overlap syndrome (OS) of lupus nephritis and AAV is defined by the presence of aminogram and ANCA positivity. We report a case of a patient presenting with the symptoms and laboratory findings suggestive of both conditions.

Case Description: A 42 y.o. woman with no PMH presented with 3 weeks of cough, dyspnea, fever, malaise, AKI and hypoxia. Her hgb was 6.3 g/dL and creatinine 17.4 mg/dl(normal 1.5 years prior). UA showed large hgb and >182 RBCs and UPCR 5.72 g/g. Cardiolipin ab was elevated but beta 2 glycoprotein ab and lupus anticoagulant ab were negative. Chest CT showed multifocal opacities. She was urgently started on hemodialysis and solumedrol 1g for 3 days then prednisone 60 mg daily. On day 2 of admission she underwent renal biopsy. Her course was complicated by hemoptysis and bronchoalveolar lavage showed diffuse alveolar hemorrhage (DAH). She was initiated on plasmapheresis. Biopsy demonstrated necrotizing crescentic GN with immunofluorescence showing full house pattern and complex deposits with strong ANCA staining of nuclei. Given the biopsy results and serologies the patient was diagnosed with LN/AAV overlap. The patient was started on Cytoxan 750mg monthly administration. She completed 7 daily sessions of plasmapheresis and renal function recovered sufficiently to stop dialysis. Two months after discharge, her renal function continued to improve with her most recent creatinine down to 2 mg/dl.

Discussion: LN and AAV overlap is rare and there are no guidelines regarding management of these patients. This case stresses the importance of having a high suspicion of LN/AAV when a young, female patient presents with new onset renal failure and DAH. The patient benefited from early, aggressive treatment targeting both disease processes including early initiation of high dose steroids. Secondly, plasma exchange should be initiated emergently with severe presentation, including DAH. Plasmapheresis did not reduce incidence of ESKD in PEXIVAS trial, however, we suspect in this case it contributed to the good outcome. Lastly, little is known about outcomes in these patients, but this is an example of a severe presentation with a positive outcome.
PO1617
A Rare Case of Crescentsc Glomerulonephritis, Diffuse Proliferative Class IV Lupus Nephritis, and Collapsing Glomerulopathy in a COVID, P-ANCA, and Myeloperoxidase-Positive Patient

Introduction: An unusual case of Diffuse Class 4 Lupus Nephritis, along with Collapsing Glomerulopathy from asymptomatic COVID infection
Case Description: 42 year old Asian female presented with painless hematuria, anasarca, reduced hearing, and eye redness over a month. She had empiric antibiotics and steroids prior to admission. On admission, she was hypertensive with anasarca. Labs revealed AKI creatinine of 2.5 mg/dl, proteinuria of 11 grams, and serum albumin 1.9 gm/dl. Urine analysis showed dysmorphic RBCs, RBC casts. Ultrasound showed 12 cm kidneys bilaterally. She had normal complements and DS DNA, antinuclear, lupus anticoagulant negative. ANA, antinuclear antibodies, COVID, PANCA, MPO all positive. Kidney biopsy showed crescentsc glomerulonephritis, diffuse proliferative glomerulonephritis Class IV, collapsing glomerulopathy, infarct house pattern on IF. EM showed sub endothelial, mesangial, and para mesangial deposits, diffuse podocyte foot process effacement, corona virions in endothelial cells. The patient did not have any COVID symptoms and was treated with pulse steroids, MIF induction, hydroxychloroquine, and ACE I. Serum creatinine improved to 1.33 mg/dl, proteinuria improved to 5.6 grams. Her eye redness and hearing impairment resolved.
Discussion: This is a rare case of diffuse class IV lupus nephritis with normal complements, DS DNA, and full house pattern on IF. She tested positive for COVID, was asymptomatic, and was able to start treatment. Corona virions and podocytopathy was noted on EM. Improvement in proteinuria, serum creatinine, albumin, and resolution of anasarca were used to monitor response to treatments. Complements and DS DNA could not monitor disease activity. Thus, clinicians should not rely purely on serologies for diagnosis but should pursue kidney biopsy for definitive diagnosis and treatment. Patients may have atypical presentations.
PO1620

Renal Survival in Anti-Glomerular Basement Membrane Disease

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Background: Anti-glomerular basement membrane (GBM) vasculitis is a rare immune mediated kidney disease. Presentation with severe kidney dysfunction in need of renal replacement therapy (RRT) often results in end stage kidney disease (ESKD). Reliable predictors of survival are needed.

Methods: Retrospective analysis of patients with anti-GBM disease from the North West of England.

Results: Seventy patients with GBM nephritis were identified, 20 patients presented double positive for anti-neutrophil cytoplasmatic (ANCA) and GBM antibodies (28.57%). Median age was 64 years (Interquartile range 43 – 76 years). 39 patients were female (55.7%). Median kidney function at presentation was estimated glomerular filtration rate (eGFR) 91.49 – 835.75 ml/min. Fifty six patients required RRT at presentation, and twelve of these patients recovered sufficient kidney function to withdraw RRT (25.5%). Median follow up was 41 months (IQR 11 – 77.5), and during follow up two additional patients developed ESKD (n = 50). The median presenting eGFR was numerically higher but not significantly different in patients that required dialysis initially and recovered residual function compared to patients that remained dialysis dependent, and no cut-off was detected (p=0.25). Patients with presenting eGFR as low as 2 ml/min recovered function.

Conclusions: Timely aggressive therapy to salvage kidney function is crucial. Better predictors of outcome are needed to optimise management in GBM vasculitis.

PO1621

Validation of the Renal Risk Score in Anti-GBM Disease

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Background: Anti-glomerular basement membrane (GBM) vasculitis is a rare immune mediated kidney disease. Risk stratification can on an aggregate nature occur resulting in end stage kidney disease (ESKD). Clinical and histological variables predicting outcome are needed to individualise therapy and improve outcome.

Methods: We performed a retrospective multicentre analysis and investigated the Renal Risk Score (RRS) proposed in anti-neutrophil cytoplasmatic antibody (ANCA)-associated vasculitis for its prognostic value in anti-GBM disease. We used the published cut-offs for percentage of normal glomeruli (N0 > 25%, N1 > 20%, N2 < 10%), estimated glomerular filtration rate (eGFR, G0 > 15 ml/min/1.73 m2, G1 ≥ 15 ml/min/1.73 m2) and a simplified cut off for tubular atrophy and interstitial fibrosis (T0 mild to moderate, T1 severe). We assigned points to each parameter (N1 = 4, N2 = 6, G1 – 3, T1 – 2 points) and patients to risk groups, low (0), intermediate (2 – 7), and high risk (8 – 11 points).

Results: Seventy patients with GBM nephritis were identified, 20 patients presented double positive for ANCA and GBM antibodies (28.57%). Median age was 64 years (Interquartile range, IQR 43 – 76 years). 39 patients were female (55.7%). Median eGFR at presentation was 91.49 ml/min (IQR 41,755 – 835,75 ml/min). Median follow up was 41 months (IQR 11 – 77.5 months), and fifty patients developed ESKD (71.4%). Forty-seven biopsies were available for scoring. Four patients were low risk, and none developed ESKD (0%). Eight patients belonged in the medium risk group, and five of these developed permanent kidney failure (62.5%). Of 35 patients in the high-risk group, 30 patients developed ESKD (85.7%). Three patients had the highest score of 11 points and remained dialysis independent (100%). The risk groups differed in renal survival (p=0.001).

Conclusions: Low percentage of normal glomeruli, higher grade of tubulo-interstitial damage and severe kidney failure are associated with poor outcome in anti-GBM disease. Combining these variables, the Renal Risk Score accurately predicted kidney survival in anti-GBM disease.

PO1622

Anti-Glomerular Basement Membrane Disease in Pregnancy

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Introduction: Anti-glomerular basement membrane (GBM) vasculitis is a rare immune mediated inflammation resulting in organ- and life-threatening disease. Presentation during pregnancy presents an additional challenge to preserve organ function and life of the unborn child.

Case Description: We report the case of a 23-year-old woman, 18 weeks pregnant, presenting with haemoptysis and acute kidney injury. Her chest X Ray demonstrated multilobar consolidation with perihilar prominence consistent with pulmonary haemorrhage. Her blood tests detected an anemia (Hb 51 g/L) and kidney failure (eGFR 17 ml/min). Her GBM antibody was 30.3 AI. She received daily plasma exchange (PLEX) for 7 days until her GBM antibody normalised. Additionally, she was commenced on 1 gram of cyclophosphamide, and after following plasma exchange sessions she received 1 gram of rituximab. Her acute kidney injury progressed (eGFR 13 ml/min), and renal replacement therapy was initiated. Intravenous fluid overload was managed with catheter dialysis which was maintained for 8 days in the high dependency unit on high flow oxygen therapy due to respiratory failure due to her diffuse alveolar haemorrhage needing daily transfusions to maintain her haemoglobin. Daily gynaecology reviews were performed. Post rituximab, PLEX was recommenced after 72 hours and continued daily for another week with 13 sessions in total. The patient stabilised, renal replacement therapy was discontinued, and she was discharged after a hospital stay of 27 days. Her baby was delivered via caesarean section due to the development of preeclampsia at week 28 gestation. Twelve months later, patient and baby are healthy with normal development percentile, and patient’s kidney function has recovered with a current eGFR of 86 ml/min.

Discussion: Timely and aggressive therapy is crucial to salvage kidney function in anti-GBM disease. Here, we present a case of a pregnant patient highlighting that a certain amount of cyclophosphamide is acceptable in life-threatening maternal conditions. Additionally, we demonstrate the possibility to significantly reduce cyclophosphamide in anti-GBM disease by adding in rituximab.

PO1623

Itilizumab, a Novel Anti-CD6 Therapy, in Systemic Lupus Erythematous Patients: Interim Safety Results from the Phase 1b EQUILISE Dose-escalation Study

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Background: CD6 is a co-stimulatory receptor predominantly expressed on T cells. The CD6 ligand, ALCAM, is expressed on antigen presenting cells, epithelial and endothelial cells. Itolizumab (ITO) is a humanized IgG1 monoclonal antibody that binds CD6 and blocks ALCAM interaction to inhibit T cell activation and trafficking.

Methods: EQUILISE is an open-label Phase 1b dose part study evaluating the safety, pharmacokinetics (PK), pharmacodynamics (PD), and clinical activity of subcutaneous doses (SC) of ITO (0.4 to 3.2 mg/kg). Part A enrolled adults with active or inactive SLE who received ≥1 SLE treatment. Treated subjects received ITO SC Q2 weeks x 2. Part B, which evaluates ITO in subjects with active proliferative Class III/IV LN for 24 weeks, is currently enrolling (NCT01428579).

Results: Part A enrolled 34 subjects: 0.4 mg/kg (n=6), 0.8 mg/kg (n=7), 1.6 mg/kg (n=7), 2.4 mg/kg (n=6), and 3.2 mg/kg (n=9). Similar baseline characteristics were noted in all cohorts. The mean age was 51, with 94% female, 74% white and ±11 years since SLE diagnosis. C3 and C4 were within normal ranges. Mean eGFR was 98 ml/min/1.73m² and the median UPCR was 91 mg/g (range 48-1505). SC dosing of 0.4 mg/kg to 2.4 mg/kg (n=26) was well tolerated, with 38% reporting an AE, predominantly mild injection site reactions, with no SAEs reported. >85% of 3.2 mg/kg subjects reported an AE, the most common was injection site reactions, with 2 non-treatment related SAEs reported in 1 subject (hypotension, syncope). 4 3.2 mg/kg subjects (50%) discontinued treatment after 1 dose voluntarily. In all cohorts, there were no notable changes in vital signs, or other lab parameters, except for transient elevations in WBC which resolved without clinical sequelae. PK and PD results show dose-proportional increases in ITO exposure and rapid and dose-dependent decreases in CD4 cell surface expression of CD6.

Conclusions: 2 SC doses of ITO up to 2.4 mg/kg SC in SLE subjects were well tolerated with high less tolerability to the 3.2 mg/kg dose, as 50% discontinued after 1 dose. The data support continued evaluation of ITO in SLE/LN. The ongoing EQUILISE Part B assesses ITO safety and efficacy in Class III/IV LN patients.

Funding: Commercial Support - Equillium, Inc
PO1624
Itolizumab, a Novel Anti-CD6 Antibody, in Systemic Lupus Patients with Proteinuria: An Interim Subgroup Analysis from EQUALISE, a Phase Ib Study
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Background: CD6 is a co-stimulatory receptor that is expressed on T cells. The CD6 ligand, ALCAM, is found on antigen presenting cells, as well as epithelial and endothelial cells. Itolizumab (ITO), a humanized IgG1 monoclonal antibody that binds CD6 and inhibits the interaction of CD6 and ALCAM, inhibits T cell activity and trafficking. ITO is being evaluated as a treatment for systemic lupus erythematosus (SLE) and lupus nephritis (LN).
Methods: EQUALISE (NCT04128579) is a Phase 1b US study of ITO in SLE patients with and without active proliferative LN. Part A enrolled SLE patients (N = 34) who had received a ≥1 SLE treatment but did not have active proliferative LN. Patients received 2 open-label doses of 0.4 to 3.2 mg/kg each on Day 1 and Day 15 with follow up through Day 57.
Results: A subgroup analysis of 16 subjects with Baseline (mean of screening and Day 1) urine protein/creatinine ratio (UPCR) > 100 mg/g was performed. Mean age was 55, 94% were female; 81% white and the mean years since SLE diagnosis was approximately 11. Mean baseline eGFR was 95 ml/min/1.73m2 and UPCR was 272 mg/g (range 50-1509). On Day 29, a geometric mean decrease in UPCR of ~45% was observed in these 16 subjects with greater decline seen for subjects with higher Baseline UPCR values. By Day 57, 6 weeks post treatment the decrease was 34% from Baseline (Figure). Notable is one subject (1.6 mg/kg dose) who had significant Baseline UPCR of 1569 and who was declined at Day 29 and at Day 57 reached 857 mg/g. SC treatment was well tolerated. Of the 6 subjects who had a total of 12 treatment-emergent adverse events (AEs), 4 were from the 3.2 mg/kg cohort. All AEs were mild or moderate in severity.
Conclusions: Patients with SLE and mild baseline proteinuria tolerated ITO treatment well. EQUALISE Part B will further explore the safety and efficacy of ITO in LN patients.
Funding: Commercial Support - Equillium, Inc

PO1625
Adding Low-Dose CYC to RTX Combined with a Tailored RTX Maintenance Regimen Seems to Favor Stable Remission in Severe ANCA Vasculitis
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Background: Rituximab (RTX) and cyclophosphamide (Cyc) are effective remission-induction therapies in ANCA-associated vasculitis (AAV). High dose CYC is however considered toxic, whereas RTX monotherapy may increase the risk of persistent MPO-ANCA seronegative conversion (OR 3.028, [95%CI, 1.262 – 7.268], p=0.048). MPO-ANCA reappearance after seronegative conversion was associated with increased relapse risk at 24 months (HR 3.651, [95%CI, 1.114-11.966], p=0.048). The risk reduction in ESKD, but absolute risk increase in serious infections was higher for CYC compared to RTX. One year risk of end stage kidney disease (ESKD) and serious infections with and without PLEX in AAV were presented across 5 serum creatinine categories: 150, 250, 350, 450 and 600µmol/L. For each scenario, participants were asked: “If they were a patient with a new diagnosis or relapse of AA V would they prefer CYC than PLEX (yes or no) given its absolute risk reduction in ESKD, but absolute risk increase in serious infections?” Multilevel multivariable logistic regression was performed to identify independent predictors of choosing treatment with PLEX.
Results: There were 549 responses. The mean age of respondents was 57.4 (SD 14.5) years, 72.3% were female, and responders were from the United States (58.1%), United Kingdom (23.7%), Canada (14.0%), and other countries (4.2%). The majority had AAV (86.7%). 190/549 (34.6%) would always choose PLEX and 87/549 (15.8%) would always decline PLEX across the baseline risks of ESKD or serious infections presented. Independent predictors for choosing PLEX included age (OR 0.98, 95% CI 0.96-0.99 per 1 year increase), country (United Kingdom OR 2.73, 95% CI 1.20-6.21), diagnosis (individuals with vasculitis other than AAV were more likely), previous dialysis (OR 3.34, 95% CI 1.37-8.16), previous PLEX (OR 5.13, 95% CI 2.50-10.49), and increased baseline risk of ESKD (Cr 350 and 450µmol/L only).
Conclusions: One third of participants would always choose treatment with PLEX across the 5 scenarios presented. The decision to choose PLEX is influenced by age, country and previous dialysis, and the baseline risk of ESKD and serious infections. Patient values and preferences are needed to inform shared decision-making regarding PLEX in AAV.

PO1627
Maintenance of Remission and Risk for Relapse in Myeloperoxidase Positive Antineutrophil Cytoplasmic Antibody-Associated Vasculitis with Kidney Involvement
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Background: Optimal time of remission-maintenance therapy in patients with MPO-ANCA associated vasculitis (MPO-AAV) is not established. Defining clinical and laboratory parameters to guide safe withdrawal of maintenance immunosuppression is required in order to mitigate the risk of relapse.
Methods: A retrospective cohort study of all patients followed at the Mayo Clinic with in RTX on MPA (MPA-AAV) and thrice weekly injections, hypoglycemia, eGFR < 60 ml/min/1.73 m², age ≥ 65 years, treated with MPO-ANCA status and remission-maintenance strategy were characterized.
Results: We analyzed 159 MPO-ANCA positive patients with active kidney involvement. A total of 66 (41.5%) patients had at least 1 relapse. MPO-ANCA patients who became and remained seronegative did not relapse (HR 0.03, [95%CI, 0.001-0.970], p=0.048). MPO-ANCA reappearance after seronegative conversion was associated with increased relapse risk at 24 months (HR 3.65, [95%CI, 1.14-11.966], p=0.012). Immunosuppression was withdrawn in 80 (50.3%) and this was predicted by persistent MPO-ANCA seronegative conversion (OR 3.028, [95%CI, 1.262 – 7.268], p=0.031). In patients who withdrew remission-maintenance therapy, 32 (40.0%) relapsed (in comparison with 34 relapses [43.0%] in those who maintained immunosuppression, p=0.097). ENT involvement (OR 6.095 [95%CI, 1.280 – 29.010], p=0.023) and MPO-ANCA reappearance (OR 9.208, [95%CI, 1.282 – 72.376], p<0.0001), were independent predictive factors for relapse after withdrawal.
Conclusions: Our results suggest that patients who seroconverted and remain MPO-ANCA negative are at lower risk of relapse: remission-maintenance treatment might be withdrawn without an additional risk of relapse. MPO-ANCA reappearance after seronegative conversion is a risk factor for relapse at 24 months. Serial MPO-ANCA determinations are useful to guide clinical decisions on remission-maintenance treatment strategies.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
POI1628

Renal Histological Biomarkers and Response to Different Induction Regimens in ANCA-Associated Glomerulonephritis: The REASSESS Study

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Background: The role of kidney biopsy on ANCA-associated vasculitis (AAV) is still debated: despite its significant prognostic value, whether it has an impact on the induction regimen choice has not been explored yet.

Methods: 323 AAV patients with biopsy-proven renal involvement were collected retrospectively from eleven centers and stratified according to the histopathological characteristics at the kidney biopsy and the induction regimen employed.

Results: The median follow-up time was 36 months; the eGFR was 19 ml/min/1.73m². 508 AA V patients with biopsy-proven renal involvement were collected and comparable in the different groups. In the unadjusted survival analysis with the K-M classification, 24% biopsies were classified as Focal, 31% as Crescentic, 33% as Mixed and 12% as Sclerotic. Renal remission rate at 6 months and relapse-free survival were 32% in the Focal, 29% in the Crescentic, 25% in the Mixed, and 22% in the Sclerotic group. The difference was significant in favor of the Focal group (P < 0.001).

Conclusions: Renal histology is an important biomarker for disease activity and it may also play a role in the choice of therapy.

POI1629

ANCA Vasculitis Induction Management in the COVID-19 Pandemic: Results of an International Retrospective Cohort Study

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Background: Induction therapy for severe ANCA-associated vasculitis (AAV) combines glucocorticoids (GC) with either rituximab (RTX) or cyclophosphamide (CYC). The coronavirus 2019 disease (COVID-19) pandemic has increased concern around using aggressive immunosuppression; whether this concern has impacted AAV management is unknown. Here, we report treatment regimens and outcomes of patients with active AAV receiving induction immunosuppression during the first wave of the pandemic.

Methods: We retrospectively studied AAV patients with new or relapsing disease receiving remission induction therapy during the first wave of the COVID-19 pandemic across sites in the US, UK and Europe. Primary outcome was achievement of complete remission at 6 months.

Results: Of 191 patients with a mean age of 65 years old, 52% were female and a majority (89%) were Caucasian. Standard induction was deployed across all sites. Out of the US, UK, and European patient populations, the US used higher GC pulses leading to a higher average cumulative GC dose for remission induction (4153 mg, 2174 mg, 3408 mg, respectively, p = 0.001) and had the highest proportion of patients given RTX induction therapy (64%; p < 0.005). Complete remission was achieved in 90% of patients. Improvement in kidney function at 6 months was similar with all treatment regimens (6 ml/min² increase, p = 0.68). Sixteen patients were diagnosed with COVID-19 and had similar exposures to CYC and RTX. There were no differences in remission rates, ESKD or death when stratified by induction therapy type.

Conclusions: Induction immunotherapy practices differ across the world, but specialists continued their standard management during the COVID-19 pandemic. AAV outcomes or rates of COVID-19 infection were not influenced by different induction regimens.

POI1630

Non-Sucrose Containing IV Immunoglobulin in ANCA Vasculitis Has No Adverse Effects on Renal Function

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Background: Intravenous immunoglobulin (IVIG) has proven to be effective as an immunomodulator in several autoimmune and inflammatory diseases, including antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Moreover, in the era of B cell-depleting therapies, secondary immunodeficiencies are common, urging supplementation by IVIG. Reported adverse effects are generally mild in nature. However, concerns have been raised about the safety profile of IVIG in relation to renal function. IVIG associated kidney injury is proposed to be mainly related to sucrose stabilized products. Non-sucrose containing alternatives are available and increasingly used. We therefore aimed to analyze the safety of non-sucrose containing IVIG with regard to renal function in patients with AAV.

Methods: AAV patients of the Maastricht University Medical Center were retrospectively analyzed for dynamics of serum creatinine levels before and after IVIG using the Wilcoxon signed rank-test. Subanalyses were performed with regard to the presence of ANCA-associated renal disease and IVIG indication. In addition, correlation analysis was conducted to evaluate the relation between serum creatinine change and cumulative IVIG dose during a 1year follow-up.

Results: 36 with 49 courses of IVIG were included in the short-term and 54 patients with 70 courses of IVIG were included in the long-term analysis. No significant differences were found between serum creatinine levels before and after IVIG in the short-term (median [IQR], 132 [88-159] and 125 [86-173] μmol/L, P = 0.380), with a median follow-up of 16 days after the initial IVIG infusion, and the long-term (median [IQR], 104 [66-147] and 110 [90-151] μmol/L, P = 0.077), after 1 year. One patient with active AAV and renal involvement had a reversible serum creatinine increase >30% 6 days after IVIG. Subanalyses showed no significant changes in serum creatinine levels with regard to renal involvement and IVIG indication. There was no association between serum creatinine change and cumulative IVIG dose 1 year after the initial IVIG infusion (P = 0.667).

Conclusions: This study shows no short-term and long-term deleterious effects on renal function in response to treatment with non-sucrose containing IVIG in patients with AAV.
Efficacy and Safety of a Combination Treatment of Mycoprotein Mefoil and Corticosteroid in Advanced IgA Nephropathy: A Multicenter, Prospective Study

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Background: It remains unclear whether immunosuppressive agents are effective in patients with IgA nephropathy (IgAN). We sought to determine the efficacy of mycoprotein mefoil (MMF) and corticosteroid combination therapy in patients with advanced IgAN.

Methods: We conducted a multicenter, randomized, placebo-controlled, parallel group study of a 48-week administration of MMF and corticosteroids in biopsy-proven advanced IgAN patients with an estimated glomerular filtration rate (eGFR) between 20-50 mL/min/1.73m² and a urine protein-to-creatinine ratio (UPCR) greater than 0.75g/day. The primary outcome was complete (UPCR<0.3g/day) or partial remission (reduction of UPCR>50% compared to baseline) at 48 weeks.

Results: Of the 48 randomized patients, complete and partial remission rates were higher in the MMF and corticosteroid combination therapy group (29.1% vs. 5.0%, P=0.05). In contrast to the combination therapy group, eGFR in the control group significantly decreased from 36 weeks onwards, resulting in a final adjusted mean change of -4.39 ± 1.22 mL/min/1.73m² (P=0.002). The adjusted mean changes at 48 weeks were 0.62 ± 1.30 and -5.11 ± 1.30 mL/min/1.73m² (P<0.005) in the treatment and control groups, respectively. The amount of UPCR was also significantly different between the two groups, where the adjusted mean difference was -0.47 ± 0.17 mg/mgCr in the treatment group and 0.07 ± 0.17 mg/mgCr in the control group (P=0.04). Overall adverse events did not differ between the groups.

Conclusions: In patients with advanced IgAN with a high risk for disease progression, combination therapy of MMF and corticosteroid appears to be beneficial in reducing proteinuria and preserving renal function.

Pharmacodynamic and Clinical Responses to BION-1301 in Patients with IgA Nephropathy: Initial Results of a Phase II/III Trial

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Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis globally, with up to 45% of patients at risk of progressing to ESKD. The initiating step in IgAN pathogenesis is the excess production of galactose-deficient IgA1 (Gd-IgA1), resulting in the formation of immune complexes that cause kidney inflammation and damage. A proliferation-inducing ligand (APRIL) is elevated in IgAN patients and correlates with higher levels of Gd-IgA1 and proteinuria, and lower eGFR. BION-1301 is a novel monoclonal antibody targeting APRIL. Here we present interim results from Part 3 of a Phase 1/2 study that characterizes the safety, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary activity of BION-1301 delivered by IV administration in patients with IgAN.

Methods: Part 3 of this Phase 1/2 study (NCT03945318) is an ongoing multicenter, multicohort, open-label study in up to 40 IgAN patients. In Cohort 1, BION-1301 is dosed at 450mg IV every 2 weeks for up to 12 months. Key objectives of the study include safety and the characterization of PK, PD, immunogenicity and changes in proteinuria. Key eligibility criteria include: (1) urine protein ≥0.5 g/24h or baseline UPCR ≥0.5 g/g, (2) stable/optimized dose of ACE-I/ARB or ACE-I/ARB intolerant and (3) biopsy-verified diagnosis of IgAN within the past 10 years.

Results: Preliminary results from the first 5 patients show BION-1301 is well tolerated with no serious adverse events and no adverse events leading to discontinuation to date. BION-1301 drives durable reductions in serum free APRIL, Gd-IgA1, IgA and IgG with a lesser reduction in IgM. A clinically meaningful reduction of 24-hour UPCR was observed within 3 months. Updated data in all 41 treated patients, along with mechanistic response kinetics, will be presented at the meeting.

Conclusions: BION-1301 is a novel anti-APRIL monoclonal antibody being developed as a potential therapy for patients with IgAN. BION-1301 treatment holds modifying potential by directly targeting the pathogenesis of IgAN. Promising early biomarker and clinical activity support the continued development of BION-1301 in IgAN.

Atrasantin Exhibits a Consistent, Predictable Pharmacokinetic Profile Among Healthy Asian Adults

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Background: Atrasantin, a potent and selective endothelin-A receptor antagonist, is under investigation for reducing proteinuria and preserving kidney function in IgA nephropathy and other glomerular diseases. Two phase 1 studies evaluated the pharmacokinetics (PK) and safety of atrasantin in healthy adults of Chinese (Study M11-521) and Japanese (Study M11-522) parentage.

Methods: Study M11-521 was an open-label, randomized (for single-dose regimens), single-center study of single and multiple doses of atrasantin in 36 healthy Chinese adults. Single doses of atrasantin tablets (0.5, 1, or 1.5 mg) were administered in Part I, and multiple daily single doses of atrasantin 1.5 mg were administered in Part II. Study M11-522 was a double-blind, randomized, placebo-controlled, single-center study of single doses of atrasantin (0.5, 0.75, or 1.25 mg) in 36 healthy Japanese adults. Blood samples were collected for analysis of plasma PK parameters, including the area under the plasma concentration-time curve (AUC) and the maximum observed plasma concentration (Cmax).

Results: In Study M11-521, atrasantin AUC increased proportionally with dose in the 0.5 mg to 1.5 mg dose range, and Cmax increased proportionally with dose in the 1 mg to 1.5 mg dose range. No statistically significant differences were observed in either the dose-normalized AUC for the comparison of the 1.5 mg and 0.5 mg dose groups (P = 0.260) or the dose-normalized Cmax for the comparison of the 1.5 mg and the 1 mg dose groups (P = 0.279). In Study M11-522, a linear increase in atrasantin mean AUC was observed across the 0.5 to 1.25 mg dose range; dose-normalized mean Cmax did not show statistically significant differences across the doses (P = 0.735). Atrasantin was generally well tolerated. No clinically significant vital signs, electrocardiogram activity, or laboratory measurements were observed, and no apparent significant differences among the dose regimens were found with respect to safety.

Conclusions: Dose-proportional increases in AUC were observed across the studied range, which includes the 0.75 mg dose being studied in ongoing clinical trials. These data support the safety and tolerability of atrasantin and suggest a consistent and predictable PK profile among patients of Asian descent.

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Background: IgA nephropathy (IgAN) is the most common biopsy-proven glomerulonephritis in the world. Approximately 40% of IgAN patients reach end-stage kidney disease (ESKD) 20 years after their kidney biopsy. The high prevalence of ESKD shows that IgAN has a high economic impact in the countries because renal replacement therapy is costly. Moreover, the disease’s onset in the second and third decades of life represents a social challenge because young adult patients are very active and highly productive in the workplace. This challenge is one more reason to move from a generalized therapy for all patients to a personalized therapy. Many randomized controlled trials (RCTs) have been conducted, stratifying IgAN patients based on the laboratory findings (serum creatinine, estimated glomerular filtration rate (eGFR) and daily proteinuria). In contrast, data from the kidney biopsy has been used only for clinical diagnosis. Aim. We have designed a RCT to study personalized therapy in biopsy-proven IgAN patients with active and chronic renal lesions.

Methods: Our clinical study of IgAN (CLiGAN) is a multicentre, prospective, controlled and open-label randomized clinical trial based on patient’s stratification at the time of their kidney biopsy. The trial has been registered in ClinicalTrials.gov (NCT 04662723). We will consider, first, the type of renal lesions followed by serum creatinine, estimated glomerular filtration rate (eGFR) and daily proteinuria. Primary and secondary end points have been established. Second, we will determine whether personalized therapy can slow the decline of the renal function and delay the ESKD. Our clinical study of IgAN (CLIgAN) is a multicentre, prospective, controlled and open-label randomized clinical trial based on patient’s stratification at the time of their kidney biopsy. The trial has been registered in ClinicalTrials.gov (NCT 04662723). We will consider, first, the type of renal lesions followed by serum creatinine, estimated glomerular filtration rate (eGFR) and daily proteinuria. Primary and secondary end points have been established. Second, we will determine whether personalized therapy can slow the decline of the renal function and delay the ESKD.

Results: We will enroll 132 IgAN patients with active renal lesions (66 patients per arm) in the first RCT (AClGAn). They will receive corticosteroids combined with renin-angiotensin system blocker (RASB) or RASB alone. Two hundred ninety-four IgAN patients with chronic renal lesions were enrolled in the second RCT (CHRONiGAn) in which they will receive sodium-glucose cotransporter -2 inhibitor (SGLT2-i) combined with RASB or RASB alone.
Conclusions: Using this approach we hypothesize that patients could receive personalized therapy based on renal lesions to ensure that the right drug gets to the right patient at the right time.

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POI1635 Enhanced Efficacy of Corticosteroid Therapy by Tonsillectomy in IgA Nephropathy
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Background: Efficacy of corticosteroid therapy in IgA nephropathy may vary among countries or races. Nowadays, the strategy to enhance efficacy of corticosteroid therapy is desired. In 2014, our randomized controlled trial demonstrated that corticosteroid therapy combined with tonsillectomy had superior anti-proteinuric effect than that of corticosteroid therapy alone (Nephrol Dial Transplant. 2014). However, the benefit of combining corticosteroid therapy with tonsillectomy for long-term renal survival was uncertain. Therefore, in a Japanese nationwide prospective cohort dataset, we aimed to evaluate whether the benefit of corticosteroid therapy may increase when it was combined with tonsillectomy, or not.

Methods: Patients were registered between April 1, 2005 and August 31, 2015 at 44 facilities throughout Japan. The primary outcome was a 50% increase in serum creatinine from baseline or dialysis initiation. Two interventions were focused in the present study: corticosteroid with or without tonsillectomy. Survival analysis was adjusted with baseline clinicopathological parameters including eGFR, proteinuria, hematuria, RAS inhibitor use and MEST-C score in Oxford classification.

Results: Enrolled 991 patients showed 75.4 ml/min as mean eGFR and 0.58 g/day as median level of proteinuria. Among them, 634 (64.0%) and 425 (42.9%) patients received corticosteroid therapy and tonsillectomy, respectively. During the median follow up of 5.5 years, 87 patients (8.8%) reached primary outcome. Adjusted hazard ratio (HR) of corticosteroid therapy for primary outcome in patients with tonsillectomy was 3-fold favorable than that in those without tonsillectomy (HR 0.18, 95% confidence interval [CI] 0.06-0.65, versus HR 0.59, 95%CI 0.34-1.01; P value for interaction between corticosteroid therapy and tonsillectomy 0.060).

Conclusions: Enhanced efficacy of corticosteroid therapy by tonsillectomy in IgA nephropathy was confirmed in a Japanese nationwide prospective cohort.

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POI1636 The Potential Role of Monthly Corticosteroid Pulse in IgA Nephropathy
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Background: The risk of corticosteroid therapy may be underestimated in IgA nephropathy (IgAN). Previous studies provided that a fifth part of patients was older than 60 years and the rate of diabetes mellitus (DM) was increased in IgAN. The novel corticosteroid therapies with not losing benefit and reduced risk of corticosteroid are desired. Here, we aimed to determine whether monthly corticosteroid pulse is non-inferior in proteinuria remission and superior in blood glucose control to standard corticosteroid therapy or not.

Methods: Design: Retrospective, non-inferiority study. Participants: Adult patients with IgAN received intervention described below between 2013 and 2020. Intervention: Monthly corticosteroid pulse alone for 6 months versus standard corticosteroid therapy having oral corticosteroid for 6 months and three times of pulse corticosteroid in the same 6 months (Lancet 1999). Outcomes: The primary outcome was proteinuria remission (<0.3g/day) at 1 year and we prespecified 0.67 in odds ratio (OR) as non-inferiority margin. The secondary outcome was safety of blood glucose care, which was defined by less than 0.3 in change of hemoglobin A1c% between baseline and 6 months.

Results: The enrolled 83 patients (22 patients >60 years old and 11 patients with DM) showed median proteinuria 0.93g/day and mean eGFR 60.5ml/min at baseline. There was no significant difference in proteinuria remission between the two groups but including the non-inferiority margin (16/21[76.2%] versus 38/62[61.3%], adjusted OR 4.10, 95%CI 0.77 to 36.1). The safety of blood glucose care in monthly corticosteroid pulse group was significantly superior to that in standard group in (19/21[90.5%] versus 35/62[56.5%], adjusted OR 14.2, 95%CI 2.02 to 98.9).

Conclusions: Compared to standard corticosteroid therapy, the current study showed that monthly corticosteroid pulse did not reach the statistical requirements for a proven non-inferiority on proteinuria remission, but significantly exhibited safety outcome in the control of blood glucose. Prospective larger studies are needed to determine the role of monthly corticosteroid pulse in IgAN.

POI1637 The Beneficial Effects of Renin-Angiotensin System Inhibitors on IgA Nephropathy with Global Sclerosis
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Background: In IgA nephropathy (IgAN), global sclerosis has been recognized as one of the risk factors for progression, because it induces glomerular hypertension and hyperfiltration in the remained glomeruli. The reno-protective effects of renin-angiotensin system inhibitors (RASI) are considered to decrease glomerular hypertension and hyperfiltration, but their effectiveness in IgAN with global sclerosis has been unknown.

Methods: Of the 871 IgAN patients diagnosed at our institution, we classified them into three grades by the ratio of global sclerosis (G) against whole glomeruli (G0 (n=225); none, G1 (n=445): at least one but <25%, G2 (n=191): ≥25%). We compared each clinical background and 20-year prognosis. Then, we examined the effect of RASI initiated during follow-up period on the long-term prognosis in patients with G1+G2 and in patients with G2 by Kaplan-Meier analysis and Cox regression analysis. To adjust the background characteristics between patients treated with or without RASI, propensity matching score was performed.

Results: The age, blood pressure, proteinuria, renal function, and histological findings were significantly severer with increasing grade in G0, G1, and G2, and 20-year renal survival rate was 83.5%, 75.0% and 54.4% in patients with G0, G1, and G2, respectively (p=0.001). After propensity matching between patients treated with or without RASI, 366 patients in G1+G2 and 90 patients in G2 were eligible for the evaluation. The 20-year renal survival rate was significantly higher in the patients with RASI than in the patients without RASI (G1+G2: 84.5% vs. 50.9%, p=0.001; G2: 63.8% vs. 33.5%, p=0.037). In multivariate Cox regression analysis considering clinical and histological findings and treatment, RASI was an independent factor to prevent progression in patients with G1+G2 and G2 (G1+G2, hazard ratio: 0.39, 95% confidence interval: 0.25-0.62, p<0.001; G2, hazard ratio: 0.35, 95% confidence interval: 0.19-0.66, p=0.001).

Conclusions: In this study, global sclerosis was associated with severer clinical and histological findings, and poor prognosis. However, RASI initiated during follow up period was found to improve renal prognosis in IgAN with at least one global sclerosis.
PO1639
Remission of IgA Nephropathy with Hydroxychloroquine
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Introduction: IgA nephropathy is the most common form of glomerulonephritis in the world. Treatment options include blockade of renin-angiotensin-system (RAS) as the first line of therapy. Steroids may be beneficial in refractory cases, however, can result in several adverse effects. Data regarding use of immunosuppression is inconclusive. Combination of RAS inhibition and hydroxychloroquine has shown to reduce proteinuria in recent studies, though, complete remission with long term use has not been described. We report the case of a 46-year-old Asian female with IgA nephropathy, who was treated with maximally tolerated RAS inhibition and hydroxychloroquine for about 24 months resulting in complete remission of proteinuria and hematuria.

Case Description: The patient was referred to nephrology for evaluation of hematuria and proteinuria (1.5 g/g, Serum creatinine 0.9mg/dl). Serological work-up was negative. She was initiated on angiotensin receptor blocker (ARB) and underwent kidney biopsy which confirmed IgA Nephropathy. There were 8 glomeruli with 20-25% sclerosis, mild to moderate chronic tubulointerstitial nephritis and fibrosis, no crescents, mild mesangial proliferation and hypercellularity with IgA staining 3+. She did not have any significant improvement in proteinuria despite maximally tolerated ARB (losartan 100 mg daily) therapy for three months. Her kidney function also declined, creatinine 1.2mg/dl. Hydroxychloroquine 200mg daily was then initiated along with regular eye exams and hepatic function tests. Repeat workup in three months showed improvement in proteinuria to 0.2g/g and creatinine 1.1mg/dl. She was continued on the same regimen for about 24-months with recent work-up showing complete resolution of proteinuria and hematuria.

Discussion: As per our literature review, this is the first reported case of IgA nephropathy treated with RAS inhibition and hydroxychloroquine over a span of almost two years resulting in complete remission. Hydroxychloroquine can be considered, in select cases, as an alternative to steroid therapy in refractory proteinuria.

PO1640
Long-Term Follow-Up Study of Immunosuppressive Therapy in IgAN Patients with CKD Stage 3 and 4
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Background: The benefits of immunosuppressive therapy in patients with IgAN remain controversial, especially for those with more severe renal pathology and reduced renal function.

Methods: A total of 496 primary IgAN patients were screened between 2012 to 2014. Patients were divided into 4 groups according to CKD stage and the treatment. The primary endpoints were doubling of creatinine, progression to ESRD or death. The secondary endpoint was decrease in eGFR. Subgroup analysis of CKD3 immunosuppressive treatment group was conducted to explore the factors affecting the prognosis after treatment.

Results: 164 patients were enrolled and mean follow-up time was 5.5 years. There were 126 patients in CKD3 stage and 38 patients in CKD4 stage. Immunosuppressive therapy significantly improved prognosis in patients with CKD stage3 (HR 0.435[95% CI 0.296-0.759]; p=0.035), but no difference for CKD stage4(p=0.364). Subgroup analysis showed baseline eGFR(OR 0.909[95%CI 0.834-0.991];p=0.031), serum IgG level(OR 0.809 [95%CI 0.658-0.995];p=0.045) were associated with primary outcome and loop diuretics (OR 0.109[95% CI 0.050-0.709], p=0.014), proportion of crescents (OR 0.200[95% CI 0.100-0.521], p=0.003), interstitial fibrosis>50%(OR 5.490[95% CI 1.323-22.727]) were associated with secondary outcome. Remission within 1 year could be an indicator of good long-term prognosis (HR 0.555[95%CI 0.296-0.759]; p=0.035).

Conclusions: For IgAN patients with CKD stage3, immunosuppressive therapy should be actively applied under the general treatment, but for patients with CKD stage4, it should be carefully. Patients with good renal function, more acute lesions of renal pathology could have a better prognosis after immunosuppressive therapy. Patients who achieved remission within 1 year would have better long-term prognosis.
PO1642
Long-Term Effectiveness of Low-Dose Prednisone Treatment in Relapses of Steroid-Sensitive Minimal Change Disease

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Background: Treatment of relapses of steroid-sensitive minimal change disease (SMCD) involves administration of high doses of prednisone for several weeks, implying significant pharmacological toxicity. In a previous pilot study, the efficacy of treatment with low doses of prednisone for the treatment of relapses in these patients was demonstrated.

Methods: Retrospective analysis of SMCD relapses treated with low doses of prednisone in two centers, was performed, and the response to treatment, the time to reach remission and the free-time of relapse was studied, comparing it with previous relapses of the same patients treated with standard doses of steroids.

Results: 85 relapses in 21 patients with SMCD were analyzed. The median age of patients was 35 years (IQR 18-53), with 62% being male. The mean proteinuria at relapse debut was 4.37 ± 4.11 g/day, serum albumin 2.47 ± 0.94 g/dl and creatinine 0.86 ± 0.33 mg/dl. Thirty-six relapses (42.3%) were treated with low doses of prednisone (LDP) and compared with 49 previous relapses (57.6%) of the same patients, treated with high doses of prednisone (HDP). The mean initial prednisone dose in relapses treated with LDP and HDP was 0.45 ± 0.1 mg/kg and 1.00 ± 0.3 mg/kg, respectively (p = 0.001). The mean cumulative dose of prednisone in relapses treated with LDP and HDP was 1771 ± 1303 mg and 3894 ± 2134 mg respectively (p < 0.001). There were no differences in treatment duration between relapses treated with low and high corticosteroids doses (124 days vs 153 respectively; p = 0.2). All patients achieved complete remission after steroid treatment. Mean time to remission was 18.44 days for relapses with LDP and 17.1 days for HDP (p = 0.6). The mean free time to relapse after treatment with low doses was 12.6 months vs 10.9 months for those treated with high doses (p = 0.6).

Conclusions: Among SMCD patients, treatment of relapses with low doses of prednisone (0.5 mg/kg) is effective and safe, allowing to minimize cumulative steroid doses and derived toxicity.

PO1643
DEFINE Physicians: An International Delphi Survey to Identify Consensus in the Care of Patients with FSGS or Idiopathic Nephrotic Syndrome

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Background: High consensus regarding clinical decisions and the importance of controlling proteinuria in IgAN was observed in this Delphi survey. Although the level of consensus related to corticosteroid use was lower for adult patients vs pediatric patients, the level of consensus was relatively high for both groups.

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Methods: DEFINE: Physicians was a 2-round Delphi survey that recruited nephrologists from North America and Europe. A total of 22 FSGS/INS statements were scored using a 1-9 Likert scale (9=strongly agree). Consensus was defined as median and mean score ≥7, and ≥75% of participants scoring agreement (ie, score 7-9). Statements not achieving high consensus (≥80% agreement) in Round 1 were revised and retested in Round 2.

Results: This study involved 207 adult and pediatric nephrologists. Median clinical experience was 18 (range 5-49) years; 103 participants (50%) worked in nonacademic settings. In Round 1, 21 statements met consensus criteria and 7 statements not achieving high consensus were revised or divided into multiple parts, creating 11 revised statements for testing in Round 2. In Round 2, 9 of 11 statements met at least moderate consensus. Round 1 statements with high consensus described prognostic significance of proteinuria and disease management (Figure 1). Controversial statements retested in Round 2 pertained to distinction between primary and secondary FSGS in adults, and to management of frequently relapsing INS in children (Figure 2).

Conclusions: The level of consensus in this Delphi survey was high for statements on treatment decisions and the importance of proteinuria control. The main area where high consensus was not reached pertained to differentiation between primary and secondary FSGS and managing frequently relapsing INS in children, suggesting that these areas require further research.

Funding: Commercial Support - Travere Therapeutics, Inc.

PO1644
Safety and Efficacy of ANG-3070 in Patients with Primary Proteinuric Kidney Disease: A Phase 2 Study Design

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Background: Primary proteinuric kidney diseases (PPKD) are among the leading causes of End-Stage Kidney Disease (ESKD). Receptor tyrosine kinases like PDGFR, DDR1, DDR2 are thought to play a role in the progression of PPKDs to ESKD. ANG-3070, a selective oral tyrosine kinase inhibitor, has demonstrated beneficial effects in chronic kidney disease animal models. Objective: Design the design of a proof-of-concept study of ANG-3070 in the treatment of PPKD patients with persistent proteinuria while on standard of care (SOC).

Methods: A 12-week, randomized, double-blind, placebo-controlled study enrolling 100 patients with biopsy-proven PPKD and persistent proteinuria, ≥1 g/day, while on the SOC including maximum tolerated RAAS inhibitors. Patients will be randomized 1:1:1:1 to 200 mg or 400 mg once-daily or 300 mg twice-daily of ANG-3070 or placebo (Fig. 1).

Results: The primary endpoint is the percentage change in 24-hr urinary protein at Week 12. Key secondary endpoints evaluated at week 12 include percentage change in 24-hr urinary albumin, number of patients with complete remission in proteinuria (24-hr urinary protein < 300 mg), number of patients with partial remissions in proteinuria (24-hr urinary protein reduction of ≥50% from the baseline and a 24-hr urinary protein < 3.5 g/day if the baseline 24-hr urinary protein > 3.5 g), number of patients with ≥50% reduction in 24-hr urinary protein from the baseline, and number of patients with a ≥50% reduction in 24-hr urinary albumin from baseline. An independent data monitoring committee will review safety throughout the study.

Conclusions: This Phase 2 study will provide data about the safety and efficacy of ANG-3070 in PPKD patients that will inform the design of a Phase 3 study.

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POI1645

Transcutaneous Auricular Vagus Nerve Stimulation (taVNS) for the Treatment of Pediatric Nephrotic Syndrome (NS)

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Background: Children with NS, especially those with frequent relapses (FRNS) or steroid resistance (SRNS), are exposed to prolonged courses of immunosuppressant medications with side effects and variable efficacy. There is an urgent need to identify novel and safe therapies to treat pediatric NS. taVNS modulates the immune system via the cholinergic anti-inflammatory pathway and has become a therapy of interest for treating immune-mediated illnesses. The objective was to conduct an open-label early feasibility study of taVNS therapy for pediatric NS.

Methods: Children with FRNS (≥2 relapses in previous 6 months) or SRNS (no remission after 4 weeks of steroids) were enrolled. Participants with FRNS were in remission and off immunosuppression (off steroids >14 days and other immunosuppression >3 months). SRNS patients were on a stable regimen of medications for 6 months prior to enrollment. Participants performed taVNS therapy 5 minutes daily for 6 months with a TENS 7000 unit. taVNS was delivered to the auricular branch of the vagus nerve via the left cymba concha. Cytokine levels were compared using the Wilcoxon test.

Results: Seven participants (3 FRNS, 3 SRNS, 1 genetic congenital nephrotic syndrome [CNS]) had a median age of 7 years (range 3-17) and 63% were male. FRNS participants remained relapse-free during the study period (two continued taVNS at 9 and 13 months and remained in remission). SRNS participants had a 25-76% reduction in urine protein to creatinine ratio (upc) compared to baseline (Figure). Upe decreased (13.7%) in the participant with CNS but remained in nephrotic range. All but one participant (non-compliant) had a reduction in TNF-α (7.33 pg/mL vs. 5.46 pg/mL, p=0.03). No adverse effects were reported.

Conclusions: taVNS prevented NS relapses in FRNS, reduced proteinuria in SRNS, and reduced TNF-α levels without any adverse effects, suggesting taVNS as a promising therapy for pediatric NS. A larger, randomized clinical trial is needed to confirm these findings.

Figure 1.

POI1646

A Study Comparing Rituximab and Modified Ponticelli (MP) Regimen in Primary Membranous Nephropathy (PMN)

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Background: The study was designed in December 2018 when the Gemritux trial had established Rituximab as an alternative to MP regimen in the treatment of PMN. So we designed a study comparing Rituximab and MP Regimen.

Methods: We allocated 35 adults with PMN and proteinuria >3.5 gm/day in a 3:2 ratio to MP regimen or Rituximab 375mg/m² on days 1,8,15 and 22. The primary outcome was complete or partial remission (CR+PR) at 6 and 12 months in the 2 groups. The other findings included trends of 24 hr urine protein, albumin, creatine and serious adverse events at 6 and 12 months in both groups.

Results: At 6 months, 12 of 21 patients (57.14%) allocated to MP Regimen and 5 of 14 patients (35.71%) allocated to Rituximab experienced remission (CR+PR) (odds ratio [OR], 2.4; 95% CI, 0.596–9.670, p value 0.10). At 12 months, 14 of 21 patients (66.66%) allocated to MP Regimen and 10 of 14 patients (71.43%) allocated to Rituximab experienced remission (CR+PR) (odds ratio [OR], 0.8; 95% CI, 0.184–3.487, p value 0.383). Serious adverse events occurred in 15% of patients receiving Rituximab and in 24% receiving the MP Regimen.

Conclusions: We found No Statistically Significant difference between Rituximab and the Modified Ponticelli Regimen in the treatment of membranous nephropathy. A head-to-head, longer follow up study comparing MP Regimen versus Rituximab is required in terms of duration of remission and side effect profile between the two treatment groups.

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: M-PLACE (NCT04145440) is an open-label, multi-national Phase IIb/III study of adults with anti-PLA2R+ MN requiring immunosuppressive therapy (IST). Cohort 1 includes de novo and IST-relapsed pts (n=20) and Cohort 2 IST-refractory pts (n=10). Participants receive nine felzartamab infusions (16 mg/kg) over six 28-day cycles (weekly in Cycle 1; monthly thereafter), followed by a 28-week observational follow-up. Concomitant IST use is prohibited. The primary endpoint is the incidence and severity of treatment-emergent adverse events. The key secondary endpoint is the immunologic response rate, as determined by anti-PLA2R Ab reductions. Exploratory endpoints include evaluations of proteinuria and kidney function.

Results: As of April 2021, 12/30 planned pts were enrolled (Cohort 1, n=8; Cohort 2, n=4). Median age was 62.5 years (range 43 to 77 years), 83% were male, and median baseline anti-PLA2R Ab titer was 178 U/mL (18 to 1027 U/mL). Seven pts had received ≥4 weeks of felzartamab therapy. At Week 4, 5/7 pts had a >50% reduction from baseline in anti-PLA2R Ab (Cohort 1, n=3; Cohort 2, n=2); the other 2/7 pts had reductions from baseline of −16.8% and −5.0% (both Cohort 1). Mean % decline in anti-PLA2R Ab from baseline to Week 4 was −53.0% (−92.0% to −5.0%). B-cell counts were not markedly changed from baseline. Felzartamab was well tolerated.

Conclusions: The M-PLACE proof-of-concept study has so far shown that felzartamab rapidly and substantially reduces anti-PLA2R Ab titers in pts with anti-PLA2R+ MN. Longer follow-up is required to assess felzartamab safety and efficacy in this population.

Funding: Commercial Support - MorphoSys AG

PO1649
Intravenous Cyclophosphamide vs. Calcineurin Inhibitors as Treatment in High-Risk Idiopathic Membranous Nephropathy: The Benefit in MAKE Is Preserved in the Presentation IV?

Anita M. Cordoba Hurtado,1 L. M. Perez-Navarro,1 Jesus D. Lima-Lucero,2 Virgilia Soto,2 Rafael Valdez-Ortiz.2 1Hospital General de Mexico Dr Eduardo Liceaga, Ciudad de Mexico, Mexico; 2Instituto Nacional de Cardiologia Ignacio Chavez, Mexico, Mexico.

Background: The use of intravenous cyclophosphamide (IV CYC) in high-risk idiopathic membranous nephropathy (IMN) has not been fully evaluated in the making primary endpoints (serum Cr doubling, ESRD, mortality). In our center, the treatment of high-risk IMN is performed with IV CYC or with calcineurin inhibitors (CNI) according to criteria of accessibility and availability of the drug. Our aim was to compare the immunosuppressive treatment scheme with IV CYC vs CNI in primary IMN events in patients with high-risk IMN.

Methods: Retrospective cohort study. Patients with a diagnosis of IMN diagnosed between January 2012 and January 2020 were included. The patients were treated with IV CYC or CNI. With a minimum follow-up of 12 months and MAKE primary events were recorded in addition to complete, partial, composite response and adverse events at the end of the study.

Results: Thirty-seven patients of which 14 (37.8%) were treated with IV CYC and 23 (62.2%) with CNI. The mean age was 46 ± 15.3 years, 54% male, and 27% hypertensive. Average PrU/ CrU 10.4 ± 4.4 gr/dL, mean albumin 1.8 ± 0.68 gr/dL, and GFR by CKD EPI of 75ml/min/1.73m². With a follow-up of 45.91 ± 23.9 months, no baseline differences were observed between the groups. Table 1 shows the comparison between IV CYC vs CNI for high-risk IMN shows similar outcomes focused on MAKE. However, the comparison in complete and partial response shows a result in favor of the use of CNI. This perspective provides clinical evidence about the use of IV CYC, which is why it is suggested that there are possible differences between our findings and those reported so far with oral CYC. Prospective clinical trials are required to have conclusive results.

Funding: None

Table 1. Outcomes by treatment IV CYC vs ICN

<table>
<thead>
<tr>
<th>Outcome</th>
<th>IV CYC</th>
<th>ICN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>28.6%</td>
<td>56.3%</td>
</tr>
<tr>
<td>Partial response</td>
<td>7.1%</td>
<td>30.4%</td>
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<tr>
<td>Composite remission</td>
<td>35.7%</td>
<td>85.9%</td>
</tr>
<tr>
<td>Relapses</td>
<td>20.8%</td>
<td>25.0%</td>
</tr>
<tr>
<td>MAKE</td>
<td>15.0%</td>
<td>18.8%</td>
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</table>

PO1650
An 8-Week Course of Cyclophosphamide and Steroids Is Effective Therapy in Patients with Membranous Nephropathy (MN) and Low PLA2Rab Levels

Coralie Vink- van Setten,1 Anne-Elis van de Logt,1 Alexander Kühl,2 Jack F. Wetzel’s.1 Radboudumc, Nijmegen, Netherlands; 2EURIMMUN Medizinische Labordiagnostika AG, Lübeck, Germany.

Background: We introduced individualized therapy in patients with MN and positive anti PL2AR antibodies (aPLA2R) by IIFT test. Treatment (cyclophosphamide combined with steroids) was stopped when the IIFT test (measured at 8, 16, or 24 weeks) became negative. After 8 weeks, 71% of patients were in immunological remission. Unfortunately, 30% of these latter patients needed renewed therapy within 12 months because of immunological and/or clinical relapse. We questioned if quantitative aPLA2R measurement would predict response.

Methods: Available, stored serum samples were retrieved, and aPLA2R levels were measured by ELISA (EURIMMUN Lübeck, Germany). Good outcome was defined as immunological remission at 8 weeks, followed by clinical remission without clinical relapse nor the need for additional immunosuppressive therapy within 12 months. Results: Serum samples of 60 patients were available for analysis. Patients were grouped according tertiles of aPLA2R (Table). Higher aPLA2R levels were associated with more severe proteinuria. Patients in the lowest tertile were more likely to develop immunological remission at 8 weeks (95% vs 65% and 50% in the middle and highest tertiles). Moreover, in the subgroup of patients who were treated for 8 weeks only, fewer patients in the lowest tertile of aPLA2R needed renewed immunosuppressive therapy, although not statistically significant (16% vs 43%, p = 0.054).

Conclusions: Individualized treatment of MN patients with cyclophosphamide and steroids has been recently introduced. In this study we show that baseline aPLA2R levels predict immunological remission at 8 weeks. Furthermore, patients with low aPLA2R levels at baseline seem to be more likely to have a good overall outcome.

Funding: Commercial Support - EURIMMUN research lab, Lübeck, Germany

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Baseline clinical characteristics and immunological remission at week 8

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal range</th>
<th>Mean +/− SD</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>62.7 ± 13</td>
<td>62.7</td>
<td>62 (50-75)</td>
</tr>
<tr>
<td>Gender</td>
<td>Male: Female</td>
<td>51%:49%</td>
<td>51 (49-51)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>125/75 mmHg</td>
<td>125/75 (110-130)</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.6-1.1 mg/dl</td>
<td>0.8 (0.6-1.2)</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>3.5-5.0 g/dl</td>
<td>4.0 (3.5-4.5)</td>
<td></td>
</tr>
<tr>
<td>Hgb</td>
<td>12-16 g/dl</td>
<td>14 (12-16)</td>
<td></td>
</tr>
</tbody>
</table>

Data shown as mean±SD or median[IQR]. *By Kruskall-Wallis test of Fishers’ exact test, as applicable

POI1651
Prospective Cohort Study of Antibody-Guided Therapy in Patients with Membranous Nephropathy

Background: Guidelines advise a standard course of 6 months of cyclophosphamide (CP) and steroids in patients with membranous nephropathy (MN). We hypothesized that monitoring of aPLA2R-antibodies (aPLA2R) may enable individualized (and shorter duration of) therapy.

Methods: Patients with MN, with positive aPLA2R and high risk of progression were included. Treatment consisted of CP (1.5 mg/kg/day combined with steroids). aPLA2R were monitored (IFT test) at 8, 16, and 24 weeks after start of treatment. If the IFT test was negative, CP was stopped and prednisone tapered. If the IFT test remained positive at 24 weeks, CP was switched to MMF and therapy continued.

Results: Sixty-five patients (48 males) were included; mean age 61 ± 12 yrs, median serum creatinine 136 [IQR 100-161] µmol/l, serum albumin 21 [IQR 16-26] g/l and UPCR 7.7 [IQR 5.4-11.1] g/10 mmol. Follow-up was 37 [IQR 27-58] months. aPLA2R test was negative in 46 patients after 8 weeks (group A), in 10 patients after 16 weeks (group B1), in 1 patient after 24 weeks (group B2) and in 8 patients aPLA2R remained positive after more than 24 weeks (group B3). In group A no clinical remission (PCR <3.0 g/10 mmol) was observed in 26 % (12 patients) compared to 21 % (4 patients) in group B1-B3 (Log-rank p=0.579). Overall 22 patients (34 %) received additional immunosuppressive (IS) therapy because of persistent proteinuria (after aPLA2R disappearance) or clinical relapse. IS free survival was lower in group A compared to group B1-B3 (Figure 1).

Conclusions: Approximately 50% of patients developed long-term clinical remission after 8 weeks of therapy. Our data support aPLA2R-guided therapy. However, in approximately 25% of patients immunological remission was not followed by clinical remission, underlining the need for better biomarkers.

Funding: Other NIH Support - Dutch Kidney Foundation

POI1652
Economic Evaluation of the MENTOR Trial Comparing Rituximab and Cyclosporine for the Treatment of Membranous Nephropathy (MN)
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Background: The MENTOR trial (Membranous Nephropathy Trial Of Rituximab) showed that rituximab (RTX) was noninferior to cyclosporine (CSA) in inducing complete or partial remission of proteinuria and was superior in maintaining proteinuria remission. However, the cost of RTX is high and it’s cost-effectiveness has not been determined.

Methods: A Markov model (Fig 1) was used to determine the incremental cost-effectiveness ratio (ICER) of RTX compared with CSA for the treatment MN from the perspective of a health care payer with a life-time time horizon ($2020 USD). The model outcomes were informed by data from the MENTOR trial and previously published literature. Cost and utility inputs were obtained from the literature.

Results: Based on 1,000 simulations, the mean additional cost of RTX therapy for MN compared with CSA was $168,064 with an improvement in utility of 6.70 QALYs (Fig 2). RTX was cost-effective (assuming a willingness-to-pay threshold of $50,000 / QALY) compared with cyclosporine, with an ICER of $25,071 per additional quality adjusted life year (QALY) over a lifetime time horizon (45 years).

Conclusions: While the initial cost of RTX is high, RTX is a cost-effective option (assuming willingness to pay thresholds of $50,000 or greater) for the treatment of MN when compared with the alternative of CSA. The cost-effectiveness will be further improved with the use of less expensive biosimilars.

POI1653
A Multicenter, Prospective, Open-Labeled Study of Acthar Gel Alone or with Tacrolimus to Reduce Urinary Proteinuria in Patients with Idiopathic DNA-JB9-Positive Fibrillary Glomerulopathy
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Background: Fibrillary Glomerulopathy (FGN) is a rare primary glomerular disease characterized by glomerular accumulation of nonbranching, randomly arranged 10-30 nm in diameter fibrils. The resulting podocyte dysfunction and progressive proteinuria leads to ESRD rates of 50% within 4 years. Herein we present data on 15 patients treated with ACTH or ACTH + Tacrolimus completing 12 months of therapy.

Methods: Study Design: Randomized prospective open labeled study of 12 months of SQ ACTH alone or with Tacrolimus in 15 patients with biopsy proven, DNA-B9 + Fibrillary glomerulopathy. Study Drug Dosing: ACTH 80 units SQ 2X/week, Tacrolimus 1.0 mg PO BID. Primary Endpoint: Change in UP/Cr ratio (mg/gm) in patients after 12 months of ACTH+gel alone or in combination with Tacrolimus. Definitions: Responders-Complete-Partial-Clinical response defined at ≤ 300 mg/gm or ≥ 50% reduction or ≥ 30% reduction in UP/Cr from baseline at 12 months.

Results: Of the 15 patients completing 12 months of treatment, 14.3% achieved complete remission (UP/Cr ratio < 300 mg/gm); 26.8% achieved a ≥ 75% reduction from baseline, while 60.0% achieved a ≥ 50% reduction in UP/Cr at 12 months. A total
PO1654

BCX9930, an Oral Factor D Inhibitor in Development for Treatment of Complement-Mediated Diseases, Inhibits Complement Alternative Pathway (AP) Activity in Healthy Subjects

Xulin Chen1, Fugang Zhu2, Cynthia D. Parker1, Melanie Corropost1, William P. Sheridan2, Matthew Davidson2, Yarladdaga S. Babu2, Biocryst Pharmaceuticals Inc, Birmingham, AL; 2Biocryst Pharmaceuticals Inc, Durham, NC.

Background: Factor D, the rate-limiting enzyme of the AP, is required for the formation of C3 convertase as well as amplification of complement activities initiated by any of the 3 complement pathways. These results support further development of oral BCX9930 for the treatment of complement mediated glomerular diseases.

PO1655

Early Eculizumab Withdrawal in Atypical Hemolytic Uremic Syndrome Is Safe and Cost-Effective

Romy N. Bouwmeester, Caroline Duineveld, Kiao L. Wijnsma, L.P.W.J. Van Den Heuvel, Jack F. Wetzel, Nicole Van De Kar. on behalf of the CUREiHUS study group Radboudumc, Nijmegen, Netherlands.

Background: The introduction of eculizumab has improved outcome in patients with atypical hemolytic uremic syndrome (aHUS). The optimal treatment strategy is debated. It is unknown if unbiased withdrawal of eculizumab is a safe strategy. Here we report the results of the CUREiHUS study, a national observational study monitoring eculizumab discontinuation in Dutch aHUS patients after three months of therapy.

Methods: All pediatric and adult aHUS patients with native kidneys and first-time eculizumab treatment (n=21) were evaluated. At last follow-up, there were no clinical sequelae, i.e. no clinically relevant increase in serum creatinine, proteinuria and/or hypertension, in the relapsing patients. No clinically relevant predictors of relapse (including the presence of a pathogenic mutation) could be determined. The total medical expenses, including costs of among others hospital admission and disease recurrence, of our population were only 33% of the fictive expenses made when patients would have received eculizumab every fortnight.

Conclusions: It is safe and (cost-)effective to discontinue eculizumab after three months of therapy in patients with aHUS in native kidneys. Larger data registries are needed to determine factors to predict relapse(s) and short- and long-term outcomes.

PO1656

Outcome of Kidney Transplantation in Atypical Hemolytic Uremic Syndrome Without Eculizumab Prophylaxis: A Single-Center Experience

Caroline Duineveld, Romy N. Bouwmeester, Kiao L. Wijnsma, Nicole Van De Kar, Jack F. Wetzel. Radboudumc, Nijmegen, Netherlands.

Background: A high risk of aHUS recurrence (60-80%) is reported after kidney transplantation. Therefore, it is suggested to perform kidney transplantation in aHUS patients with eculizumab prophylaxis. In 2017 we reported a favorable outcome after kidney transplantation in aHUS patients without eculizumab prophylaxis, using kidney donors with absence of aHUS and a known negative aHUS check-up. The aim of this study is to report on a larger cohort of 26 patients.

Methods: All pediatric and adult aHUS patients with native kidneys and first-time kidney transplantation between 2013 and 2020 were evaluated.

Results: We included 26 aHUS patients (M 9; F 17, median age at transplantation 47y, range 22-69). In 22 patients (85%) 24 genetic variants were found: C3 (N=14), CFH (N=8), CFB (N=2). Recurrence risk was considered high in 18 patients and moderate in 8 patients. Nineteen patients received a graft from a living donor (LD) and 7 patients a graft from a deceased donor (DD). All patients showed full recovery of hematological thrombotic microangiopathy (TMA) parameters after start of eculizumab. A renal response was noted in 18 patients. After a treatment duration of 13.6 weeks (range 2.1-43.9), eculizumab was withdrawn in all patients (Figure 1). During follow-up (80.7 weeks (0.0-236.9)), a relapse occurred in four patients (19.0%). Median time to first relapse was 14.3 weeks (7.1-62.0). Eculizumab was re-initiated within 24 hours in all relapsing patients. At last follow-up, there were no chronic sequelae, i.e. no clinically relevant increase in serum creatinine, proteinuria and/or hypertension, in the relapsing patients. No clinically relevant predictors of relapse (including the presence of a pathogenic mutation) could be determined. The total medical expenses, including costs of among others hospital admission and disease recurrence, of our population were only 33% of the fictive expenses made when patients would have received eculizumab every fortnight.

Conclusions: It is safe and (cost-)effective to discontinue eculizumab after three months of therapy in patients with aHUS in native kidneys. Larger data registries are needed to determine factors to predict relapse(s) and short- and long-term outcomes.
PO1657
Podocytes Soften in Proteinuric CKD: A Potential New Mechanism for Proteinuria?
Luisa Ulloa severtino, Xiaolin He, Franciska Lausecker, Rachel Lennon, Mira Krendel, Darren A. Yuen, Yuen Lab "St Michael's Hospital, Toronto, ON, Canada; 2University of Manchester Faculty of Biology Medicine and Health, Manchester, United Kingdom; 3State University of New York Upstate Medical University, Syracuse, NY.

Background: Proteinuria is one of the most common manifestations of glomerular injury, and an important predictor of disease progression. Podocytes are a critical component of the glomerular filtration barrier, and as such podocyte injury is a major cause of proteinuria. Historically, investigators have focused on biochemical changes in podocytes that occur following podocyte injury. In contrast, little is known about the changes in the physical properties of the highly specialized epithelial cells.

Methods: 3 different models of proteinuric glomerular disease were studied: (1) Akita Ren-/- mice (a murine model of diabetes and renin-mediated hypertension that we have recently shown develops progressive glomerulosclerosis that mimics human diabetic kidney disease), n = 7; (2) Myo1e-/- mice, a model of genetic FSGS characterized by deficiency of a non-muscle myosin involved in actomyosin contraction, n = 6), and (3) Col4a5-/- mice, a mouse model of Alport’s syndrome (n = 12). The stiffness of glomeruli, glomerular basement membrane (GBM), and podocytes was measured using atomic force microscopy (AFM) and associated histology (picrosirius red, silver, and WT1 staining). Similar stiffness measurements were performed in human FSGS and healthy kidney donor biopsies.

Results: AFM measurements revealed that glomerular stiffness increased in Akita Ren-/- and Col4a5-/- mice, a finding that correlated with the degree of glomerulosclerosis. Glomerular stiffness was not increased in Myo1e-/- mice. GBM stiffness was increased in Akita Ren-/- and Myo1e-/- mice, but not in Col4a5-/- Alport’s mice. In all 3 mouse models, as well as in human FSGS biopsies, podocytes were softer than in healthy control kidneys.

Conclusions: Taken together, these are the first data demonstrating that podocytes soften in proteinuric glomerular disease. Given the major rearrangements in the actomyosin network that occur in podocytes of proteinuric kidneys, our data suggest that softening is solely a consequence of podocyte injury, or if it also contributes to ongoing podocyte damage.

PO1658
Novel Small Molecule Compounds Protect Podocytes from Injury In Vitro and In Vivo
Richard Helmut1, Manuel Noben,1 Ha Won Lee,1 Jean-Michel Saffin,2 Jochen Reiser,1 Susanne Heynen-Genel,1 Vinette Gupta1,1 Gunta lab 'Rush University Medical Center, Chicago, IL; 2Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA.

Background: Podocyte dysfunction and loss is a key determinant of proteinuria and glomerular injury. Thus, maintaining healthy podocytes is a therapeutic strategy against kidney disease. We previously developed a high-content imaging-based assay and used it to screen a number of small molecule compounds that show protection of podocytes from injury, suggesting it to be a viable strategy for the discovery and development of novel podocyte-protective agents.

Methods: Differentiated mouse podocytes were seeded on collagen-I coated multi-well plates as previously described (Lee et al. JASN, 2015). Cells were exposed to puromycin aminonucleoside (PAN, podocyte inducing agent), with compounds from the screening libraries, or DMSO as control, for 48 hours. Cells were fixed and stained which allowed detection using the Opera High-Content Screening (HCS) System. Columbus software was used to quantify morphology properties such as roundness, as well as the overall F-actin signal. Drosophila based screening assy were used to determine efficacy of selected hits in vivo.

Results: PAN damage resulted in quantitative reduction in F-actin fiber numbers and intensity, and increased roundness in podocytes in the ultra-miniaturized assay system. Screening of a library of chemical compounds identified ~28 hits that dose-dependently reduced podocyte damage. A set of 9 compounds showed significant protection in a drosophila model of kidney injury, supporting the findings from the high-throughput screening assay.

Conclusions: Our 1536-well plate-based assay system identified a number of small molecule compounds that dose dependently protected podocytes from damage in vitro. A drosophila model of kidney injury validated most of the in vitro data from the podocyte, screening assay, as well as in vivo and in vivo mechanistic studies are underway to elucidate new insights into podocyte pathways that are therapeutically targeted by the selected hits. These agents hold promise as novel therapeutics for kidney disease patients with podocyte pathologies.

Funding: NIDDK Support

PO1659
Characterization of the Direct Effect of Mycophenolic Acid on Murine Podocytes
Seif El Din Abo Zed,1 Agnes Hackl,2 Katrin Bohl,3 Gregor Fink,1 Eva Nüsken,1 Kai D. Nüsken,1 Bernhard Schermer,1 Lutz T. Weber,2 Nephrologisches Forschungslabor 'Children's and Adolescents' Hospital, Faculty of Medicine and University Hospital of Cologne, Cologne, Germany; 2Department II of Internal Medicine and Center for Molecular Medicine Cologne, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany; 3Exzellenzcluster CECAD in der Universität zu Köln, Köln, Germany.

Background: Mycophenolic Acid (MPA) is the active component of Mycophenolate Mofetil, a selective, noncompetitive inhibitor of the inosine monophosphate dehydrogenase. Blockade of the de novo purine synthesis depletes the pool of deoxyguanosine triphosphate, leading to a specific suppression of proliferation of B- and T-lymphocytes. MFM has an established role as a therapeutic agent in nephritic nephropathy syndrome, where it currently serves as a second line option for frequent relapsing and steroid dependent cases. Although its immunological functions are well studied, direct effects of MPA on podocytes remain largely unknown. With first preliminary results showing a protective effect in vivo, the present study aims to examine the direct effect of MPA on murine podocytes and its abilities to alter albumin-induced podocyte injury.

Methods: Cultured murine podocytes were exposed to albumin for 48 hours, with one group receiving treatment with MPA for the second 24 hours. Cells were stained with a Synaptotagmin antibody and additional markers to visualize components of the cytoskeleton. Currently, we are analyzing apoptosis through a TUNEL assay as well as alterations in intracellular Calcium content with Fluo-4 and fura red. In addition, we study podocyte injury under MPA intervention by migration assays. We will also study small GTPases content and activity through a pull-down assay for RhoA and Rac1. In an unbiased approach, podocytes were exposed to either 2 hours of 10 mg/1 MPA or an additional 22 hours of 4 mg/1 MPA. Total RNA was isolated and subjected to gene expression analyses.

Results: Synaptotagmin immunofluorescence shows significant alterations of the actin cytoskeleton through albumin exposure. MPA treated cells reveal a restorative ability of the drug, with a recovery of stress fiber formation and a reduction of albumin-induced vacuole formation. MPA expression data from cultured podocytes were analyzed.

Conclusions: First results show a promising effect of MPA on stress fiber formation. The additional functional assays will be finished by late summer this year and will give an important insight to MPA abilities to influence pathways, known to be affected during the development of proteinic diseases. The RNA seq results will provide an objective and detailed picture of the direct effects of MPA on podocytes.
PO1661
Spatially Resolved Analysis of Glomerular Structures in Alport Syndrome and FSGS

Laura Perin,1 Hasim Soloyan,2 Paolo Cravedi,3 Fadi E. Salem,2 Andrea Angeletti,1 Sargis Sedrakyan.1 1Children’s Hospital of Los Angeles, Los Angeles, CA; 2Mount Sinai Health System, New York, NY; 3Università di Bologna, Bologna, Italy.

Background: Many transcriptomics studies highlighted the molecular mechanism underlying glomerular phenotypes, but very little is known about interglomerular heterogeneity and how each glomerulus is affected during progressive CKD. Using Spatial transcriptomics, which allows the characterization of the gene expression based on morphological context, we showed important differences between glomeruli of Alport Syndrome (AS) and FSGS patients and defined the interactive gene networks involved in glomerulosclerosis using healthy glomeruli as reference.

Methods: Using the Nanostring GeoMX Spatial Profiling (DSP, Whole Transcriptomic Atlas) we generated spatial maps of gene expression of human AS (COLA4A5 and COLA4A5) and FSGS glomeruli (both males and females) and compared them to age-matched healthy controls. A total of 90 regions of interest were selected. After data QC and Q3 normalization, data were analyzed using different platforms and integrated with histopathology assessment.

Results: Data distinguished genes associated with podocyte, glomerular endothelial and mesangial cell phenotype. Unsupervised clustering and dimensionality reduction analysis showed clear differences between not only diseased and normal glomeruli (which presented homogenous gene expression profile), but also between glomeruli of AS vs FSGS. Though glomeruli of AS and FSGS were histologically similar within each sample, they presented different transcriptomics profiles (for instance, while oxidative phosphorylation, focal adhesions were common to all gloms in AS, Apelin, PK3-Akt, and Hippo signaling were unique to only a few glomeruli). Marked differences between males and females were observed in both AS and FSGS glomeruli (sheer stress and leukocyte transmindedial migration was more typical in AS male than female, while insulin signaling was only present in AS female. Similar heterogeneity patterns were observed in FSGS). In contrast to FSGS, AS were more enriched for genes associated with TCA cycle, protein processing in the ER, and neurotrophin signaling.

Conclusions: DSP revealed significant interglomerular heterogeneity in AS and FSGS regardless of age and gender leading to the discovery of pathways defining disease phenotypes at single glomerular level. These preliminary data using DSP may allow the discovery of potential new therapeutic targets for CKD patients.

Funding: NIDDK Support

PO1662
EGR1 Is an Injury Marker in Podocytes

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Background: There is no good marker that depicts injured podocytes in human histology samples as well as deamin staining in rodent samples. EGR1 (Early Growth Response 1) is a transcriptional factor that regulates cell survival, proliferation, and cell death in response to growth factors, DNA damage, and ischemia. We have reported that injured podocytes express EGR1 in the early stages of damage in animal experiments and that EGR1 is expressed on podocytes in human glomeruli. This study aims to explore an association between EGR1 staining in podocytes and podocyte injury that injured podocytes express EGR1 protein in the early stages of damage in animal models.

Methods: DSP revealed significant interglomerular heterogeneity in AS and FSGS regardless of age and gender leading to the discovery of pathways defining disease phenotypes at single glomerular level. These preliminary data using DSP may allow the discovery of potential new therapeutic targets for CKD patients.

Funding: NIDDK Support

PO1663
The CLVS1 H310Y Variant Associated with Steroid-Responsive Nephrotic Syndrome Affects Podocyte Function and Glomerular Filtration Barrier Integrity

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Background: We identified a rare homozygous variant, p.H310Y, in the gene encoding clavesin1 (CLVS1) as a novel cause of steroid sensitive nephrotic syndrome (SSNS). We performed a follow-up of the CLVS1 gene in zebrin resulted in edema phenotypes that could be rescued with WT CLVS1 mRNA but not the H310Y variant. CLVS1 knockout in cultured human podocytes decreased endocytosis, increased reactive oxygen species (ROS) accumulation, and increased apoptosis. These aberrant phenotypes were rescued in the presence of glucocorticoids, mimicking the steroid responsive phenotype of CLVS1 H310Y patients. Treatment with ROS inhibitors also rescued the reduced viability phenotype in CLVS1 KO podocytes.

Methods: To better understand the effects of the CLVS1 H310Y variant on podocyte homeostasis, we created human podocyte cell lines with CRISPR-Cas9 mediated heterozygous and homozygous CLVS1 H310Y knock-in (KI) mutations. We evaluated the KO and KI podocytes through automated live-cell imaging. Additionally, we further evaluated the effects of reduced CLVS1 function on podocyte function in vivo in zebrafish.

Results: CLVS1 is functionally required for glomerular filtered in human glomeruli. Additionally, homozygous H310Y KI podocytes displayed similar corticosteroid responsive phenotypes to CLVS1 KO lines, including increased apoptosis that could be rescued with ROS inhibition, while heterozygous KI lines were unaffected. Furthermore, we confirmed that the H310Y variant reduces binding to a critical antioxidant transporter, alpha tocopherol transfer protein (V<0.001), likely contributing to the ROS phenotypes. Electron microscopy analysis and quantification of excreted proteins revealed podocyte effacement and decreased glomerular filtration barrier integrity in zebrafish with knockdown of orthologous CLVS1 when compared to controls (V<0.001).

Conclusions: Our data further demonstrates the importance of clavesin1 in the maintenance of podocyte viability and GFB integrity. It also suggests that oxidative stress may be compromised in patients carrying pathogenic CLVS1 variants and highlights the potential for alternative therapies for NS patients that target ROS accumulation in podocytes.

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PO1664
Rare Variants in RCAN1-3 Genes Are Enriched in Patients with CKD

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Background: We recently identified rare variants in the gene encoding Regulator of Calcineurin Type 1 (RCAN1) as a novel cause of FSGS/RRSNS. Cells expressing mutant RCAN1 and human podocytes with reduced RCAN1 displayed increased CN activity that resulted in increased susceptibility to apoptosis compared to WT RCAN1. There are two additional proteins in the RCAN family, RCAN2 and RCAN3, both of which are capable of regulating CN activity. To further elucidate the role of pathogenic variants in RCAN genes in the etiology and pathogenesis of chronic kidney disease, we screened patients with rare variants in RCAN-3 genes. In addition, we performed kinase screening to identify compounds that can rescue the phenotype induced by defective RCAN1.

Methods: In collaboration with the Genome England Consortium, we examined associations between potentially pathogenic variants in RCAN1-3 genes and kidney disease using the large multi-ethnic National Health Service database. We compared the percentage of patients with rare (MAF <0.01), functional RCAN1-3 variants in patients with CKD (renal and urinary tract disorders) and patients with neurological disorders. We also used target kinase inhibition to examine additional potential RCAN1 regulatory kinases.

Results: Of the 4,153 patients in the UK National Health Service data set with CKD, 39 (0.94%) had rare functional RCAN-1 variants compared to 87 (0.57%) of the 15,141 patients with neurological disorders, revealing a significant enrichment of rare pathogenic variants in RCAN1-3 genes in patients with kidney disease compared to those without (V=0.0006). Pharmacological inhibition of additional RCAN regulatory kinases including DYNKL1 (Harmane) or BMK1 (Ax15836 and XMID-85) could rescue the elevated CN activity (p=0.496, 0.398 and 0.0912 respectively) and reduced viability (p=0.05) in disease causing mutant RCAN1 expressing cells compared to WT controls.

Funding: RCAN1-3 genes in patients with kidney disease compared to those without (V=0.0006). Pharmacological inhibition of additional RCAN regulatory kinases including DYNKL1 (Harmane) or BMK1 (Ax15836 and XMID-85) could rescue the elevated CN activity (p=0.496, 0.398 and 0.0912 respectively) and reduced viability (p=0.05) in disease causing mutant RCAN1 expressing cells compared to WT controls.

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PO1665
Spatial Transcriptomic Profiling of Collapsing Glomerulopathy
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Background: Collapsing glomerulopathy is a histologically distinct variant of focal and segmental glomerulosclerosis that presents with heavy proteinuria and portends a poor prognosis. Collapsing glomerulopathy can be triggered by viral infections such as HIV and SARS-CoV-2. However, it is not known if distinct molecular mechanisms drive histologically indistinguishable lesions of collapsing glomerulopathy in different clinical contexts.

Methods: Transcriptional profiling of collapsing glomerulopathy lesions is difficult since only a few glomeruli may exhibit this histology within a kidney biopsy. Therefore, we used recently developed spatial transcriptional profiling to quantify 1,852 transcripts in individual glomeruli from HIV and SARS-CoV-2 infected patients with biopsy confirmed collapsing glomerulopathy.

Results: We compared transcriptional signatures on the basis of disease or histology and identified distinct pathways of injury in HIV and SARS-CoV-2 associated collapsing glomerulopathy and thrombotic microangiopathy (Figure). Focused validation using downregulated and identified distinct pathways of injury in HIV and SARS-CoV-2 associated collapsing glomerulopathy.

Conclusions: Spatial transcriptional profiling represents a powerful new method to dissect transcriptional programs of pathologically discernible kidney lesions.

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PO1666
Protein Kinase R Inhibition Ameliorates Mitochondrial Dysfunction in the Tg26 HIV-Associated Nephropathy Mouse Model
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Background: Double-stranded RNA (dsRNA)-activated protein kinase (PKR) is a sensor for dsRNA in response to viral infections, including HIV-1. We previously reported that APOL1 risk alleles damage podocytes through double-stranded RNA-activated protein kinase (PKR) activation (Okamoto, Comm Biol, 2018). Here, we hypothesized that PKR activation could be a mechanistic pathway shared by HIV- and APOL1-mediated nephropathies. Hence, we investigated the effects of PKR inhibition on HIVAN in the well-characterized Tg26 mouse model, which expresses HIV regulatory and accessory genes.

Methods: We evaluated the kidney phenotype of Tg26 mice and wild-type mice treated with the PKR inhibitor (C16) from 6 to 12 weeks of age. We profiled kidney gene expression by RNA-seq and mitochondrial function by the extracellular flux assay using ex vivo glomerular tissues.

Results: Kidney disease manifestations, including albuminuria (mean [IQR]) (668 mg/g Cr [60, 1064] vs 2564 [1785, 5646], p=0.03) and global glomerulosclerosis (0.0% [0.0-0.0] vs 8.1 [2.3, 15.8], p=0.008), were reduced in the C16 treated group compared to the vehicle control group. C16 treatment increased mitochondrial gene expression and restored spare respiratory capacity as measured by extracellular flux assay (Fig.B).

Conclusions: PKR inhibition ameliorated mitochondrial dysfunction associated with the HIVAN phenotype observed in Tg26 mice, suggesting that PKR activation contributes to the development of mitochondrial dysfunction in HIVAN.

Funding: NIDDK Support

PO1667
Recurrent Nephrotic Plasma Activates Pro-Fibrotic Signalling Pathways Downstream of Protease-Activated Receptor 1
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Background: Post-transplant recurrence of steroid-resistant nephrotic syndrome (SRNS) is thought to be due to an unknown “circulating factor”, the identity of which has so far remained elusive. Our previous work suggests a signaling role for protease-activated receptor-1 (PAR-1), leading to impaired podocyte function. The signaling pathways downstream of PAR-1 in podocytes are unknown and could reveal novel mechanistic insights into the disease.

Methods: Conditionally immortalized human podocytes (ciPods), glomerular-like structure spheroids, and human kidney organoids were treated with PAR-1 agonist peptide or nephrotic plasma (NP), in the absence or presence of four different PAR-1 antagonists.

Results: PAR-1 agonist and patient relapse NP, but not paired remission plasma, induced the phosphorylation of VASP, JNK, and proteins involved in pro-fibrotic pathways. These changes were inhibited by PAR-1 inhibitors, but not by TGF-β1 inhibition. Four PAR-1 inhibitors demonstrated specific antagonistic properties. The phosphorylation of VASP and JNK in a 3D spheroid model and from stem-cell derived kidney organoids corroborated the finding from the 2D model. Functionally, relapse NP induced podocyte motility and podocyte loss from spheroids both of which were also selectively rescued by PAR-1 inhibitors. Treatment of kidney organoids with relapse NP induced the same VASP and pro-fibrotic phosphorylation in podocytes and the loss of podocyte-specific markers.

Conclusions: We propose that the circulating factor acts as a pro-fibrotic effector by activating PAR-1. A greater understanding of these signaling pathways will lead to the identification of novel therapeutic targets for this disease.

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PO1668
Molecular and Functional Characterization of Human Urinary APOL1 G2/G2 High-Risk Genotype Podocyte
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Background: APolipoprotein L1 (APOL1) risk variants, G1 and G2, increase the risk of various non-diabetic kidney diseases in the African population. To date, the precise mechanisms by which APOL1 risk variants induce injury on podocytes and other kidney cells remain unclear. Trying to unravel these mechanisms, most studies used animal or cell models created by gene editing.

Methods: Conditionally immortalized human podocyte cell lines from urine of a donor carrying APOL1 high-risk genotype, G2/G2, was developed. The APOL1 G2/G2 cell lines were characterized for podocyte markers at both the mRNA and the protein levels, using real-time quantitative PCR, Western blot and immunofluorescence staining. Following induction of APOL1 expression by 50 µg/ml polyinosinic-polycytidylic acid (poly(I:C)), we assessed the functional features of APOL1-induced podocyte dysfunction, such as cell detachment, cell viability, cell death, autophagy, cytokotosis organization and podocyte permeability. As control, APOL1 wild type (G0/G0) podocytes previously generated from a Caucasian donor were used.

Results: We successfully generated human APOL1 G2/G2 urinary podocyte cell lines. Upon exposure to poly(I:C), G2/G2 and G0/G0 podocytes upregulated APOL1 expression resulting in podocytes detachment, decreased cell viability and increased apoptosis rate in a genotype-independent manner. G2/G2 podocyte cell lines exhibited altered features, including upregulation of CD2AP, alteration of cytokotosis, reduction of autophagic flux and increased permeability in an in vitro model under continuous perfusion.

Conclusions: The human APOL1 G2/G2 podocyte cell model is a useful tool for unraveling the mechanisms of APOL1-induced podocyte injury and the cellular functions of APOL1.

PO1669
Topology Mapping of Membrane-Inserted ApoL1
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Background: ApoL1 inserts into membranes at pH 6.0 where it has anion permease activity. Titration of the cis compartment to pH 7.5 suppresses the anion permease and activates a cation channel. How ApoL1 is arrayed in the membrane-inserted form at various pH values is unclear.

Methods: Cys was substituted for Ser or Thr at positions throughout ApoL1 and resulting mutants expressed in E. coli. Purified mutants were allowed to insert into phospholipid vesicles at pH 6.0, held at pH 6.0 or titrated to pH 7.5, and reacted with extravesicular membrane-impermeant fluorescent Cys modifying reagent, Alexafluor-568-maleimide. Unreacted reagent was quenched. Non-membrane-inserted protein was removed by chaotropic extraction and Sepharose 4B chromatography. Membrane-associated protein was separated on SDS-PAGE along with ApoL1 standards for quantification. Ratio of fluorescence intensity to mass of ApoL1 protein was normalized to that of protein modified after detergent denaturation to determine relative accessibility of each Cys to the modifying reagent.

Results: Cys substitutions were generated at amino acid positions 40, 80, 149, 180, 200, 204, 226, 247, and 365. We found three patterns of reactivity after membrane insertion. Cys at positions 40, 149, and 365 showed reactivity that was roughly comparable to that in detergent solution with little difference between pH 6.0 and 7.5, consistent with exposure to the aqueous solution on the cis face of the membrane under all conditions. In contrast, Cys at positions 186, 226 and 247 showed decreased reactivity after membrane insertion that was similar at both pH 6.0 and pH 7.5; these positions are not fully accessible from the external solution. Finally, Cys at positions 80, 173, 200, and 204 had decreased reactivity at pH 6.0 with increase in reactivity at pH 7.5, suggesting these positions may be initially buried in the membrane upon insertion at low pH, but titration to neutral pH induces a structural transition that exposes them to the external solution.

Conclusions: Mapping accessibility of individual amino acid positions in ApoL1 support a model in which a substantial structural transition accompanies the pH shift-induced activation of the cation channel.

Funding: NIDDK Support

Relative reactivity of membrane-inserted cysteine substitution mutants at pH 6.0 or 7.5

PO1670
Deep Learning-Based Segmentation and Quantification of Podocyte Foot Process Morphology
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Background: The advent of super-resolution light microscopy enabled imaging of the nanoscale dimensions of podocyte foot processes and the slit diaphragm and subsequent quantification of morphological alterations upon glomerular injury. However, these morphological analyses require manual work, which is time-consuming and investigator-dependent.

Methods: We used novel sample preparation protocols and applied super-resolution STED microscopy and conventional confocal microscopy to image podocyte foot processes in murine and human kidney tissue. Deep learning-based segmentation was utilized to automatically segment both the slit diaphragm pattern as well as several thousands of individual foot processes per sample.

Results: Our algorithm, the automatic morphological analysis of podocytes (AMAP), segmented the FPs and the SD at high accuracy and more effectively as compared to a previously published semi-automatic dataset. The morphological quantifications show a high agreement with our previous analysis, thereby confirming the correlation of albuminuria with certain morphological alterations of podocytes. In addition, we applied AMAP to human patient tissue and found different patterns of effacement in different disease entities.

Conclusions: The combination of three-dimensional optical imaging and deep-learning-based segmentation can be used to perform extensive morphological analyses of podocyte in health and disease. It confirms our previous semi-automatically performed analyses in a mouse model of FSGS and can be applied to patient material in order to assess morphological alterations in glomerular disease while eliminating investigator bias. We believe AMAP can in the future complement the diagnostic algorithms in research and clinical pathology.

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Underline represents presenting author.

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PO1671

Podometric Differences in Different Cortical Zones and Associations with the Number of Non-Sclerotic Glomeruli

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Background: Reduced nephron and podocyte number are common features in CKD. While it is well known that glomerular volume and glomerular density (glomerular number per cortical area) differ between cortical zones, zonal differences in podometrics and correlations with nephron number have not previously been explored.

Methods: Non-sclerotic glomerular number per kidney was estimated using the physical disector/fractionator combination. Podocyte density, podocyte number, podocyte volume and volumetric density of podocyte to glomerulus in each cortical zone were estimated using model-based stereology on a single histological section immunostained with two podocyte markers and imaged by confocal microscopy.

Results: Fifty autopsy kidneys were studied. The median age was 68 years ranging from 28 to 85 years. Median eGFR was 74 mL/min/1.73m². The median number of non-sclerotic glomeruli per kidney was 421,547 (IQR, 289,095–548,233). Non-sclerotic glomerular number was directly correlated with podocyte number per tuft, podocyte density and smallest podocyte volume. Podocyte number and volumetric density of podocytes were similar across the cortical zones.

Conclusions: These results demonstrate for the first time that a higher number of non-sclerotic glomeruli is directly associated with three beneficial indices of podocyte health. Podocyte number and volumetric density of podocytes were similar across the cortical zones.

Funding: Government Support - Non-U.S.

PO1672

Can Podocyte Number and Density Predict the Response to Therapy in Patients with Primary FSGS?

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Background: Podocyte loss is a key event in primary focal segmental glomerulosclerosis (FSGS). Common first-line therapy for patients with primary FSGS involves steroid therapy with or without blood pressure control; however 40-70% of patients achieve no remission. Animal studies have shown that treatment efficacy is achieved partly through preservation of podocyte number, as well as podocyte protective effects. Animal studies have also determined that podocyte number and density are predictive of FSGS severity. Therefore, this study aimed to determine if podocyte number and density can predict the response to therapy in patients with primary FSGS.

Methods: A retrospective cohort study of renal biopsies was conducted from 2009-2020 in Melbourne, Australia at a tertiary hospital (Monash Medical Centre). Patients diagnosed with primary FSGS were screened (n=84). Patients were excluded for lack of consent for samples to be used for research purposes (n=38), risks of other forms of FSGS (n=13), insufficient clinical data available (n=2), no biopsy tissue available (n=7) or insufficient clinical data available (n=2). Included patients were allocated into groups of treatment responders (n=11) or non-responders (n=8) based on urinary/serum data 6 months following initial diagnosis and commencement of treatment. Biopsies were immunofluorescently stained for podocyte-specific markers. Model-based stereology was used to estimate podometrics. Sections were re-stained with PAS to measure the glomerulosclerotic index (GSI).

Results: Podocyte number per glomerulus in responders (347 (215-606); median (IQR)) was 45% higher than in non-responders (190; 143-263) (P=0.03). Podocyte density in responders (76; 58-142 per 10⁶m² of glomerular volume) was similar to non-responders (66; 44-88 per 10⁶m² of glomerular volume) (P=0.38). GSI was significantly higher in non-responder patients (1.1; 0.6-2.3) than responders (0.6; 0.2-0.9) (P=0.04), and was significantly and negatively correlated with podocyte number (r = -0.64; P=0.003) and podocyte density (r = -0.48; P=0.04).

Conclusions: Podocyte number per glomerulus in diagnostic renal biopsies could be used as a predictor of treatment response for patients with primary FSGS.

Funding: Government Support - Non-U.S.

PO1673

Nephrotic Syndrome in a Patient with Systemic Lupus Erythematosus: Is it Lupus Podocytopathy?

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Introduction: Lupus podocytopathy (LP) is a rare form of lupus nephritis (LN) that clinically mimics minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS). We present a case of LP in a patient with systemic lupus erythematosus (SLE).

Case Description: A 73-year-old female with a history of SLE (on Hydroxychloroquine), and nephrolithiasis presented with left flank pain for 2 weeks. Physical exam was notable for peripheral edema and left costovertebral angle tenderness. Labs showed a creatinine 1.02 mg/dL (baseline 0.7), serum albumin 2.6 mg/dL, and urine microalbumin/creatinine (MA/Cr) ratio of 7.5 g/g. Further workup revealed a positive ANA, negative anti-dsDNA antibodies, and normal complements. Kidney biopsy showed FSGS, tiv variant, and 100% podocyte foot process effacement (PPE). She was started on high-dose prednisone, simvastatin, ACE inhibitor, and furosemide with potassium supplementation for significant pedal edema. Two months later, her MA/Cr ratio improved to 3 g/g. Prednisone was slowly tapered off over a 7-month period during which symptoms were well-controlled and MA/Cr ratio continued to improve.

Discussion: Nephrotic syndrome in patients with SLE raises suspicion for LP, which represents 1% of LN biopsies. Biopsy findings include diffuse PPE (>70%) on electron microscopy, and absence of immune deposits on light, immunofluorescence, and electron microscopy. LP is divided into MCD or FSGS, with the latter having higher rates of hypertension, acute kidney injury on presentation, and overall worse outcomes. Treatment consists of a short course of high-dose glucocorticoids; however high rates of relapse are observed and tend to coincide with SLE activity.
PO1674

Minimal Change Disease as a Sequela of Psoriasis in an Adult
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Introduction: Minimal change disease (MCD) is usually found in children but can be an uncommon presentation in adults. Relation to psoriasis has not been significantly established even though the latter has been associated with kidney disease such as IgA nephropathy, focal segmental glomerulosclerosis leading to kidney failure. This is an interesting case given that this is a young patient with psoriasis presenting with a flare in the setting of newly diagnosed MCD.

Case Description: A 34-year-old male with history of psoriasis presented with severe body edema after psoriatic flare two weeks prior admission. He was found to have exceptionally low serum albumin of 1.4g/dl, massive proteinuria with spot urine protein creatinine ratio of 7.6 and significant hyperlipidemia. Protein electrophoresis did not show glomerular pathology or spikes in proteins and extensive serological workup was normal. Kidney biopsy reported MCD. Patient improved quickly with steroids of 1mg/kg/day, IV furosemide and albumin infusion. Six months later, the patient was readmitted with new psoriasis flare and again nephrotic syndrome with 7.2g of proteinuria. His symptoms resolved quickly with same treatment used on the first admission. Follow up in clinic one-month post discharge showed normal renal function with proteinuria now at 100mg/day.

Discussion: While there has been evidence of link between psoriasis and kidney disease, finding of MCD is a unique development. The idea can be postulated that since psoriasis is a disease due to dysfunction of T-cells among other causes, a flare can be the initiating event leading to dysregulation of an otherwise stable immune system. This T-cell dysregulation has also been noted in MCD. The underlying cause of MCD is not clear. However, a lot of studies suggest that T-cell dysfunction is one of the implicated agents, known for cell destruction, causing damage to the glomerular membrane leading to the loss of proteins. The rarity of this case belies the complexity of the immunological process leading to the presentation and further research needs to be done to document and establish this as the pathologic process linking the two diseases.

PO1675

Collapsing FSGS from Acquired Nephrin Antibody
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Introduction: Deficits in nephrin and other podocyte components are known to result in congenital nephrotic and familial FSGS syndromes. Weins et. al. recently described acquired anti-nephrin antibody localizing in glomerular podocytes of patients with minimal change disease.

Case Description: A 16 year old male referred for new onset nephrotic syndrome progressive over 2 weeks was found to have serum albumin 1.2 gm/dl, UPCR 3.1, and elevated lipids with BP 160/100 mm Hg. Hepatitis B/C, HIV, SLE screens were negative. Renal biopsy demonstrated focal collapsing lesions with diffuse podocyte effacement. Immunofluorescence showed punctate IgG, kappa and lambda light chain staining in podocytes, but no albumin. Anti-human IgG colocalized with nephrin in the granular staining. ParvoB19 and COVID-19 titers were negative. Creatinine rose from 0.65 to 1.65 and UPCR to 10.3 but improved rapidly with high dose prednisone and ACEi. Serology for circulating anti-nephrin 2 weeks into treatment was negative, consistent with previous finding that circulating antibody levels quickly drop to low or undetectable with partial clinical remission.

Discussion: This case strengthens evidence that anti-nephrin antibodies cause disruption of the slit pore diaphragm which appears to be readily responsive to immune therapy. Anti-nephrit mediated podocytopathy may present with a spectrum of glomerular histopathology, which on the background of other susceptibility factors, can lead to more severe presentations such as collapsing FSGS.
slit diaphragms. Confocal imaging of IgG/nephrin IF confirms substantial overlap in the fine podocyte granules (arrows), but not in coarse PRGs (asterisks). A diagnosis of early primary FSGS is made. Sera collected on post-biopsy days 19, 25 and 27 are serologically positive for anti-nephrin. The patient was started on oral glucocorticoids, and on d27 was in partial remission (UPCR 2.6g/gCr, SAld 2.8g/dl). Anti-B cell therapy is considered.

Discussion: Our findings reveal that autoimmune-mediated anti-nephrin podocytopathy can trigger irreversible podocyte injury leading to FSGS, likely in patients with additional predisposing factors. This enhances our understanding of diffuse progressive podocytopathies; accurate and early diagnosis identifies patients who benefit most from B-cell-targeted immunosuppressive therapy.

PO1677

Nephrotic Syndrome Secondary to Minimal Change Disease Following Moderna COVID-19 Vaccine

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Introduction: Minimal Change Disease (MCD) has been reported following vaccines against hepatitis, pneumococcus, influenza and measles. In the COVID-19 era, 3 cases of new-onset MCD and one case of MCD relapse have been reported following the Pfizer-BioNTech COVID-19 vaccine. We herein report a case of MCD after receiving the first dose of Moderna COVID-19 vaccine.

Case Description: A 43-year-old Ethiopian man with no significant past medical history presented with progressive bilateral lower limb edema for two weeks. His symptoms started 7 days after receiving the first dose of COVID-19 vaccine. He then developed dyspnea and scrotal swelling over the following 10-14 days. On physical examination, his blood pressure was 150/92 mm Hg. There was decreased air entry at lung bases, significant bilateral lower limb pitting edema extending to above the knees and scrotal swelling. Lab investigations revealed hypoalbuminemia, hyperlipidemia and proteinuria of 15 grams. There was no hematuria and his immunologic and serologic work up was negative. Renal biopsy showed minimal change disease with underlying IgA nephropathy. There was no global or segmental glomerulosclerosis, mesangial or endocapillary proliferation. Patient was started on oral prednisolone and furosemide. His edema resolved, serum albumin doubled and proteinuria decreased within the first week of treatment.

Discussion: Symptoms of MCD have been reported 4 days to 16 weeks after vaccination. Although the pathogenesis of MCD is not fully understood, studies suggest that T-cell dysfunction might play a role. More studies are needed to determine the incidence and pathophysiology of this adverse event post COVID-19 vaccine. It is not clear in this case if or when the second dose of the COVID-19 vaccine should be administered.

PO1678

Antiproteinuric and Podocytoprotective Effects of Direct Oral Anticoagulant Therapy in Glomerular Disease

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Background: Podocyte injury is a key determinant of chronic kidney disease (CKD) progression toward end stage kidney disease. We and others have recently uncovered a putative podocytopathic role for intraglomerular thrombin during proteinuric glomerular disease. Direct oral anticoagulant (DOAC) therapies limit thrombin activity but their ability to improve podocyte health and potentially slow CKD progression remains unknown. Thus, the aim of this study is to determine if DOACs reduce thrombin-mediated podocytopathy during glomerular proteinuria. We hypothesized that DOACs would preserve podocyte health and function in a podocyte-specific model of proteinuric glomerular disease.

Methods: Diphtheria Toxin was used to induce proteinuria in transgenic rats expressing human diphtheria toxin receptor (DTR) in a podocyte-specific manner and was subsequently treated with 1) Dabigatran (20 mg/kg; Dabi), 2) Rivaroxaban (3 mg/kg; Riva), or 3) Sham (saline) and compared to healthy controls (n=7-9/group). Morning spot urine was collected on day 0 and 10 post-DT. Glomeruli were isolated from the kidney, dissociated into single-cell suspensions, and analyzed by flow cytometry after immunofluorescent synaptophysin antibody and TUNEL staining.

Results: Both Dabi and Riva significantly reduced proteinuria (Fig A) and terminal podocyte injury (TUNEL positive podocyte fraction; Fig B). In addition, there was a trend toward in situ podocyte preservation with both DOACs with a significant overall effect of DOAC therapy on podocyte survival (Fig C).

Conclusions: Both Dabi (a direct thrombin inhibitor) and Riva (a direct factor Xa inhibitor) reduce proteinuria and enhance podocyte health in a podocyte-specific model of proteinuric glomerular disease. These data suggest that DOACs may be repurposed as a novel approach to slow or halt proteinuric glomerular disease progression. Because thrombotic disease is a life-threatening co-morbidity of both glomerular disease and CKD, this approach may enable simultaneous thromboprophylaxis and glomerular disease therapy.

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PO1679

A Highly Efficient and Reproducible Differentiation Protocol for Induced Pluripotent Stem Cell-Derived Podocytes

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Background: Podocyte processes intertwine to create a slit diaphragm, which, when damaged, leads to proteinuria, dysfiltration, and eventually to renal failure. It is critical to be able to study the disease and test therapeutic interventions in patient-derived cells, and assess genetic and environmental aspects. Current protocols for differentiation of iPSCs into podocytes (iPods) suffer from a lack of podocyte maturity or low reproducibility. Our goal was to test and optimize multiple protocols to establish a more translatable, physiologically relevant, and reproducible method.

Methods: We compared two distinct published protocols [Ciampi 2016; Musial 2018]. Additional conditions were tested, including varying the extracellular matrices, media, and length of differentiation. Podocyte signature was evaluated by IF, flow cytometry, and Nanorstring analysis. For models of injury, we utilized prolineamine sulfate (PS) or puromycin aminonucleoside (PAN) treatment. A mouse podocyte cell line was used as a control.

Results: Both protocols generated iPods with similar efficiency, as measured by synaptopodin, nesprin and podocin staining. iPods generated from protocol-1 could be maintained in culture up to 14 days but remained relatively immature, based on the expression of collagen α1α2α1 (IV) and lack of α3α5ε4 (IV). Response to PS and PAN treatment was variable compared to mouse podocytes. Altering the matrix from collagen to laminin-521 did not improve reproducibility. iPods from protocol-2 developed more filopodia and complex cell-cell junctions and appeared more homogeneous, with extended survival up to 4 weeks post-differentiation. PS treatment induced a significant and reproducible dose-time-dependent decrease in synaptopodin expression, and a more robust accumulation of phalloidin aggregation. Both effects were effectively prevented by cyclopasin A, a calcineurin inhibitor, in a similar manner as in mouse podocytes. iPods from protocol-2 also showed a more consistent dose-dependent response to PAN injury.

Conclusions: We achieved a more robust and translatable iPods platform utilizing human iPSC. Patient-derived iPods will be an invaluable tool to validate new therapeutic approaches for podocytopathy-driven kidney disease.

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PO1680

Novel Ex Vivo Culture System Reveals Mechanosensitive “Sarcocere-Like Structures” During Early Podocyte Spreading

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Background: Chronic kidney disease and ESKD are widespread health problems with no cure, in part because the biophysics underlying them are still not clear. A recently discovered feature of injured podocytes includes the de novo assembly of sarcocere-like stress fibers, identified by their alternating myosin and synaptop Sin-a-actin-4. It is not known whether these indicate a transient healing phenotype or are a feature of the cascade leading to foot process effacement.

Methods: To model the early events of podocyte injury, we developed a new in vitro system that enables the study of podocytes outside of their native microenvironment, but with in vivo-like mechanobiological and extracellular matrix (ECM) features. This system includes controllable stiffness, micropatterned substrates for spreading, and the use of primary podocytes as they migrate from freshly isolated glomeruli.

Results: When cultured on micropatterns of physiologically relevant extracellular matrix proteins and appropriate stiffness, myosin- and synaptopodin-positive stress fibers developed within two days of culture, then disappeared after six days, and the appearance of these stress fibers was sensitive to substrate stiffness and could be disrupted by inhibiting actomyosin contraction (blebbistatin), culturing cells with stiffness outside of the physiologic range, or presenting cells with substrates associated with pathology.

Conclusions: These results reveal the role of mechanobiological factors in podocytes represented by the mechanoresponsive sarcocere-like structure and establish a novel system for characterizing this mechanobiology in vitro.

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PO1681

Primary Cilia in Podocyte Health and Disease

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Background: Primary cilia are highly specialized elaborations of the plasma membrane that direct many of the signaling cascades critical for pre- and post-natal development and disease. While renal primary cilia are recognized as key genetic and cellular targets in polycystic kidney disease, the presence and function of primary cilia within the renal corpuscle and glomerulus have yet to be fully characterized. The purpose of our study was to perform a focused and quantifiable characterization of primary cilia of glomerular cell populations in health and disease.

Methods: Renal biopsy samples were obtained from patients with Minimal Change Disease (MCD; N=6), Focal Segmental Glomerular Sclerosis (FSGS; N=5), and control renal tissue (CON; N=4). Immunofluorescence analyses (IF) were used to quantify primary cilia number and length, as well as the expression of Sonic Hedgehog (SHH) protein, the ligand component of the Hedgehog signaling pathway and one measure of primary cilial function.

Results: Mean percent ciliation was significantly increased in MCD and FSGS when compared to CON. Analysis of individual glomerular primary cilia revealed increased cilary length (μm) in both MCD and FSGS when compared to CON. Further analysis comparing primary cilia length in WT-1-positive nuclei (WT-1+; podocytes) also revealed a pronounced increase in cilia length in MCD and FSGS podocyte primary cilia versus CON. Despite increased length of primary cilia, glomerular SHH expression was significantly decreased in both MCD and FSGS when compared to CON. Glomerular diseases MCD and FSGS are therefore associated with an overall increase in podocyte primary cilia length and ciliation, an effect which corresponded to a decrease in SHH expression.

Conclusions: These data provide evidence in support of a role for primary cilia in glomerular disease pathogenesis. Ongoing and future research is needed to establish a mechanistic explanation for these changes observed in glomerular and podocyte primary cilia number and length. A more thorough understanding of the role(s) of primary cilia in glomerular cells, and specifically in podocytes, remains critical for both our understanding of disease pathogenesis as well as for the pharmacologic treatment of glomerular chronic kidney disease.

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PO1682

Establishing a Podocyte-PEC Cross-Talk Model Using an Open Microfluidic Co-Culture Device

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Background: Although focal segmental glomerulosclerosis (FSGS) is initially caused by podocyte injuries, their neighboring parietal epithelial cells (PECs) also undergo molecular changes that further damage the glomerulus. The cross-talk between podocytes and PECs is poorly understood, in part due to a lack of appropriate experimental models for study. Our goal is to establish an in vitro coculture model to induce podocyte injury and determine the mediators and responses of PECs.

Methods: Mouse podocytes labeled with EGFP and PECs labeled with tdTomato were cultured in two neighboring channels of an open microfluidic device that we engineered. The chambers remain separated until more media is added to overflow the half wall in between. To induce injury, podocytes were exposed to increasing concentrations...
of cytotoxic sheep anti-glomerular antibodies (or media alone as control) for 2 hours. The two groups were then washed 4× to remove unbound antibodies. Diffusion calculations suggested moderate sized (10 kDa) signaling molecules take approximately 2 days to reach the other chamber. Immunochemistry characterized podocyte injury and PEC activation and epithelial-mesenchymal transition (EMT).

Background: Podocytes are highly specialized cells that bridge membrane-spanning proteins to cortical actin, shaping the cellular architecture. The loss of podocyte function, which occurs in glomerular diseases, can impair filtration and lead to proteinuria. Recent studies have shown that CLIC5A (clic5a, also known as PIEZO2) is involved in the mechanosensitive ion channel activity of podocytes, which plays a crucial role in the regulation of glomerular filtration. However, the mechanisms underlying the mechanosensitive ion channel activity of podocytes remain unclear.

Methods: First, we confirmed CLIC5A expression and localization at the nephrocyte membrane using immunofluorescence microscopy. Then, we investigated the functional role of the mechanosensitive ion channel Piezo in nephrocyte injury via hypertrophy.

Results: We found that CLIC5A interacts directly with the Ezrin C-terminal domain, but not with other proteins. This suggests that the 16 C-terminal amino acids of Ezrin were necessary for the interaction and Ezrin phosphorylation at T567 increased CLIC5A binding. Expression of a C-terminal ezrin fragment (Ezrin 432-586, phosphomimic T567D), but not C-terminally truncated Ezrin (Ezrin 432-570) effectively blocked CLIC5A-stimulated Rac1 activation. In glomeruli 49±4% of endogenous CLIC5A was in the cytoplasmic, 33±3% in membrane and 18±1% in the cytoskeleton-associated fraction. As expected, PI(4,5)P2 hydrolysis reduced Ezrin phosphorylation and shifted Ezrin from membrane and cytoskeletal fractions into the soluble pool. Similarly, PI(4,5)P2 hydrolysis suggests that CLIC5A localizes to the plasma membrane because of its direct interaction with Ezrin.

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PO1685

The Mechanosensitive Ion Channel Piezo Activates Rho1 in Drosophila Nephrocytes

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Background: Podocytes constantly face biomechanical forces such as shear stress and hydrostatic pressure. Increasing forces result in morphological changes, detachment from the glomerular basement membrane and loss into the primary urine. This highlights a requirement for podocytes to sense changes in their physical environment and induce a reaction to respond to increased biomechanical force.

Methods: Here, we investigated the functional role of the mechanosensitive ion channel Piezo in Drosophila nephrocytes.

Results: First, we confirmed Piezo expression and localisation at the nephrocyte membrane using immunofluorescence microscopy. In vivo analysis revealed that Piezo was necessary for the development of glomerulus and podocytes. In the absence of Piezo, podocytes were sequestered from glomerulus, and glomerulus were not formed. Additionally, we observed a significant increase in podocyte hypertrophy in Drosophila mutants with reduced piezo expression. These results collectively suggest that Piezo-induced Increases in hydrostatic pressure and shear stress are crucial for the maintenance of podocyte function and morphology.

Conclusion: Taken together, our data confirms the functional expression of Piezo in nephrocytes, indicative of its role in regulating Glomerular filtration. This study highlights the importance of Piezo in the mechanosensitive response of podocytes to biomechanical forces.
PO1687
Characterization of a Novel FSGS-Associated ACTN4 Mutation in Drosophila melanogaster
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Background: Decisive for podocyte morphology and homeostasis during health and disease is a specialized and highly regulated organization of the actin cytoskeleton. In this context, the actin cross-linking protein Alpha-actinin4 (ACTN4) has been shown to play a crucial role in podocyte architecture and function. Mutations in the ACTN4 gene are associated with focal segmental glomerulosclerosis (FSGS). Here, performing gene panel sequencing in a pediatric patient presenting with steroid resistant nephrotic syndrome and FSGS, a de novo, potentially disease causing variant of ACTN4 was identified, which was previously undescribed and not found in available genome or exome databases. Our aim is to elucidate the pathogenic potential of this variant for podocytes and FSGS progression.

Methods: To elucidate pathogenic effects of the newly identified ACTN4 variant, we employed the genetic toolbox of Drosophila. The fly holds podocyte-equivalent cells called nephrocytes, which are responsible for filtration and detoxification of the hemolymph. Cell-specific genetic manipulation enabled us to analyze RNA-mediated knockdown of Actin in the single fly homog, in nephrocytes and its impact on cell morphology and function. Rescue experiments with the novel human ACTN4 variant will now enable us to most possible pathogenic consequences of the mutation when compared to wildtype as well as previously described disease-associated variants of ACTN4.

Results: Knockdown of Drosophila Actin in nephrocytes leads to severe functional and morphological defects, including a reduction by 50%, morphologically mislocalization of the ZO-1 homolog Polychaetoid as observed as well as overall reduction of nephrocyte diaphragms. First rescue experiments with wildtype human ACTN4 led to partial rescue of functional and morphological phenotypes observed upon Actin knockdowns.

Conclusions: Our results underline the importance of Actin in nephrocyte biology. Capacity of wildtype human ACTN4 in rescuing the knockdown associated phenotypes indicates the model’s suitability. Further experiments will be performed to elucidate the pathogenic consequences of the novel ACTN4 variant also in comparison to previously described pathogenic mutations.

PO1688
The Calcium-Sensing Receptor Restores Podocyte Function in Proteinuric Humans and Mice
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Background: Calcimimetic agents allosterically increase the calcium (Ca2+) sensitivity of the calcium-sensing receptor (CaSR), which suppresses the secretion of parathyromone in the parathyroid gland and therefore regulates Ca2+-homeostasis. The CaSR is furthermore expressed in the tubular system and to a lesser extend in podocytes. Activation of CaSR reduces glomerular proteinuria and podocyte damage in animals. However, the precise role of the podocyte CaSR is still unclear.

Methods: A CaSR knockdown (KD) in murine podocytes and podocyte-specific CaSR knockout (KO) in BALB/c mice were generated to study its role in proteinuria.

Results: Podocyte CaSR KD abolished the calcimimetic R-568 mediated -influx, reduced the number of actin fibers, cellular attachment and migration velocity in podocytes. In contrast, the activation of the CaSR with R-568 protected podocytes from Adriamycin (ADR)-induced cytoskeletal rearrangement and reduction in adhesion capacity. In vivo ADR-induced proteinuria enhanced glomerular CaSR expression in wild type mice (control vs ADR: 33.5±2.0 vs 75.8±7.8 CaSR positive podocytes (%); p=0.0286). In podocyte-specific CaSR KO ADR treatment resulted in a higher albuminuria (control vs KO: 27.9±3.8 vs 85.9±5.2 g/galbin/creatinine; p=0.023 at day 7), podocyte foot process effacement, podocyte loss (control vs KO: 350±28.3 vs 2969±457.2 p57+cells/mm2; p=0.0238 at day 8) and glomerular sclerosis compared to wild type littermates. In addition, four children with nephrotic syndrome, objecting glucocorticoid therapy, were treated with the calcimimetic cinacalcet for 1 to 33 days. Proteinuria declined transiently by up to 96 %, serum albumin increased and edema resolved.

Conclusions: The activation of CaSR regulates key podocyte functions and protects from ADR induced cellular damage in vitro. The CaSR reduces toxic induced proteinuria, podocyte loss and glomerular damage in mice. Our findings suggest a major role of CaSR signaling in glomerular disease.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO1691

Regression of Severe Preexisting Glomerular Pathology in a Mouse FSGS Model in Response to Treatment with Macula Densa-Derived Biologicals

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Background: Macula densa (MD) cells localized at the glomerular vascular pole synthesize and release numerous vasoactive autacoids and newly identified angiogenic (e.g. CCN1) and glomerulotrophic factors that act in a paracrine fashion to maintain high renal/glomerular blood flow and endogenous tissue remodeling. The present study aimed to test the tissue regenerative therapeutic potential of MD-derived biologicals in vivo in a mouse model of focal segmental glomerulosclerosis (FSGS).

Methods: Balb/C mice with Adenovirus-induced stable, severe FSGS and albuminuria (albumin/creatinine ratio ACR>10,000/g) were randomized into 5 groups and started daily ip injections (150μl each) of saline (S), human recombinant (hr) CCN1 in low-dose (0.3 ng/mouse) (L), hrCCN1 high-dose (2 μg/mouse) (H), DMEM/F12 control (D), and conditioned culture media of the new MD cell line mdD5® (MD) for 4 weeks. Transcutaneous GFR (MediBeacon) and ACR were measured weekly. Terminal histological analysis was performed using PAS and Trichrome staining.

Results: Kidney injury was severe at the onset (GFR 1160±1 μL/min/100 g BW, ACR 1219±637) and was sustained throughout the 4 weeks of treatment in control S and D groups (GFR: 108±143, 992±164, ACR: 1022±786, 3958±1638, respectively). In contrast, a progressive and significant improvement in kidney function was observed in response to both L, H, and MD treatment (ACR reduced to 134±273, 921±173, 113±173, 921±270, 131±1113, 131±1113 in S; 47±2 in L, 57±3 in D based on Picrosirius ± index (67±2 in MD vs 80±3.4 in S; 113±173±2.3 in H vs 0.9 in D), GS index (131±1113±573, 921±270, 113±173±2.3 in H vs 0.9 in D), and GFR: 1080±188, 492±164, 1022±786, 3958±1638, respectively). In response to both L, H, and MD treatment (ACR reduced to 134±273, 921±173, 113±173, 921±270, 113±173±2.3 in H vs 0.9 in D), GS index (131±1113±573, 921±270, 113±173±2.3 in H vs 0.9 in D), and GFR: 1080±188, 492±164, 1022±786, 3958±1638, respectively). Mechanistically we found that Cd44 expression was upregulated at both mRNA and protein levels in response to MD treatment. The effects of MD treatment on kidney function are consistent with previous studies demonstrating the therapeutic potential of MD-derived biologicals in mouse models of FSGS.

Conclusions: MD-derived biologicals have the potential to improve kidney function in a mouse model of FSGS. Treatment with MD-derived biologicals improved significantly in response to treatment with MD biologicals. These findings suggest that MD-derived biologicals have potential therapeutic applications in the treatment of FSGS.

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PO1692

Insulin-Like Growth Factor 1 Receptor (IGF1R) Suppression in the Glomerular Podocyte Has Beneficial and Detrimental Consequences Dependent on the Level of Inhibition

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Background: Insulin signaling to the glomerular podocyte via the insulin receptor (IR) is known to be critical for normal kidney function. This study aimed to define the physiological importance of the closely related insulin-like growth factor 1 receptor (IGF1R) in podocytes.

Methods: Transgenic mice with conditional inactivation of podocyte IGF1R were generated to determine the effects of IGF1R suppression in vivo. In vitro, conditionally immortalised genetic IGF1R knockout and wild-type podocytes treated with IGF1R inhibitor pircodophyllin (PPP) were characterised using global proteomic analysis.

Results: Transgenic mice with partial podocyte-specific IGF1R knockout, generated using conventional Cre recombinase, had no apparent basal renal phenotype but did not survive past 24 weeks. Transcutaneous GFR (MediBeacon) and ACR were measured weekly. Terminal histological analysis was performed using PAS and Trichrome staining.

Conclusions: In vivo preclinical study confirmed that the supplementation of key MD cell-derived factors in the form of injectable biologicals can augment endogenous kidney tissue repair and restores kidney function in a mouse model of FSGS. Targeting key MD cell-derived factors in the form of injectable biologicals can augment endogenous staining density) improved significantly in response to treatment with MD biologicals.

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PO1693

Calcium/Cammodulin Kinase 4 Induces FSGS by Promoting Apoptosis While Inhibiting Autophagy in Podocytes

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Background: Podocyte injury and death precede the development of focal segmental glomerulosclerosis (FSGS), but the involved mechanisms remain poorly understood. Calcium/calcmodulin kinase 4 (CaM/K4), a serine threonine kinase, is increased in podocytes of people with FSGS and in experimental models of FSGS.

Methods: B6, B6 Camk4/fl/fl.podocyte or Camk4/fl/fl.podocyte mice were created and injected with i.v. adriamycin. Urine was collected on days 0, 3, 7, or 14, and kidney samples were collected on day 7 or 14 after adriamycin injection. Cultured human podocytes in the presence and absence of CAMK4 inhibitor (KN93) were exposed to adriamycin after which immunofluorescence and western blot was performed. Pull down mass-spectrometry and co-immunoprecipitation analysis was performed to identify proteins involved in cell death and those that directly interact with CaM/K4 in FSGS.

Results: We found that lack of Camk4 in podocytes suppressed the development of kidney pathology including the presence of hyaline deposits in glomeruli, podocytopenia and tubulointerstitial damage with intratubular casts in mice injected with adriamycin. Proteinuria in mice lacking Camk4 in podocytes exposed to adriamycin, was reduced at 7 days and remained low through the 14th day when compared to control mice. Mechanistically we found that Camk4 phosphorylates 14-3-3, releasing pro-apoptotic protein BAD which in turn binds to the antiapoptotic protein BCL-2, thereby allowing BAX, to aggregate on mitochondria and induce release of cytochrome c through mitochondrial pore formation, followed by caspase activation and apoptosis. In parallel, CAMK4 inhibits autophagy, a process needed for the renovation of damaged organelles, through the mTOR pathway, by directly phosphorylating AKT and S6 kinase.

Conclusions: We demonstrate that mice lacking Camk4 specifically in podocytes are protected from FSGS-like disease after exposure to adriamycin. These mice also demonstrate markedly reduced proteinuria and podocytopenia. We found that apoptosis leads to cell death while autophagy is protective in FSGS. The characterization of the specific molecular events which lead to podocyte loss and glomerulosclerosis point to putative therapeutic targets and biomarkers for FSGS.

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PO1694

A Noncanonical Role for IRE1α in Podocyte Endoplasmic Reticulum (ER)-Phagy

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Background: Glomerular diseases involving podocyte (glomerular epithelial cell; GEC) injury feature endoplasmic reticulum (ER) stress and activation of the unfolded protein response (UPR). Inositol requiring enzyme-1α (IRE1α), a UPR transducer, mediates chaperone production and autophagy in podocytes during ER stress. Selective autophagy of the ER (ERphagy) is dependent on ER-resident adaptors (e.g. RTN3L) and is stimulated by ER stress. ER-derived coat protein complex II (COPII) vesicles may participate in the delivery of ER cargo to autophagosomes; however, regulation and importance of ERphagy in glomerular disease are not understood.

Methods: We employed mice with podocyte-specific deletion of IRE1α and littermate controls. IRE1α knockout (KO) and control GECs were produced from these mice. GECs were incubated with tunicamycin (TM) to induce ER stress.

Results: Mass spectrometry analysis of TM-stimulated control and IRE1α KO GECs showed that in addition to ER chaperones, proteins in the secretory pathway, including the COPII component Sec23B, were increased in an IRE1α-dependent manner. By immunoblottting, TM enhanced Sec23B and RTN3L expression in control, but not IRE1α KO GECs. By immunofluorescence microscopy, in control GECs, TM increased the biogenesis of LC3 and Sec23B particles, as well as colocalization of Sec23B with LC3 and RTN3L with LC3; increases were attenuated in IRE1α KO GECs. Thus, deletion of IRE1α impaired delivery of COPII vesicles and RTN3L-coated ER fragments to autophagosomes. Knockdown of Sec23B with siRNAs abolished the increased LC3 expression in control GECs. By blocking protein synthesis with cycloheximide, TM stimulated degradation of RTN3L in control GECs, consistent with ERphagy flux, but RTN3L degradation was impaired in IRE1α KO cells. Similarly, TM induced degradation of 63/45 kDa collagen IV in control, but not IRE1α KO GECs, suggesting that collagen IV is an IRE1α-dependent ERphagy substrate. In adriamycin nephrosis, where IRE1α activates an adaptive UPR and autophagy, expression of Sec23B and RTN3L was increased in glomeruli of control, but not IRE1α KO mice.

Conclusions: During ER stress, IRE1α redirects a subset of Sec23B-positive COPII vesicles to deliver RTN3L-coated ER fragments to autophagosomes. ERphagy is a novel outcome of the IRE1α pathway in podocytes and may play a cytoprotective role in glomerular diseases.

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PO1695
ACE Inhibition Modulates Insulin-Like Growth Factor 1 (IGF-1) Filtration to Regulate Compensatory Kidney and Glomerular Hypertrophy

Background: Modeling suggests that preventing glomerular volume (GV) increase could serve as a therapeutic target to mitigate hypertrophy-associated progressive glomerulosclerosis (GS). We, therefore, evaluated how GV is regulated, and how Angiotensin-Converting Enzyme inhibition (ACEI) could reduce compensatory GV increase.

Methods: Uni-nephrectomized (Uni-Nx) wild-type Fischer344 rats were used to model progressive GV triggered from the single kidney state, and the effect of ACEI was analyzed. ACEI started either before or after Uni-Nx. Urine IGF ELISA assay, computer-assisted morphometry, single-cell, bulk transcriptomics, immunofluorescence, and human databases were analyzed.

Results: ACEI started before, but not after Uni-Nx, reduced short (Panel A) and long-term (Panel B) compensatory GV increase, and the associated 8-fold peak of urine IGF-1 post-nephrectomy (Panel C). An IGF-IR inhibitor (piropodophyllin) also reduced compensatory kidney hypertrophy (Panel D). Post-Uni-Nx, a decrease in both serum IGF-1 and glomerular kidney IGF-1 transcript were noted, and IGFFBP3 (the major blood IGFBP) was present in podocyte cytoplasm in the absence of detectable podocyte IGFFBP3 transcript, suggesting that IGF-1 and IGF-IGFBP complex had come from blood. A model was developed to predict how IGF-1, IGF-2, and IGF-IGFBP protein complexes would interact with the glomerular filter, and its predictions were confirmed in ERCB database. The importance of hypertrophied IGF-1 as a driver of glomerular failure in single kidney states was further supported by human kidney allograft half-life analysis.

Conclusions: Hyperfiltrated IGF-1 drives compensatory GV increase leading to long-term proteinuria and GS. Timing of ACEi in relation to Uni-Nx can reduce both IGF-1 hyperfiltration and GV increase, thereby prolonging single kidney lifespan.

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PO1696
Angiotensin II Induces Oxidative Podocyte Injury via the Upregulation of Nox4
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Background: Angiotensin II (Ang II) induces glomerular and podocyte injury via systemic and local vasoconstrictive or non-hemodynamic effects including oxidative stress. The release of free radicals from podocytes may participate in the development of glomerular injury and proteinuria. We studied the pathophysiological roles of oxidative stress in Ang II-induced podocyte apoptosis.

Methods: Mouse podocytes were incubated in media containing various concentrations of Ang II and at different incubation times and transfected by Nox4 or AT1R siRNAs or negative control scrambled siRNA for 24 h. The changes of podocyte oxidative stress and apoptosis were observed by confocal imaging, western blotting, realtime PCR, FACS and TUNEL assay according to the presence of Ang II.

Results: Ang II increased the generation of superoxide anions and intracellular reactive oxygen species (ROS) levels but suppressed the podocyte proliferation. Ang II increased Nox4 protein expression and podocyte apoptosis, measured using western blotting and real-time PCR analysis which was also reversed by probucol. Nox4 suppression by small interfering RNA (siRNA) reduced the oxidative stress induced by Ang II. These results suggest that Ang II induced oxidative stress via the upregulation of Nox4 protein in a transcriptional mechanism. Ang II promoted podocyte apoptosis that was reversed significantly by probucol and Nox4 siRNA. Ang II-induced podocyte apoptosis were also recovered by Ang II type 1 receptor (AT1R) siRNA.

Conclusions: Our findings suggest that Ang II induced podocyte oxidative stress and apoptosis through AT1R and Nox4. These findings suggest that Ang II promoted podocyte oxidative stress and apoptosis through AT1R and via the upregulation of Nox4, which could be prevented by Nox4 inhibition and/or antagonizing AT1R as well as antioxidants.

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PO1697
Anillin Serves a Protective Function in a Mouse Model of HIV-Associated Nephropathy
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Background: HIV-associated nephropathy (HIVAN) is characterized by a rapid progression to end stage kidney disease with limited treatment options. We previously demonstrated that mutations in the gene encoding anilin (ANLN) can cause FSGS and showed that ANLN is upregulated in the glomerulitis of HIVAN patients as well as the HIVAN Tg26 mouse model. ANLN is an F-actin binding protein that affects cell proliferation and survival, two cell processes that are predicted to play a key role in the phenotype associated with HIVAN. We hypothesized that ANLN upregulation is one of the drivers of glomerular failure in HIVAN mice, therefore modulating ANLN expression may present an alternative therapeutic strategy for HIVAN.

Methods: To evaluate the therapeutic potential of reduced functional ANLN in a HIVAN mouse model, we created a mouse line using CRISPR Cas9 mediated gene editing that contains an early stop codon in the Anln gene (ANLNx). We then bred heterozygous ANLNx mice with Tg26 HIVAN mice and evaluated proteinuria and mortality over 16 weeks for each genotype. Sclerotic glomeruli from 3 mice in each group were evaluated and quantified at 16 weeks by age pathologists blinded to genotype.

Results: There was no improvement in glomerular disease phenotype associated with the reduction of functional ANLN in the Tg26 HIVAN model. Urine albumin to creatinine ratio at 8, 12, and 16 weeks were similar between ANLNx and Tg26 heterozygotes compared to Tg26 HIVAN mice (p=0.383, 0.0863. 0.0761 for each time-point). Mice heterozygous for both the ANLNx and Tg26 alleles also did not display any increase in survival compared to mice carrying only the Tg26 allele (p=0.361). Evaluation and scoring of PAS stained kidney sections by independent pathologists revealed similar levels of sclerosis between Tg26 HIVAN mice and mice heterozygous for both the ANLNx and Tg26 alleles.

Conclusions: Genetic ablation of ANLN does not improve kidney disease phenotypes in Tg26 HIVAN mice. ANLN upregulation likely represents a survival mechanism in Tg26 HIVAN mice and not a cause of injury.

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PO1698
The Role of LRP1 in Podocytes
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Background: Recent studies have demonstrated the importance of endocytosis for podocyte health. However, little is known about the function of the internalized cargo proteins. We investigated the role of the low-density lipoprotein receptor-related protein 1 (LRP1), a large endocytic scavenger receptor, in podocytes in vitro and in vivo.

Methods: We used immunoblotting and -fluorescence to determine quantity and localization of LRP1 in cultured human podocytes. siRNA knockdown (KD) of LRP1 and an antagonist were used to investigate potential functional importance in vitro. We used zebrafish morpholino knockdown models of LRP1 homologs to study the function of LRP1 in vivo. LRP1 expression in healthy and diseased human renal tissue was determined by immunohistochemistry.

Results: LRP1 is highly expressed in cultured podocytes where it localizes to the perinuclear and perinuclear region. It colocalizes with early and late endosomes, in line with its role in endocytic trafficking. Interaction with β1-Integrin (ITBI) was confirmed by immunoprecipitation and colocalization. siRNA KD of LRP1 resulted in a reduction of podocyte number and cell size. Morpholino KD of both LRP1 isoforms in zebrafish led to pericardial effusion and generalized edema, hinting at a renal phenotype. Interestingly, LRP1 has nearly absent baseline expression in healthy human glomeruli. Glomerular expression is significantly increased in human biopsies of various podocytopathies. However, LRP1 does not colocalize with the podocyte marker nephrin in human tissue.

Conclusions: LRP1 is a highly expressed endocytic receptor in cultured podocytes. Ablation of LRP1 function caused by siRNA KD or pharmacological inhibition resulted in disarrayment of podocyte shape, implicating a crucial role in adhesion and cytoskeletal regulation in vitro. Colocalization and immunoprecipitation with ITBI suggests interaction with an integrin trafficking. The importance of LRP1 for kidney function is corroborated by our zebrafish experiments where LRP1 silencing led to a renal phenotype. Since glomerular LRP1 expression is increased in proteinuric diseases, it could function as a mediating or compensating factor in glomerular injury. However, its absence from podocytes in vivo makes its function for podocytes outside of the culture environment unclear. Our findings thus exemplify the difference in podocyte adhesion regulation between podocytes in vitro and in vivo.

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PO1699

Dach1 Is Essential for Maintaining Normal Podocytes
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Background: Dach1 is a transcription factor, determining cell fates in various organs. Dach1 polymorphism has been reported to be associated with nephrotic syndrome and chronic kidney diseases. We previously found that Dach1 was highly expressed in normal podocytes and rapidly disappeared after induction of podocyte injury, similarly to WT1. We aimed to elucidate the function of Dach1 in podocytes in vitro.

Methods: Because Dach1 null mice die shortly after birth, kidneys were harvested at P0 and histologically examined. To study the role of Dach1 in mature podocytes, podocyte-specific Dach1 deleted mice were generated by mating Dach1fl/fl mice with Nphs1-Cre or Nphs2-CreERT2 mice. Eleven Nphs1-Cre/Dach1fl/fl mice with Nphs2-CreERT2/Dach1fl/fl mice were analyzed at 8-35 weeks of age. 14 indicating inefficient Cre-mediated recombination. Nevertheless, all examined samples showing normal slit membrane, and no abnormal leakage of albumin. Immunostaining for WT1, nephrin, podocin, synaptopodin and nesprin was normal. Only a small number of podocytes lacked Dach1 staining in Nphs1-Cre/Dach1fl/fl and Nphs2-CreERT2/Dach1fl/fl mice, indicating inefficient Cre-mediated recombination. Nevertheless, all Nphs1-Cre/Dach1fl/fl exhibited normal albuminuria (UACR 4.7±1.6 mg/g vs. 0.06±0.007), which increased with age, and seven (65%) mice showed FSGS. Seven (50%) Nphs2-CreERT2/Dach1fl/fl mice exhibited abnormal albuminuria, and three (21%) mice showed early sclerotic lesions. Immunostaining showed that sclerotic lesions lacked Dach1 as well as WT1, synaptopodin and nesprin. Most of Dach1 negative podocytes in non-sclerotic glomeruli had normal staining for podocyte marker proteins.

Results: These results indicate that Dach1 does not determine the fate of differentiation into podocytes but is indispensable for maintaining normal integrity of mature podocytes.

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PO1700

TAZ Is Important for Structural and Functional Integrity of Podocytes
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Background: Podocyte is an important component of the glomerular filtration barrier (GFB). Maintenance of integrity of slit-diaphragm(SD) structure is critical for normal kidney function. Podocytes lost most epithelial cell tight junction components except for Zonula occludens-1 and -2 (ZO-1 and ZO-2). In podocytes, ZO-1 is an important binding partner of nephrin, and mice with podocyte-specific ZO-1 deletion showed significant growth retardation and severe proteinuria starting at 2 weeks of age, but the regulation of ZO-1 expression in podocytes are not clear. TAZ (transcriptional coactivator with PDZ-binding motif) and its paralog Yes-associated protein (YAP) are two crucial effectors of the Hippo signaling pathway. Recent study has shown that TAZ is present in human podocytes both in vitro and in vivo, as its expression domain coincides with glomerular cells labeled with synaptopodin. Additionally, the RI is present in cultured podocytes both before and after the temperature shift used to induce quiescence, and it appears to increase after differentiation. There is also expression modulation of RNH1 in response to PAN to determine if changes in RI expression occur as a response. RNH1 inhibition was performed in a transgenic zebrafish line that allows for the detection of proteinuria via a GFP-tagged protein in the circulation. At 60hpf the severity of the edema phenotype and the fluorescence levels were recorded.

Results: Our preliminary data shows that the RI is present in human podocytes both in vitro and in vivo, as its expression domain coincides with glomerular cells labeled with synaptopodin. Additionally, the RI is present in cultured podocytes both before and after the temperature shift used to induce quiescence, and it appears to increase after differentiation. There is also expression modulation of RNH1 in response to PAN treatment of podocytes. In our zebrafish model, RNH1 knockdown resulted in up to a 40% increase in mild to severe edema and over 30% decrease in fluorescent suggesting that a reduction in RI might compromise the filtration barrier enough to lead to proteinuria. Taken together our initial data show a promising avenue for research where the balance between members of the RNaseA superfamily and their cytoplasmic inhibitor may represent a powerful mechanism that allows the cells to modulate the proteinuria response to stimuli. An imbalance in this relationship might ultimately affect the integrity of the cells in the kidney.

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PO1701

Neurexin1α Containing Splice Site 4 Interacts with Nephrin and Contributes to Maintenance of the Integrity of Podocyte Slit Diaphragm
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Background: Neurexins (NRXNs) are synaptic cell adhesion molecules having essential roles in the assembly and maturation of synapses. It is known that NRXN1α contains 6 splice sites (SSs), and multiple splicing variants were diffusely expressed in neuronal tissues. We have previously reported that NRXN1α is expressed at slit diaphragm (SD), a cell-cell junction of podocyte, and is downregulated in injured podocytes. The report also showed that NRXN1α expressed in podocytes is a unique variant containing SS1, 3, 4, and 5, which is a rare variant in neural tissues (Am J Physiol, 300:R340, 2011). However, the role of NRXN1α at SD is not well understood yet.

Methods: The interaction of NRXN1α with SD-associated molecules was analyzed by the immunoprecipitation (IP) assay. The function and structure of SD of NRXN1α KO mice were precisely analyzed.

Results: The interaction of NRXN1α with SD molecules such as nephrin and ephrin-B1 was detected by the IP assay with rat glomerular lysates. IP assay with the HEK cell expression systems showed NRXN1α containing SS4 interacted with nephrin, but NRXN1α lacking SS4 did not. The interaction between NRXN1α and nephrin was dissociated, if nephrin was phosphorylated. The interaction of NRXN1α with ephrin-B1 was not detected in the HEK system, suggesting NRXN1α interacts with ephrin-B1 via nephrin. Abnormal proteinuria (92.1 µg/day vs. 23.8 µg/day, p<0.05) and clear proteinuria in urine (12.67 vs 27.86 µg/mg, p<0.05) were observed in NRXN1α KO mice as compared with WT1. We aimed to elucidate the function of Dach1 in podocytes

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PO1703

Atypical Caspase 3-Dependent Death in Podocytes
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Background: Apoptosis of podocytes has been widely reported in many in vitro studies, but definitive apoptosis has never been documented in vivo podocytes. To elucidate this discrepancy, we analyzed dying process in podocytes in vivo and in vitro. Methods: Primary mouse podocytes were transiently transfected with ICD25 and EGFP expression plasmids and treated with a ICD25-targeting immunotoxin, LMB2 (1nM), and observed 1 day later. In some experiments, the cultured podocytes were transfected with Bak1 or Bax siRNA before treatment with LMB2. In vivo experiments, podocyte injury was induced by injecting LMB2 (1.25ng/gBW) into NEP25 mice, which express ICD25 in podocytes, and analyzed 7 days later.

Results: In vivo studies, administration of LMB2 caused loss of co-introduced EGFP in 56.8±13.6%, incorporation of propidium iodide in 13.6±2.5%, activation of caspase 3 (Casp3) in 19.6±2.6% and TUNEL staining in 4.5±1.3% without significant increase in LDH activity in the culture medium. These phenomena were not observed in cells without ICD25 or without LMB2. Ac-DEVD-CHO (10uM), a Casp3 inhibitor, attenuated the loss of EGFP by 38.2%. Inhibition of Bak1 and Bax using siRNAs attenuated EGFP loss by 77.6% and 28.4%, respectively. These indicate that LMB2 induced the typical Casp3 dependent intrinsic apoptosis in podocytes in vivo. In in vivo studies, kidneys of NEP25 mice contained podocytes positive for cleaved (c) Casp3 and those for cLaminA, a product of Casp3, but no TUNEL+ podocytes. EM analysis showed no apoptotic body, but occasionally rupture of plasma membrane of podocytes. The urinary sediments contained podacyclin-positive podocytes (2.5±0.3%). Among these, 39.3±1.7% were stained for cCasp3 and 21.7±5.5% were stained for TUNEL. To evaluate the effect of glomerular filtration, NEP25 mice were similarly injected with LMB2 and subjected to 5/6 nephrectomy 1 day before sacrifice. The obstructed kidney contained more cLaminA+ podocytes than the contralateral kidney. In addition, detachting podocyte cell bodies were frequently observed in the contralateral kidney by SEM analysis, but never in the obstructed kidney.

Conclusions: Thus, due to physical force of glomerular filtration, podocytes doomed to Casp3 dependent death are quickly lost by detachment or plasma membrane rupture before completing full apoptotic processes. This accounts for the absence of podocyte apoptosis in vivo.

PO1704

Mice Deficient in Aminopeptidase A Have Worse Glomerular Injury in Response to Chronic Renal Mass Reduction
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Background: Aminopeptidase A (APA) is a membrane-bound metalloproteinase expressed in podocytes and tubular epithelia. It is a key enzyme in metabolizing angiotensin (Ang) II and diverting Ang I from the formation of Ang II. A recent finding expressed in podocytes and tubular epithelia. It is a key enzyme in metabolizing angiotensin (Ang) II and diverting Ang I from the formation of Ang II. A recent finding expressed in podocytes and tubular epithelia. It is a key enzyme in metabolizing angiotensin (Ang) II and diverting Ang I from the formation of Ang II. A recent finding expressed in podocytes and tubular epithelia. It is a key enzyme in metabolizing angiotensin (Ang) II and diverting Ang I from the formation of Ang II. A recent finding.

Methods: Primary mouse podocytes were transiently transfected with ICD25 and EGFP expression plasmids and treated with a ICD25-targeting immunotoxin, LMB2 (1nM), and observed 1 day later. In some experiments, the cultured podocytes were transfected with Bak1 or Bax siRNA before treatment with LMB2. In vivo experiments, podocyte injury was induced by injecting LMB2 (1.25ng/gBW) into NEP25 mice, which express ICD25 in podocytes, and analyzed 7 days later.

Results: In vivo studies, administration of LMB2 caused loss of co-introduced EGFP in 56.8±13.6%, incorporation of propidium iodide in 13.6±2.5%, activation of caspase 3 (Casp3) in 19.6±2.6% and TUNEL staining in 4.5±1.3% without significant increase in LDH activity in the culture medium. These phenomena were not observed in cells without ICD25 or without LMB2. Ac-DEVD-CHO (10uM), a Casp3 inhibitor, attenuated the loss of EGFP by 38.2%. Inhibition of Bak1 and Bax using siRNAs attenuated EGFP loss by 77.6% and 28.4%, respectively. These indicate that LMB2 induced the typical Casp3 dependent intrinsic apoptosis in podocytes in vivo. In in vivo studies, kidneys of NEP25 mice contained podocytes positive for cleaved (c) Casp3 and those for cLaminA, a product of Casp3, but no TUNEL+ podocytes. EM analysis showed no apoptotic body, but occasionally rupture of plasma membrane of podocytes. The urinary sediments contained podacyclin-positive podocytes (2.5±0.3%). Among these, 39.3±1.7% were stained for cCasp3 and 21.7±5.5% were stained for TUNEL. To evaluate the effect of glomerular filtration, NEP25 mice were similarly injected with LMB2 and subjected to 5/6 nephrectomy 1 day before sacrifice. The obstructed kidney contained more cLaminA+ podocytes than the contralateral kidney. In addition, detachting podocyte cell bodies were frequently observed in the contralateral kidney by SEM analysis, but never in the obstructed kidney.

Conclusions: Thus, due to physical force of glomerular filtration, podocytes doomed to Casp3 dependent death are quickly lost by detachment or plasma membrane rupture before completing full apoptotic processes. This accounts for the absence of podocyte apoptosis in vivo.

PO1705

Glomerular Endothelial Cell-Derived MicroRNA-192 Regulates Podocyte Nephronectin in Membranous Glomerulonephritis
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Background: Autoantibodies binding to podocyte antigens cause idiopathic membranous glomerulonephritis (iMGN). It remains elusive how autoantibodies reach the subepithelial space because the glomerular filtration barrier (GFB) is normally size-selective and impermeable for antibodies.

Methods: Kidney biopsies from patients with iMGN, cell culture, zebrafish and mice models were used to investigate the role of nephronectin (NPNT) regulating microRNAs (miRs) for the GFB.

Results: Glomerular endothelial cell (GEC)-derived miR-192-5p and podocyte-derived miR-378a-3p are upregulated in glomeruli of patients with iMGN whereas NPNT expression is reduced. Overexpression miR-192-5p as well as morpholino-mediated npnt knockdown induced edema, proteinuria and podocyte effacement similar to podocyte-derived miR-378a-3p in zebrafish. Moreover, structural changes of the glomerular basement membrane (GMB) with increased lucidity, slicing and lamellation especially of the lamina rara interna similar to ultrastructural findings seen in advanced stages of iMGN were found (Fig. 1). IgG size nanoparticles accumulated in lucidity areas of the lamina rara interna and lamina densa of the GMB in npnt knockdown zebrafish models. Loss of slit diaphragm proteins and severe structural impairment of the GMB were further confirmed in podocyte-specific Npnt knockout mice. GECs downregulate podocyte Npnt by secretion of miR-192-5p containing exosomes in a paracrine manner.

Conclusions: Podocyte NPNT is important for proper GFB function and GFB structure and is regulated by GEC-derived miR-192-5p and podocyte-derived miR-378a-3p. We hypothesize that loss of NPNT in the GFB is part of the pathophysiology of iMGN and enables subepithelial immune complex deposition in iMGN.
PO1706
Identification of the Mechanism Underlying the Toxicity of Systemically Administered miR-145-5p on Podocytes Based on Podocyte Essential Genes
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Background: MicroRNAs are emerging as effective therapeutic agents. MiR-145-5p dysregulation has been shown to be involved in kidney injury. To determine whether supplementation of miR-145-5p would alleviate kidney injury in mouse models, we first tested the miR-145-5p enriched extracellular vesicles (miR-145-5p EVs) sample for toxicity or side effects on healthy control mice.

Methods: miR-145-5p EVs were injected to mice intravenously every day for a total of 6 days. A group of mice were simultaneously injected with miR-145-5p inhibitor using TransIT®-EE Delivery Solution. Cultured cells were transfected with RNAiMAX or Fugene.

Results: miR-145-5p EVs resulted in proteinuria and podocyte foot process effacement in normal control mice, and this effect was abolished by miR-145-5p inhibitor. We demonstrated that systemically administered miRNA can enter podocytes. miR-145-5p EVs could enter cultured podocytes and cause F-actin loss. miR-145-5p mimic caused a similar reduction of F-actin in the cells. We speculated that miR-145-5p is toxic to podocytes because it is not normally expressed in podocytes and exogenous miR-145-5p can effectively target genes essential for podocytes. By using the concept that genes commonly expressed in all individual podocytes are likely podocyte essential genes, we predicted that podocyte genes when knocked down with shRNA/RPMK. We found that 32 of them are predicted to be targeted by miR-145-5p. Functional annotation of the 32 genes revealed small GTPase mediated signal transduction as the top function. Among genes associated with the small GTPases pathway, Arhgap24 is known to be responsible for podocyte injury and podocyte hypertrophy activity. We found and miR-145-5p significantly repressed Arhgap24 expression in podocytes in vivo and in vitro. miR-145-5p increased activity of both Rac1 and Cdc42.

Conclusions: MiR-145-5p induced podocyte injury through targeting podocyte essential genes associated with small GTPase mediated pathway. Our study provides a novel approach to investigate how a miRNA affects a given cell type, allowing not only identification of the molecular mechanism underlying an observed side effect of a miRNA drug but also prediction of miRNA drug toxicity on various cell types.

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PO1707
Glomerular mRNAs Are Alternatively Spliced and Polyadenylated During Podocyte Injury in Animal Models of Nephrotic Syndrome
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Background: Glomerular disease, often manifesting as nephrotic syndrome (NS) with high proteinuria, is characterized by podocyte loss and injury. Furthermore, alternative mRNA processing, such as alternative splicing (AS) and alternative polyadenylation (APA) play important roles in physiology, development, and disease; however, there is very limited knowledge on their roles in glomerular disease. We hypothesized that AS and APA events of glomerular RNAs is associated with podocyte injury and proteinuria in NS.

Methods: Glomerular damage characterized by proteinuria was induced by purumycin aminonucleoside (PAN) or adriamycin (ADR) to mimic human minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS), respectively. Urine and serum chemistries, kidney histology and glomerular RNA-seq analyses were performed. APATrap and JunctionSeq bioinformatics analyses software were used to detect APA and AS glomerular events. Correlation of differentially expressed genes (DEGs) was performed with known glomerular disease genes and polyadenylation and splicing factors.

Results: Robust proteinuria was induced in both PAN-MCD and ADR-FSGS models, accompanied by hypoproteinemia, hypercholerolemia and histological alterations in the kidneys (protein casts and podocyte hypertrophy). Out of 13,265 genes, MCD model resulted in 1033 and FSGS model in 1308 glomerular DEGs with abs(log2FC)>1 and P<0.05. Of 80 analyzed genes with established roles in glomerular disease, 30 were altered in both MCD and FSGS. Significant APA was identified in 71 and 746 genes in MCD and FSGS models, respectively, and of 173 polyadenylation factors analyzed, 21 were altered in MCD and 24 in FSGS. Significant AS was identified in 136 and 1875 genes in MCD and FSGS models, respectively. In accordance, of 50 splicing factors analyzed, 3 were altered in MCD and 5 in FSGS. Specifically, the identified APA and AS events affected genes of the slit diaphragm complex such as Npx1, Npx2, and Tpil1, which are critical determinants of podocyte structure and function.

Conclusions: Association of global glomerular mRNA alteration due to AS and APA with podocyte and glomerular injury is a newly recognized phenomenon, with potential implications for therapy and molecular understanding of the disease.

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PO1708
Continuous Non-Mutagenic DNA Damage in Podocytes Activates Inflammatory Response and May Accelerate Kidney Aging
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Background: Podocytes are suggested to contribute to kidney aging because of their terminal differentiated features. We have previously reported the association of KAT5-mediated DNA damage repair with altered DNA methylation in podocytes (Cell Rep 2019). However, the role of podocyte DNA damage itself on DNA methylation changes and kidney aging has remained to be adequately elucidated.

Methods: To investigate the significance of DNA double-strand breaks (DSBs) in podocytes, we generated podocyte-specific I-Ppol-expressing mice (podocin-Cre ROSA26-STOP- I-Ppol). I-Ppol is a homing endonuclease which causes non-mutagenic DSBs. RNA-seq and MeDIP-seq analysis were performed using isolated podocytes in I-Ppol mice and wildtype controls.

Results: I-Ppol mice showed severe albuminuria (WT 43±3.4 μg/gcr, I-Ppol 2224±7.3 μg/gcr, p<0.01) with diffuse foot process effacement in podocytes but glomerulosclerosis and interstitial fibrosis were not observed at 12 weeks of age. Interestingly, infiltration of CD11b-positive cells was shown in I-Ppol mice, which is a similar finding in 2-year-old aged mice. The aged mice showed increased DNA damage and DNA methylation. In I-Ppol mice, rapid deterioration of renal function with glomerulosclerosis and tubulointerstitial fibrosis developed around the age of 20 weeks. RNA-seq analysis revealed that inflammatory-related genes were upregulated in podocytes of I-Ppol mice. Senessent-associated secretory phenotype (SASP)-related gene expression was also increased. MeDIP-seq analysis revealed that 5219 differentially methylation regions (DMRs) were identified in I-Ppol mice compared with controls. Interestingly, there was no significant correlation between the distance from the I-Ppol cutting site and DMRs. DNA methylation was increased in genes containing I-Ppol cutting sites or podocyte epithelial genes such as nephrin and podocin, whereas it was decreased in inflammatory related genes, suggesting gene-specific DNA methylation changes following DNA damage.

Conclusions: The phenotype of the I-Ppol mice may reflect one aspect of accelerated kidney aging. Repeated DNA damage repair in podocytes may cause altered DNA methylation independent of primary DNA damaged sites with promoted inflammation and podocyte morphological changes.
POI1710

Delayed Treatment with a Novel Highly Selective Small-Molecule Agonist of MC5R Attenuates Podocyte Injury and Proteinuria in Parvinum Aminonucleoside Nephrosis
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Background: Clinical studies indicate that the melanocortin peptide ACTH is effective in inducing remission of nephrotic glomerulopathies like MCD and FSGS, even those resistant to steroids, suggesting that a steroid-independent melanocortinergic mechanism might contribute. However, the type of melanocortin receptor (MCR) that conveys this beneficial effect as well as the underlying mechanisms remains controversial. Recently, burgeoning evidence suggests that MC5R is likely involved in glomerular pathobiology. This study aims to test the effectiveness of a novel highly selective MC5R agonist (MC5RA) in parvinum aminonucleoside (PAN) nephrosis.

Methods: MC5RA was generated by N-terminal modification of the melanocortin core tetrapeptide His-D-Phe-Arg-Trp-NH2 with an aromatic group, resulting in a triphenylpropionyl melanocortin analog with a 100-fold selective agonistic activity on MC5R. Rats were injured with a tail vein injection of PAN, and 5 days later, were randomized to daily MC5RA or vehicle treatment.

Results: Upon PAN injury, rats developed heavy proteinuria on day 5, entailing an established nephrotic glomerulopathy. Following vehicle treatment, proteinuria continued to progress on day 14 and was sustained till day 21, accompanied by evident histologic signs of podocyte damage: marked by ultrastructural lesions of glomeruli, including extensive effacement of podocyte foot processes and podocyte microvillus transformation, and concomitant with loss of podocyte homeostatic markers, such as synaptopodin and nephrin, and de novo expression of proteinuria marker desmin. Rescue treatment with MC5RA significantly attenuated urine albumin excretion and mitigated the loss of podocyte markers proteins, resulting in improved podocyte ultrastructural changes. In vitro in cultured podocytes, MC5RA prevented the PAN-induced disruption of actin cytoskeleton integrity and apoptosis. Mechanistically, MC5RA treatment reinstated inhibitory phosphorylation and thus averted hyperactivity of GSK3β, a central point of multiple podocytopathic pathways, in PAN-injured podocytes in vitro and in vivo.

Conclusions: Pharmacologic targeting of MC5R by using the highly selective small-molecule agonist is likely a promising and feasible therapeutic strategy to improve proteinuria and podocyte injury in glomerular disease.

Funding: NIDDK Support

POI1711

Tadalafil, a PDE5 inhibitor, Exhibits Renoprotective Effects Preventing Podocyte Damage in an Adriamycin-Induced Nephrotic Syndrome Model
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Background: Phosphodiesterase (PDE)-5 inhibitor is reportedly a renoprotective compound. Although PDE5 expression is confirmed in the glomeruli, its relationship with renal dysfunction remains elusive. We have previously investigated the renoprotective effects of tadalafil in a CKD model (Tomita N, et al. Physiol Rep. 2020), suggesting that such an effect would be related to podocyte damage attenuation. In this study, we investigated how tadalafil, a PDE5 inhibitor, could affect a rat nephrotic syndrome model.

Methods: Wistar ST rats were established as nephrotic syndrome models by administrating adriamycin (ADR) injection. The animals were divided into 3 groups: control (n = 6), ADR (n = 5), and ADR + tadalafil (n = 5). Tadalafil was administered 10 mg/kg daily. After 2 weeks of treatment, the urinary protein and serum albumin levels were evaluated, and the kidney tissue was harvested. WT1-positive cells were identified as podocytes by WT1 immunostaining. Moreover, human renal glomerular epithelial cell damage was induced in vitro by ADR supplementation. After 24 h of ADR treatment with or without tadalafil, cell viability was determined by CCK-8.

Results: The ADR injection induced high urinary protein and low serum albumin levels. Two weeks of tadalafil treatment attenuated proteinuria compared to the ADR group (P<0.01). ADR reduced the WT1-positive cell number and the tadalafil treatment prevented the reduction (P<0.05). Moreover, the ADR treatment resulted in reduced cell viability in vitro. The tadalafil treatment improved cell viability compared to the ADR treatment only (P<0.05).

Conclusions: This study suggests that the treatment with tadalafil, a PDE5 inhibitor, could effectively prevent podocyte damage in the case of nephrotic syndrome.

POI1712

Targeting mTOR Signaling Improved Kidney Function in APOL1 Risk Variant Mice with Chronic Exposure to Inflammatory Stimuli
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Background: Inheriting two copies of APOL1 risk variants significantly increases the likelihood of developing chronic kidney disease in African Americans. Many different pathways of disease have been proposed using cell-based model systems. Here we try to understand risk variant pathophysiology using a transgenic mouse model.

Methods: Transgenic mice with a single copy of human APOL1 G0 and G2 were generated using bacterial artificial chromosome (BAC) on a FVB background. Mice were injected with interleukin gamma (IFN-γ) plasmid via hydrodynamic tail vein injections to induce APOL1 expression. Since mTOR activation has been frequently observed in podocytes during FSGS, we blocked the pathway using rapamycin to see if it could improve disease outcomes. Mice were injected with 2mg/kg of rapamycin every other day (3 days/week, intraperitoneally) for a total of 2 weeks. Paraffin embedded tissue sections were used for immunohistochemistry and Periodic acid–Schiff (PAS) staining. Glomerular isolations were performed using Dynabeads. APOL1 oligomerization was assessed using blue native PAGE.

Results: 7 Days after IFN-γ plasmid injection, the podocytes of G2 mice stained positive for phospho-S6 ribosomal protein indicating mTOR activation accompanied by proteinuria. Blocking mTOR activation using rapamycin reversed ribosomal protein S6 phosphorylation, reduced proteinuria, and improved tissue histology as seen by PAS staining. We hypothesized that rapamycin might be activating autophagy and clearing APOL1 oligomers, but found no evidence for this mechanism of rescue. Instead, we were able to replicate the rescue we had observed with rapamycin using a cell cycle inhibitor, suggesting that rapamycin might be rescuing G2 phenotype by inhibiting podocyte cell cycle entry downregulating risk variant mediated injury.

Conclusions: Persistent expression of APOL1 risk variants pushes podocytes into cell cycle entry. Inhibiting mTOR signaling and subsequent cell cycle entry alleviated injury.

Funding: Other NIH Support - NIMHD, Other U.S. Government Support

POI1713

PLIN5 Deficiency in Podocyte Negatively Affects the Communication Between Lipid Droplets and Mitochondria in Alport Syndrome
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Background: Alport Syndrome (AS) is a hereditary disease caused by mutations in collagen type IV. We and others have demonstrated pathogenic renal lipid droplets (LD) and triglyceride (TG) accumulation in experimental AS (Col4a3KO mice). Excessive FA breakdown and the loss of LD-mitochondrial contact, thus contributing to disease progression. Here we try to understand how these mechanisms of disease have been proposed using cell-based model systems. Here we try to understand risk variant pathophysiology using a transgenic mouse model.

Methods: In vitro, Immortalized AS podocytes and WT podocytes were established and characterized in our laboratory by breeding the Col4a3KO mice (Jackson Laboratory) to B6.Cg-Aij. AS transgenic mice (Charles River). PLIN5 expression was determined by RT-PCR and western blot analysis in AS podocytes and kidney cortex in AS mice when compared to controls. TG lipolysis and FFA quantification were determined and normalized to protein content. LD-Mitochondrial contact was determined by TEM and electron microscopy.

Results: PLIN5 deficiency was observed in the kidney cortex of Col4a3KO mice when compared to controls (p<0.001). We demonstrate that PLIN5 is expressed in podocytes, and the expression of PLIN5 is significantly decreased in AS podocytes compared to WT podocytes (p<0.01). AS podocytes also showed significantly increased rates of TG lipolysis (p<0.05), intracellular free fatty acids (p<0.05) and apoptosis (p<0.01) when compared to WT podocytes. AS podocytes had reduced number of LD-mitochondrial contacts (p<0.05), implying that and apoptosis. Moreover, Ezetimibe, which restored LD-mitochondrial contact in vitro (P<0.05) and improved kidney function in vivo, was found to restore PLIN5 expression in vitro and in vivo (P<0.05).

Conclusions: Our study suggests that podocyte PLIN5 deficiency may cause podocyte injury in AS through excessive TG lipolysis and inefficient FA transfer from LD to Mitochondria, leading to mitochondrial dysfunction and contributing to disease progression.
UCP2 Regulates Mitochondrial Dynamics and Podocyte Injury by OMA1-Dependent Proteolytic Processing of OPA1

L-WNK1 Inhibition Protects from Glomerular Injury in Mice

L-WNK1 Inhibition Protects from Glomerular Injury in Mice

Shiga Toxin Targets the Podocyte in Haemolytic Uraemic Syndrome (HUS) Resulting in Glomerular Endothelial Cell Complement Dysregulation

Protective Role of the Epithelial STAT5 Pathway in Kidney Injury

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO1719
Podocyte Damage in Chimeric Kidney Organoids
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Background: We previously found that when a portion of podocytes are injured, other podocytes are secondarily injured in a mouse model, which may underlie the relentless progression of chronic renal failure. In the present study, we tested whether this phenomenon is observed in kidney organoids.

Methods: Nephrone progerotics cells (NPCs) were established by culture-dependent purification (CDP) method from 12.5 dpc NEP25 and RiboTag mouse kidneys (Cell Stem Cell, 2016, 19, 516-29). Podocytes of NEP25 mice express hcDC25 and can be injured by hcDC25-targeted immunotoxin. LMB2. Podocytes of RiboTag mice express hemagglutinin (HA)-tagged ribosomal protein. Kidney organoids were generated by transient stimulation with FGFI2 and CHIR99021 of NPC aggregates and subsequent 8-day culture. On day 8, LMB2 (20 nM) was added to induce injury in hcDC25+- podocytes.

Results: We confirmed that podocytes in both organoids are stained for nephrin, podocin and WT1. Podocytes derived from NEP25 NPC expressed hcDC25 and were injured by LMB2, and those from RiboTag NPC expressed HA and were resistant to LMB2. When two types of NPCs were mixed at 1:1 ratio, organoids showed a chimeric pattern containing hcDC25+ and HA+ podocytes (Fig). 2 days after LMB2 treatment, hcDC25 staining completely disappeared accompanied by cleaved (c) lamin A staining, a cell death marker. HA staining was retained, but WT1 was diminished and podocin disappeared (Fig 2). Occasionally, c-lamin A was positive in HA+ cells. RNA of Ribotag podocytes can be obtained by immunoprecipitation with anti-HA antibody. qPCR revealed that Nphsl (0.31), Nphs2 (0.04), Wil1 (0.37) were decreased to the indicated fold by LMB2 and that Gadd45β was increased to 4.82-fold.

Conclusions: Thus, podocyte damage damages podocytes in kidney organoids that lack glomerular filtration.

Funding: Government Support - Non-U.S.

PO1720
Increased Old Astrocyte Specifically Induced Substance (OASIS) in Podocytes Leads to the Progression of Nephrotic Syndrome
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Background: Old astrocyte specifically induced substance (OASIS) is a transcription factor of the CREB/ATF family. Previously, we found that OASIS was expressed in podocytes in murine kidneys. However, the pathophysiological roles of OASIS in podocytes remain unclear. The aim of this study is to elucidate the role of OASIS in podocytes.

Methods: To assess the relevance of OASIS to renal pathology, the expression of OASIS in glomeruli of lipopolysaccharide (LPS)-treated mice or streptozotocin (STZ)-treated diabetic mice was examined by laser capture microdissection, followed by immunoblotting. To further investigate the functional roles of OASIS in podocytes, podocyte-restricted OASIS overexpressing transgenic (OASIS TG) mice were established. Urinary albumin-creatinine ratio (uACR) was measured. Podocyte injury was assessed by electron microscopy. Tubular injury was evaluated by PAS staining and by measuring related genes, and COL1A1 and LCN2 mRNA expression. Masson’s trichrome staining and quantitative PCR for fibrosis-related genes, COL1A1 and FNI, were performed to analyze tubulointerstitial fibrosis. To explore the effect of OASIS on podocyte actin cytoskeleton in vitro, phalloidin staining was performed on lentivirus-induced OASIS overexpressing murine cultured podocytes. The increased OASIS in podocytes contributed to nephrotic progression.

Results: OASIS expression was increased in glomeruli of both LPS-treated and diabetic mice. uACR was significantly increased in OASIS TG mice (uACR (μg/mg)): control; 35.1±8461.4, n=9 for control, n=7 for OASIS TG), and electron microscope analysis showed that OASIS overexpression in podocytes caused foot process effacement. In addition, damaged tubules and LCN2 upregulation were observed in OASIS TG mice. Furthermore, Masson’s trichrome staining showed that OASIS overexpression in podocytes evoked kidney fibrosis, and the expression of COL1A1 and FNI were upregulated in OASIS TG mice. Consistent with in vivo study, OASIS overexpressing podocytes showed the reduction in actin stress fiber formation.

Conclusions: The increased OASIS in podocytes contributes to nephrotic progression.

Funding: Government Support - Non-U.S.
PO1721
Podocyte-Derived RARRES1 Aggravates Kidney Disease Progression by Inducing Both Glomerular and Tubular Injury
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Background: Our previous study demonstrates that the expression of retinoic acid receptor responder protein 1 (RARRES1) increases in glomeruli of patients with diabetic nephropathy (DN) and focal segmental glomerulosclerosis (FSGS). The glomerular expression of RARRES1 also correlates with cGFR slope and predicts glomerular disease progression. Single-cell RNA-sequencing of the kidney showed that RARRES1 was expressed mostly in podocytes within the kidney. Mechanistically, WT-RARRES1 is cleaved into a soluble form which subsequently induces podocyte apoptosis whereas mutant RARRES1 with cleavage defect failed to induce podocyte apoptosis in vitro. Here, we further determined whether increased expression of WT-RARRES1 in the podocytes aggravated progression of glomerular disease.

Methods: Mice with podocyte-specific overexpression of human WT- RARRES1 or mutant RARRES1 with cleavage defect were generated and then subjected to aging, adriamycin (ADR) administration or streptozotocin (STZ) injection. To identify the role of podocyte-derived soluble RARRES1 in tubular cells, HK2 cells were treated with soluble RARRES1 obtained from podocyte supernatants.

Results: In vivo, podocyte-specific overexpression of WT-RARRES1 resulted in severe proteinuria and marked glomerular injury in mice with aging, adriamycin-induced nephropathy, or STZ-induced diabetic nephropathy as compared to the control mice with overexpression of mutant RARRES1. In vitro, tubular vacuolation and interstitial injury were also observed in these mice with podocyte-specific overexpression of RARRES1. In addition, we showed that soluble RARRES1 collected from podocyte supernatants was endocytosed in HK2 cells to induce cellular injury. Similarly, cleaved forms of human RARRES1 in the mice with podocyte-specific human RARRES1 overexpression was found in the tubular compartments, indicating that soluble RARRES1 generated from podocytes may act on tubular cells through glomeruli-tubule crosstalk.

Conclusions: Our study suggests that RARRES1 is a risk gene for glomerular disease progression through its direct effects in podocytes as well as indirect effects in tubular cells probably via glomeruli to tubules crosstalk.

Funding: NIDDK Support, Veterans Affairs Support

PO1722
Podocyte-Specific Extracellular Vesicles Yield Novel Insight into Intercellular Signaling in the Glomerulus

Background: Extracellular vesicles (EVs) have been identified to play an essential role in basic pathological processes such as priming of the metastatic niche, autoimmunity and propagation of insulin resistance. Nevertheless, knowledge about their role in kidney health and disease remains scarce. A new group of EVs, shed upon apoptosis with the ability to induce a proliferative effect in neighboring cells, was recently identified in cell culture models as well as experimental glomerulonephritis. This study aimed to characterize these medium-sized EVs and the signaling propagated by them in podocyte damage.

Methods: Using differential centrifugation and filtration we established a protocol to separate medium-sized EVs from cell culture supernatants, kidney tissue and urine samples. We performed scanning and transmission electron microscopy and image flow cytometry, we investigated the release dynamics of podocyte-specific vesicles in different models of murine podocyte damage in vitro and in vivo. Furthermore, cross culture experiments and life microscopy were used to determine the effect of podocyte-specific medium-sized EVs on parietal epithelial cells.

Results: Podocyte-specific medium-sized EVs were detected in baseline podocyte culture supernatant, untreated murine kidney tissue as well as the urine of healthy human volunteers. Vesicle quantification revealed a drastic increase of vesicle release upon podocyte damage both in vitro and in vivo. Interestingly, podocyte-specific EVs exerted different effects on the proliferative and migratory behavior of primary parietal epithelial cells.

Conclusions: Our study represents the first investigation of podocyte-specific medium-sized extracellular vesicles, their release dynamics and functional implications in health and disease. Ongoing analyses aim to characterize their proteomic content and effect other renal epithelial cells. As these vesicles can be separated without advanced equipment such as ultracentrifuges, we believe they could also be a valuable source for biomarker research in various nephropathies.

PO1723
Effects of Varying Mild Tubular Injury on Subsequent Glomerular Injury Janka Babickova,1,2 Haichun Yang,3 Agnes B. Fogo.1 Vanderbilt University Medical Center, Nashville, TN; 2University of Bergen, Bergen, Norway.

Background: Tubular injury predisposes to CKD, including glomerular injury. We analyzed effects of mild tubular injury on subsequent glomerular injury.

Methods: Mice were divided into 5 groups (WT and AS males and female mice) with (human CD25 receptor on podocytes and Diphtheria toxin (DT) receptor on proximal tubules) received DT (25, 50, or 100ng/kg; 2x one week apart, n=5/group) to induce tubular injury, or vehicle (VEH). Uninephrectomy was done 4 wks later, 5 wks later glomerular injury was induced by LMB2 toxin (CD25 ligand) and mice were sacrificed 10 days later.

Results: In males, urinary KIM-1 was significantly higher vs VEH with all DT doses on d3 after DT injections, lowest in DT30 and similar with DT50 and DT100. KIM-1 levels were significantly higher in females; numerically higher in DT50 and DT100 vs VEH by wk 6. Uninephrectomy was significantly increased at d3 only in DT100 vs VEH. NGAL levels normalized in all DT groups by week 6. In females, KIM-1 levels were increased by d3 with highest level with DT100. KIM-1 levels were only numerically higher vs VEH in a dose-dependent manner in males. Urinary NGAL was only nonsignificantly elevated. On d3, NGAL levels were significantly higher vs VEH in females, normalized by wk 6, with numerically highest level in DT100. Males had higher levels of KIM-1 vs females at all timepoints, while NGAL showed similar levels in males and females at DT100 on d3, but higher levels in females at DT100 dose at wk 6. In males, albumin excretion was elevated and sacrificed at d5 after podocyte injury showed numerically higher levels by 67% in DT100 vs VEH. In females, albuminuria gradually increased, with levels lower than in males in all groups. Ultrastructural analysis after podocyte injury showed similar significant foot process effacement, glomerular capillary fenestration loss and increased GBM thickness in all groups.

Conclusions: Sex differences in response to tubular injury and albuminuria were observed. Even very mild tubular injury, recovered by assessment of KIM-1 and NGAL-1 led to numerical increase in albuminuria after second hit glomerular injury in both sexes. The sex-dependent differences in KIM-1 and NGAL-1 further support differential susceptibility of nephron segments to injury in females vs males, which may play a role in glomerular sensitization to injury.

Funding: NIDDK Support

PO1724
Effect of Glomerular Disease on the Podocyte Cell Cycle Laura Perin,1 Camille H. Nicolas Frank,2 Xiaoang Hou,1 Gregory Clair,3 Fadi E. Salem,4 Roger E. De Filippo,5 Paolo Cravedi,6 Kevin V. Lemley.7 1Children’s Hospital of Los Angeles, Los Angeles, CA; 2Harvard Medical School, Boston, MA; 3Pacific Northwest National Laboratory Biological Sciences Division, Richland, WA; 4Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Progression of glomerulosclerosis is associated with loss of podocytes and subsequent glomerular tuft instability. A decreased number of podocytes may be able to preserve tuft stability through cell hypertrophy associated with cell cycle re-entry. At the same time, re-entry into the cell cycle can lead to podocyte detachment from the glomerular basement membrane, if podocytes cross the G1/S checkpoint and undergo apoptosis.

Methods: To study cell cycle dynamics during CKD development, we used a Fucci mouse model (fluorescence ubiquitination-based cell cycle indicator) affected by X-linked Alport Syndrome (AS). This model has progressive CKD and expresses cell cycle fluorescent reporters exclusively in podocytes. We quantified podocytes cell cycle distribution in WT and AS mice at different ages and collected podocytes in G0 and G1 for proteomics studies.

Results: We showed that with the development of CKD, an increasing fraction of podocytes in vivo are in G1 or later cell cycle stages. A decreased number of podocytes may be able to preserve tuft stability through cell hypertrophy associated with cell cycle re-entry. At the same time, re-entry into the cell cycle can lead to podocyte detachment from the glomerular basement membrane, if podocytes cross the G1/S checkpoint and undergo apoptosis.

Conclusions: Our data showed that, during progressive CKD, the podocyte cell cycle distribution changes dramatically, suggesting that cell cycle manipulation may have a role in the therapy of progressive glomerular diseases characterized by podocyteopathy.

Funding: Private Foundation Support

PO1725
Glucocorticoid- and Pioglitazone-Induced Proteinuria Reduction Correlates with Glomerular Extracellular Matrix Remodeling in Experimental Nephrotic Syndrome Sagar Bhavna, Shipra Agrawal, Amanda P. Waller, Katelyn Wolfgang, Saranga Wijeratne, James Fitch, Peter White, Bryce A. Kerlin, William E. Smoyer. Nationwide Children’s Hospital, Columbus, OH.

Background: Nephrotic Syndrome (NS) is a common glomerular disease in children. While glucocorticoids (GC) are the mainstay of childhood NS treatment, pioglitazone (Pio; an FDA-approved PPARγ agonist to treat type 2 diabetes) has been reported to reduce proteinuria in experimental NS and to directly protect podocytes from injury. Since both GC and Pio activate nuclear receptors (NR3C1 and PPARγ, respectively) we hypothesized that their proteinuria-reducing effects result from overlapping glomerular gene transcriptional patterns.

Methods: We performed transcriptome analyses on glomeruli isolated from GC (immunosuppressive)- and Pio (non-immunosuppressive)-treated rats 11 days after induction of NS with PAN (n=4/group).

Results: Unsupervised clustering revealed partial reversibility of PAN-associated mRNA expression changes by treatment with either GC or Pio. IPA analyses identified 29 genes-of-interest common to GC- and Pio-induced proteinuria reduction, which included ECM remodeling, lipid metabolism, DNA-binding and cytoskeletal organization. Based on expression differences using real-time PCR,
29 genes-of-interest were selected for further analysis, which on clinical correlation with a SIF-1 SIFG database (Neuropathy) suggested a direct relevance of glomerular ECM regulation in NS. Also, glomerular cell deconvolution using published single-cell glomerular transcriptome profiles identified podocyte- and mesangial cell-specific perturbations in gene expression during NS and with treatments. Finally, validation of selected genes of interest with PAN-induced injury of human podocytes and mesangial cells confirmed significant upregulation of LGAQLS (primary role in cell adhesion) and MMP2/ACTA2 (primary role in ECM degradation/cell motility or integrity) respectively.

Conclusions: These studies identified podocyte- and mesangial cell-specific transcripts common to both proteinuria-reducing treatments that identify possible targets for future treatment for NS.

PO1726
Alterations of Intestinal Microbiota in Patients with ESRD Undergoing Hemodialysis
Takeo Koshida,1 Tomohito Gohda,2 Takuya Sugimoto,2 Takashi Ashahara,3 Masanori Ishizaka,1 Maki Murakoshi,1 Yusuke Suzuki,11 ‘Department of Nephrology, Juntendo University Faculty of Medicine, Tokyo, Japan;’ Yakult Central Institute, Yakult Honsha Co. Ltd, Tokyo, Japan.

Background: The alteration in the intestinal microbiota is reported to be associated with various diseases, indicating that the development and progression of end-stage kidney disease also might be associated with dysbiosis.

Methods: The stool samples were collected from patients with hemodialysis (n = 41, HD group) and those with normal renal function (n = 40, NRF group). Both groups are comprised of patients with (HD_DS, n = 20; NRF_DS, n = 19) and without diabetes (HD_non-DS, n = 21; NRF_non-DS, n = 21). We conducted 16S RNA gene amplicon sequencing using stool samples to analyze the intestinal microbiota.

Results: The reduced abundance of the genera Megamonas and Fusobacteribacter, and the enriched abundance of the genera Family XIII AD3011 group (Anaerovoracaceae family), UBA_1819 (Ruminococcaceae family), and Pseudomonas in the stool samples of HD patients were observed significantly compared with those of NRF patients. Compared with patients with NRF, the relative abundance of the genera Megamonas was decreased and that of Family XIII AD3011 group was increased significantly in patients with HD, although those relative abundance did not alter between NRF_non-DS and HD_non-DS. The relative abundance of the genera Streptobacteria in HD_non-DS was significantly decreased than that in NRF_non-DS, although that relative abundance did not differ between NRF_DS and HD_DS. In the microbial beta diversity, there was no difference between NRF_DS and NRF_non-DS by weighted and unweighted UniFrac analysis, however, there was significant difference between HD_DS and HD_non-DS by weighted UniFrac analysis (p = 0.007). These results suggest that the gut microbiota alters with renal function decline, and varies depending on the presence or absence of diabetes.

Conclusions: The intestinal microbiota might be varied substantially depending on renal function and the presence or absence of diabetes.

PO1727
Nutritional Intervention in Intensive Care Unit Patients Undergoing CRRT
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Background: Providing adequate calories and protein constitutes an important part of critical care, and inadequate nutrition for critically ill patients is associated with poor prognosis. Therefore, increased loss of amino acids, electrolytes, and water-soluble vitamins during continuous renal replacement therapy (CRRT) could be a therapeutic target. We evaluated whether enforcing protein, trace elements and vitamin supply could improve the prognosis of CRRT patients.

Methods: A nutritional intervention (100 mg/day of Thiamine, 25–30 kcal/kg of energy, 1.8 g/kg of protein, and 50–100 mcg/day of microelement with selenium) was conducted in patients subject to CRRT from May 2020 to December 2020. The primary outcomes were 28-day mortality, CRRT day, ICU stay, and ventilator-free day, and the outcomes before and after the intervention were compared.

Results: Total 88 patients were included during the study period and compared with 88 patients in the previous year. The average age was 68.05 years old, 56 (63.5%) patients were male. At day 1 APACHE-II score was 35.41±2.9, SAPS3 88.1±16.8, SOFA 10.4±2.7. There were 9 (10.2%) patients with ECMO, 78 (88.6%) using ventilator. There were 19 (21.6%) pneumonia with ARDS patient, 18 (20.5%) cardiac disease, 9 (10.2%) UTI sepsis, 11 (12.5%) gastrointestinal bleeding and sepsis, 6 (6.8%) cerebral hemorrhage, and others. The main reason for CRRT was hemodynamic instability. Baseline characteristics including APACHE-II score, SAPS 3, and SOFA were not significantly different between the nutritional intervention and the non-intervention patients. Nutritional intervention did not induce significant changes in 28-day mortality (36 versus 37, p = 0.56) and CRRT days (7.3 ± 6.9 versus 6.3 ± 5.2, p = 0.29). However, nutritional intervention showed minimal improvement in ICU stay (22.1 ± 23.9 vs 20.7 ± 22.1, p = 0.05) and ventilator-free days (17.8 ± 22.3 vs 12.4 ± 14.4, p = 0.05).

Conclusions: This study suggests that support for protein, trace elements, and vitamins may have a positive effect in CRRT patients. Therefore, the nutritional requirements of patients with CRRT should be carefully assessed, individualized, and considered as an important axis of CRRT treatment.
PO1732
Long-Term Safety of Tenapanor for the Control of Serum Phosphorus in Patients with CKD on Dialysis: Serum Electrolytes and Albumin
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Background: Tenapanor, an investigational first-in-class phosphate absorption inhibitor (PAI), blocks the paracellular absorption of phosphate in the gastrointestinal tract by local inhibition of the sodium-hydrogen exchanger (NH3). Tenapanor is being studied as a non-binder approach for the management of hyperphosphatemia in patients on dialysis and it is dosed as one pill (10, 20, or 30 mg) twice daily. Due to its novel mechanism of action, it is important to understand its safety profile, including any potential effects on serum electrolytes and albumin.

Methods: This report evaluates the effects of tenapanor on serum electrolyte and albumin concentrations using data from 3 pivotal trials in which tenapanor met its primary phosphorus-lowering endpoint. Trials included a 12-week monotherapy study (BLOCK), a 52-week monotherapy study (PIREEDOM), and a 4-week tenapanor + phosphate binder combination study (AMPLIFY). Serum electrolytes and albumin were measured per study protocol in central research laboratories.

Results: Tenapanor was generally well tolerated, with diarrhea being the only adverse event reported by >5% of patients. Diarrhea was typically mild to moderate in severity, was transient, and resolved with continued treatment. Data from all 3 trials showed that tenapanor treatment, either alone or in combination with phosphate binders, resulted in no clinically meaningful changes in measured serum electrolytes or albumin at any time point. Data from patients treated with tenapanor continuously for 52 weeks in the longest trial, PIREEDOM, are shown in the table.

Conclusions: In these clinical trials, tenapanor inhibited paracellular absorption of phosphate and decreased serum phosphorus with an acceptable safety profile, with no observed effect on serum electrolytes or albumin in patients on maintenance dialysis with hyperphosphatemia.

Funding: Commercial Support - Ardeley, Inc.

PO1733
Patient-Reported Experience with Tenapanor in the OPTIMIZE Trial
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Background: Tenapanor (TEN), a first-in-class phosphate absorption inhibitor (PAI) that works via the paracellular pathway, provides a novel approach for hyperphosphatemia management. The primary goal of this study is to evaluate how to optimize the treatment of hyperphosphatemia in patients with chronic kidney disease (CKD) on dialysis with the use of TEN and its novel mechanism of action.

Methods: Patients with serum phosphorus (sP) >5.5 and ≤10.0 mg/dL during stable dialysis treatment, especially as new treatment options are available on the market to help patients.

Results: When thinking generally, nephrologists estimate that nearly one-half of end-stage renal disease patients (3.4% of HD patients and 3.6% of PD patients). On their last visit with their dialysis patients, nephrologists noted that only 4% of patients were diagnosed with a rash, itch, or pruritus (3.7% of HD patients and 5.6% of PD patients). Interestingly, only approximately one-third of those patients were diagnosed with uremic pruritus, indicating there are more patients presenting with a rash or itch who are not actually being diagnosed. Despite the impact on patient treatment, nephrologists report that only 25% of HD patients diagnosed with uremic pruritus are pharmacologically treated; this drops to 17% of PD patients with uremic pruritus. Treatments vary wildly and have varying levels of reported success among physicians. Nephrologists do recognize the impact pruritus can have on a patient’s quality of life, making the high rate of undertreatment especially troubling. On a 1-10 scale rating unmet need for a new therapeutic agent, 62% of nephrologists rated a high unmet need for pruritis in dialysis patients.

Conclusions: While many recognize that itching impacts many dialysis patients, actual diagnoses and treatment are rare, driven by a lack of effective treatment options. Elevating awareness among nephrologists will help with patient identification and treatment, especially as new treatment options are available on the market to help patients.
64.2% of patients (63.8% and 64.8% in Cohort 1 and Cohort 2, respectively) identified an improved perception of their medication regimen as the top reason for the improved perception, and 30.5% of patients (31.3% and 29.6% in Cohort 1 and Cohort 2, respectively) reported an improved perception of the form or frequency of bowel movements as the top reason for improved perception of their treatment routine.

Conclusions: Patients who were switched to TEN or added TEN to a reduced PB therapy regimen reported improved experience with their sP management. The findings from this analysis show that TEN may improve patient experience with sP management regimens. Further research is needed to elucidate what factors affect a patient’s perspective of sP management.

Funding: Commercial Support - Ardelyx, Inc.

POI1734

Apparent Paradoxical Relations of Serum Phosphate and Albumin Variability with Outcomes Are Explained by the Directional Change

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Background: Evidence indicates that variability of serum phosphate (P) and albumin (Alb) is associated with higher risk of mortality. We aimed to study the variability of P and Alb with all-cause mortality taking into account the interaction with the averaged levels.

Methods: All adult incident HD patients (pts) treated in Fresenius Medical Care NA clinics between 2010&2018 were included. Serum P and Alb levels were averaged from month(mo) 1 to 6 after HD initiation. Variability of P and Alb were described by standard deviation (SD) and directional changes (DR). All-cause mortality was recorded between mo 7 and 18. Cox proportional hazards models with spline terms were applied to explore the association between variability of P & Alb and all-cause mortality. Additionally, tensor product smoothing splines were computed to study the effect of interactions between averaged values of parameters and their variability with outcomes.

Results: We enrolled 353,142 pts. Averaged P was 4.98 mg/dL; median SD and DR were 0.92 and 1.10. Baseline Alb was 3.61 g/dL, median standard deviation (SD) and median DR were 0.21 and 0.40. Across different levels of P, higher SD of P were associated with higher risk of mortality, especially in those pts with lower averaged P. Contrasting, in pts with low Alb, higher SD was associated with reduced mortality. Results from Group 1, an unidirectional relation between DR and outcome was observed, whereas the relation between DR with outcomes was bidirectional for P (Fig1 &2).

Conclusions: The relationship between P variability and mortality was apparent at all levels of P. In well-nourished pts, higher P variability are associated with increased risk of mortality, which is related to the adverse effects of both an increase and a decline of this parameter. In pts with low Alb, the apparently paradoxical association between higher levels Alb variability and better survival due to an improvement of nutritional and inflammatory status, related to a positive DR. Due to possible nonlinear relations between risk factors and outcomes in patients on HD, variability should ideally be explored by various metrics.

POI1735

Restrict Dietary Phosphorus to Decrease Proteinuria and Prevent Decline in Glomerular Filtration Rate in CKD Stages 1 and 2

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Background: Though dietary phosphorus restriction is therapeutic for disordered phosphorus homeostasis, restriction of dietary phosphorus is not advised in CKD. Aim: Does early control of dietary phosphorus ameliorates proteinuria, prevent decline in glomerular filtration rate and prevent rise in FGF-23.

Methods: One year longitudinal study on 79 CKD stages 1 and 2 patients. eGFR, serum creatinine, phosphorus, calcium, FGF-23, soluble o-Klotho iPTH FGF 23, blood pressure, were evaluated and compared with 35 controls. 3 days dietary intake was taken using standard methodology on first visit, 6 and 12 months. CKD patients were grouped based on dietary phosphorus intake: Group 1 (n 42): normal phosphorous intake (1000mg/day) and Group 2 (n=37): high phosphorous intake (>1000mg/d). Patients in Group 2 were educated on high and low phosphorus foods and counselled to adopt a plant-based diet, for low phosphorus absorption with directed diet plan. Data were analysed using SPSS.

Results: At baseline there was no significant difference in the GFR (group 1 53.85±12.58 vs group 2 53.23±16.30 mL/min/1.73 m2), serum creatinine between the groups. In group 2; GFR, sKlotho, serum phosphorus and FGF-23 correlated significantly with dietary phosphorus intake. In group 2, FGF-23, serum phosphorus, dietary protein and phosphorus intake were significantly higher and sKlotho was significantly lower than group 1. There was significant difference in serum phosphorus (p 0.000), iPTH, (p 0.004), FGF23 (p<0.005), Klotho (p<0.000), dietary protein (Group 1 37.57±3.40; Group 248.79±5.86 p 0.000) and phosphorus (Group 1868.96±69.99 mg/d and Group 2 1312.26±137.77 mg/d p<0.000) intake and dietary phosphorus to protein ratio (p<0.000) between groups 1 and 2. On dietary intervention in group 2 GFR increased p 0.0002 from 80.93±15.34 to 84.11±15.38, and to 87.43±18.27 ml/min at 6 and 12 months respectively, Urinary protein declined to 22.0±4.33 mg/mL. FGF 23 declined from 60.67±6.26 to 58.00±7.07 to 53.29±9.48 pg/mL at 12 months. Dietary phosphorus: protein ratio reduced significantly from 27.1±6±4.35 to 24.7±5±4.34 p<0.000 at 12 months (p<0.000). Urinary phosphorus excretion increased from 574.37±21.42 to 624.64±137.67 at 12 months.

Conclusions: Restricting dietary phosphorus in stages 1 and 2 can prevent progression of CKD and for control proteinuria.

POI1736

Understanding Obesity Management in CKD Patients


Background: Obesity is a global epidemic that is directly and indirectly linked to progression of chronic kidney disease (CKD). Nephrologists’ attitude towards obesity management is not understood.

Methods: We surveyed 14 nephrologists practicing in an academic centre in London, Ontario, Canada to investigate their perception and management of obesity. Then we performed a retrospective chart review of patients in a CKD clinic with obesity (BMI >30kg/m2). Ten follow-up visits were randomly selected for each nephrologist between Jan-Dec 2019. Each chart was assessed for documentation of obesity and a management plan such as lifestyle counselling, pharmacologic intervention, or specialist referral.

Results: There were 13 responses (93%). Responses from a 5-point Likert scale, agree and strongly agree, have been combined. All nephrologists agreed that obesity negatively impacts CKD patients. 92% reported that discussing obesity evokes a negative response and 39% thought patients want to discuss obesity. Interestingly, 0% of nephrologists thought patients know that obesity has effective treatments. 85% of nephrologists talked to their patients about obesity, but 0% felt that they had time to treat it. With regards to management, 54% of nephrologists were comfortable with non-pharmacologic treatment, but only one was comfortable with pharmacologic treatments. 85% of respondents felt that patients should be referred to a specialist. A total of 140 charts were reviewed with a mean age 66 years, weight 105 kg, and BMI 37 kg/m2. Only one chart had obesity as a clinic issue and documented a weight loss discussion using non-pharmacologic strategies.

Conclusions: Our results suggest that obesity is rarely managed despite nephrologists’ desire to treat it. This care gap can be addressed using robust Quality Improvement principles. Our centre will improve obesity management by developing a clinical handbook for nephrologists on how to efficiently address obesity with patients as well as a partnership and streamlined referral process to an obesity specialist.

Funding: Clinical Revenue Support

POI1737

Changes over Time in DASH Diet Accordance by Racial/Ethnic Groups Among US Adults

Tanushree Banerjee,1 Charles E. McCulloch,1 Deidra C. Crews,2 Nilka Rios Burrows,2 Alain Koyama,3 Hal Morgenstern, 4 Rajiv Saran,5 Neil R. Powe.1 1University of California San Francisco, San Francisco, CA; 2Johns Hopkins University, Baltimore, MD; 3Centers for Disease Control and Prevention, Atlanta, GA; 4University of Michigan, Ann Arbor, MI.

Background: Recommendations for healthy dietary patterns may vary for individuals with and without CKD. Racial/ethnic disparities in dietary quality exist, yet there is limited understanding of how dietary patterns have changed over years in different racial/ethnic groups. We examined trends in accordance to a Dietary Approaches to Stop Hypertension (DASH) diet by different racial/ethnic groups in adults with and without CKD.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
POI738

Food Purchasing Patterns Among Participants of a Dietary Intervention Trial for African Americans with Hypertension and CKD


Background: Financial resources and the surrounding food environment can impact healthy food purchasing patterns and may play a role in disparities in CKD. We examined predictors of healthy food purchases among control group participants of a clinical trial who were assigned to receive a $30 per week grocery allowance for 4 months ($480 total) but received no specific guidance on purchases.

Methods: We examined purchasing patterns of 50 participants using receipts linked to a grocery club card. The primary outcome of interest was the number of fresh or frozen fruit or vegetable items purchased, dichotomized at the median to those purchasing <= 6 and > 6 types of fruits/vegetables. Predictors examined included participant sociodemographic factors and food environment factors (i.e. living in a healthy food priority area). Statistical analyses included descriptive statistics and multiple linear regression.

Results: All participants were African American; median age was 63 yrs; 64% were female. Most (78%) were either unemployed or retired; 58% received a H.S. diploma/GED or less. Half had annual income < $25,000. Purchases made included both food and non-food items and many used other funds beyond those from the study. Adjusting for income, women purchased 2.3 more fruit/vegetable items than men (95% CI 0.2-4.5). However, prevalence of poor accordance did not change in NHB and MA with CKD. For MA, a significant change in prevalence was noted among no-CKD (p trend = 0.008), but not in those with CKD.

Conclusions: Poor accordance to a DASH diet was greater in adults with no-CKD. However, prevalence of poor accordance did not change in NHB and MA with CKD. Efforts to further improve promotion and accordance to DASH diets may help address CKD progression and health disparities in the US.

Funding: Other U.S. Government Support

POI1740

Barriers and Facilitators to DASH Diet Adherence Among Black Adults with CKD: A Qualitative Study

Crystal C. Tyson,1 Laura P. Svetkey,1 Isa Granados,1 Danielle L. Kennedy,2 Travia K. Dunbar,1 Pao-Hwa Lin,3 Gary G. Bennett,3 Cynthia H. Redd,3 L. Ebony Boulware,1 Laura J. Fish,3 Duke University School of Medicine, Durham, NC; 2Duke University, Durham, NC; 3Duke Cancer Institute, Durham, NC.

Background: Black individuals are disproportionately burdened by hypertension and chronic kidney disease (CKD). The Dietary Approaches to Stop Hypertension diet (DASH) improves hypertension in Black individuals and is associated with improved CKD outcomes. Yet, adherence to DASH among Black individuals is low. We conducted a qualitative study to assess barriers and facilitators to DASH adherence in Black adults with CKD.

Methods: We conducted focus groups and individual interviews with Black adults with CKD stages 3 or 4 (n=22). Questions included perceptions of CKD and DASH, barriers and facilitators to adopting DASH. Qualitative content analysis was used to analyze interview transcripts.

Results: Among 22 participants (2 focus groups, 8 individual interviews), 13 (59%) had CKD stage 3, 13 (59%) were female, the median age was 61 years, and 19 (90%) had hypertension. Some participants reported having previously heard of DASH, which they perceived as a healthy diet. Participants perceived DASH as culturally-compatible based on 3 emergent themes: 1) Blacks individuals already eat DASH-recommended foods (“Blacks eat pretty much like this”); 2) traditional (e.g., southern or soul-food) recipes can be modified into healthy versions (“you can come up with decent substitutes to make it just as good”); and 3) DASH is not uniform among Black individuals (“I can’t say that I eat traditional”). Barriers included unfamiliarity or inconvenience measuring portion sizes, inadequate cooking skills, unsupportive household members, and high cost of healthy foods. Eleven (52%) reported “rarely” or “never” having leftover money to
purchase healthy food after paying monthly bills. Facilitators included having local access to healthy food, living alone or with supportive household members, and having will power and internal/external motivation for change.

Conclusions: Black adults with CKD were interested in adopting DASH and viewed it as a healthy, culturally-compatible diet. Recognizing that diet in Black adults is not viewed as a healthy, culturally-compatible diet. Recognizing that diet in Black adults is not

Funding: Other NIH Support - NHLBI

POI741

Priorities for Person-Centered Obesity Management in ESKD


Background: Although obesity is a pervasive kidney transplant barrier, little is known about the social, dietary, and process-of-care challenges to addressing obesity among individuals with ESKD.

Methods: Using purposive sampling we recruited adults with ESKD and obesity (N=40) and ESKD health care professionals (HCPs, N=20) in the United States for semi-structured interviews to elicit perspectives about obesity and barriers and strategies for healthy weight loss. Recorded phone interviews lasting 1.5 hours were transcribed verbatim and analyzed using inductive and deductive thematic analysis.

Results: Median patient age was 55 (interquartile range [IQR] 47,63) years, median dialysis exposure was 5 (IQR 3,10) years, 51% were female, 27% were Black, and median BMI was 37.8 (IQR 33.5, 40.8) kg/m². Greater dietary added sugar, total carbohydrate, and carbohydrate to fiber ratio was associated with higher average daily blood sugar (P=0.001, P=0.006, respectively). Each 1-point greater HEI score (healthier eating) was inversely associated with average daily blood sugar for fatty acid (-1.09 mg/dL; 95% CI -2.11, -0.07), added sugar (-1.76 mg/dL; CI -3.11, -0.4), vegetable (-2.85 mg/dL; CI -5.5, -0.2), and fruit (-2.63 mg/dL; CI -5.03, -0.22). HEI total score did not show significant association with the CGM readings.

Conclusions: Greater added sugar, saturated fats, and dietary carbohydrate to fiber ratio are strongly associated with greater average daily blood sugar. Sugar, carbohydrates, and saturated fats contribute to glycemic variability. Healthy eating centered on low sugar, low fat, and high vegetable and fruit intake may improve glycemic control in both diabetic and non-diabetic CKD patients.

Funding: NIDDK Support, Commercial Support - Dialysis Clinics Incorporated

POI743

Late Stage 3 CKD Is an Independent Risk Factor for Sarcopenia, but Not Proteinuria

Yong Seon Choi, Jung Nam An, Jwa-kyung Kim, Sung gyun Kim, Young rim Song. Hallym University Sacred Heart Hospital, Anyang, Gyeonggi-do, Republic of Korea.

Background: Most epidemiologic studies assessing the relationship between chronic kidney disease (CKD) and sarcopenia have been performed in dialysis patients. This study aimed to evaluate the relationship between estimated glomerular filtration rate (eGFR), proteinuria, and sarcopenia in patients with non-dialysis-dependent CKD.

Methods: A total of 892 outpatients who did not show any rapid changes in renal function were enrolled in this observational cohort study. We measured the muscle mass using bioimpedance analysis and handgrip strength (HGS), and sarcopenia was defined as low HGS and low muscle mass.

Results: Sarcopenia was found in 28.1% of the patients and its prevalence decreased as body mass index (BMI) increased; however, in patients with BMI ≥ 23 kg/m², the prevalence did not increase with BMI. As eGFR decreased, the lean tissue index and HGS significantly decreased. However, the eGFR did not affect the fat tissue index. The risk of sarcopenia increased approximately 1.6 times in patients with eGFR < 45 mL/min/1.73 m². However, proteinuria was not associated with sarcopenia. With a decrease in eGFR, the lean muscle mass and muscle strength decreased, and the prevalence of sarcopenia increased.

Conclusions: In patients with late stage 3 CKD, further assessment of body composition and screening for sarcopenia may be needed.

POI742

Association of Nutritional Data and Glycemic Variability in CKD Patients

Nandakishor Kapa, Harshanna Badheshha, Tae Youn Kim, Olivia A. Moss, Chenroa R. Vargas, Seung M. Jin, Henning Langer, Usman Rehman, Jennifer E. Norman, Armin Ahmad, Thomas Jue, Maryam Afkarian, Baback Roshanravan. University of California Davis Medical Center, Sacramento, CA.

Background: Insulin resistance is highly prevalent in chronic kidney disease (CKD) and strongly associated with adverse clinical outcomes. Glycemic variability measured by continuous glucose monitoring (CGM) is a clinical measure of insulin resistance. The association of dietary recalls and healthy eating measures with CGM readings in CKD are unknown.

Methods: We recruited diabetic (n=7) and non-diabetic (n=8) participants with eGFR=60mL/min who had CGM performed over 2 weeks. The ASA24 Dietary Assessment Tool was used to perform dietary recalls on 3 random days over the CGM period. The Healthy Eating Index 2015 (HEI-2015) was used to determine how closely an individual’s eating pattern matched Dietary Guidelines for Americans’ recommendations. A linear mixed model adjusting for diabetes status was used to determine association of dietary measures from ASA24, HEI-2015 scores, and CGM readings over 3 days.

Results: Participants had a mean age 59±11years, eGFR 35.5±4.6mL/min/1.73m² and BMI 32±6kg/m². Greater dietary added sugar, total carbohydrate, and carbohydrate to fiber ratio was associated with higher average daily blood sugar (P=0.001, P=0.006, respectively). Each 1-point greater HEI score (healthier eating) was inversely associated with average daily blood sugar for fatty acid (-1.09 mg/dL; 95% CI -2.11, -0.07), added sugar (-1.76 mg/dL; CI -3.11, -0.4), vegetable (-2.85 mg/dL; CI -5.5, -0.2), and fruit (-2.63 mg/dL; CI -5.03, -0.22). HEI total score did not show significant association with the CGM readings.

Conclusions: Greater added sugar, saturated fats, and dietary carbohydrate to fiber ratio are strongly associated with greater average daily blood sugar. Sugar, carbohydrates, and saturated fats contribute to glycemic variability. Healthy eating centered on low sugar, low fat, and high vegetable and fruit intake may improve glycemic control in both diabetic and non-diabetic CKD patients.

Funding: NIDDK Support, Commercial Support - Dialysis Clinics Incorporated

HEI-2015 Scores Associated with CGM in Non-Diabetic and Diabetic CKD Patients

<table>
<thead>
<tr>
<th>HEI-2015 Score (%)</th>
<th>Average daily blood sugar (mg/dL)</th>
<th>Glycemic variability (% of time above target)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEI Fatty Acid</td>
<td>-1.09 (-2.11, -0.07)</td>
<td>-0.38 (&lt;1.85%, 0.63)</td>
</tr>
<tr>
<td>HEI Added Sugar</td>
<td>-1.76 (-3.11, -0.4)</td>
<td>-1.11 (&lt;2.4, -0.47)</td>
</tr>
<tr>
<td>HEI Total Carbohydrate</td>
<td>-2.95 (-5.3, -0.2)</td>
<td>-1.18 (&lt;3.4, 0.46)</td>
</tr>
<tr>
<td>HEI Total Fat</td>
<td>-2.63 (-5.03, -0.22)</td>
<td>-1.39 (&lt;3.2, -0.59)</td>
</tr>
</tbody>
</table>

POI744

Association of Serum Selenium Levels with the Response to Erythropoiesis-Stimulating Agents in Maintenance Hemodialysis Patients

Minoru Yasukawa, Shigeyuki Ariai, Michito Nagura, Daigoro Hirohama, Osamu Yamazaki, Yoshifuru Tamura, Yoshihide Fujigaki, Shigeru Shibata, Teikyo Daigaku Igakuka Daigakuin Igaku Kenkyuka, Ibarashi-ku, Japan.

Background: Reduced response to erythropoiesis-stimulating agent (ESA) has been shown to be associated with poor outcomes in maintenance hemodialysis (MHD) patients. Selenium is a trace element that modulates diverse physiological processes, such as immune responses and cardiovascular function. Previous studies also indicate that selenium and selenoproteins are involved in erythropoiesis. However, its role in the control of anemia in chronic kidney disease patients remains unclear. In this study, we determined serum selenium levels in MHD patients and analyzed their association with hemoglobin levels and the doses of ESA.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: The study included 174 patients who received MHD from four dialysis facilities. We obtained data on demographics, laboratory, comorbidities, hemodialysis prescription and medication by medical record abstraction. Concentration of selenium was measured in serum using ICP-MS.

Results: The mean age was 67.2 years, 77% were male, and 44% of patients received dialysis at least for five years. The average serum selenium concentrations in our cohort were 10.7 ± 2.9 µg/dL, and 88 patients (51%) had a selenium levels of less than 10.5 µg/dL (a lower limit of normal serum selenium levels for adult Japanese population). Patient characteristics, including age, sex, BMI, dialysis vintage, and comorbidities were not significantly different between the low selenium (Low) group and normal selenium (Normal) group. However, the percentage of patients receiving ESA tended to be higher in Low group than in Normal group, whereas hemoglobin levels as well as percentage of patients receiving iron therapy were similar between the groups. In a subgroup analysis involving 146 patients who received ESA, we found a significant negative correlation between serum selenium levels and ESA-resistance index (ERI) (r = -0.25, p = 0.002).

Conclusions: Our study indicates that low levels of serum selenium are associated with poor response to ESA. The relationship between selenium and response to ESA in MHD patients merits further evaluation in larger populations.

PO1745
Serum Irisin and Prediction of Cardiovascular Events in Elderly Patients with CKD Stage 3-5
Teresa Del Mastro, Teresa Arcidiacono, Monica Avino, Arianna Bologna, Nadia Edvige Folligno, Federico Persico, Giuseppe Vezzoli. IRCCS Ospedale San Raffaele, Milano, Italy.

Background: Irisin is a circulating myokine released from skeletal muscles after physical exercise. Irisin production decreases during the course of chronic kidney disease (CKD) as a potential consequence of sarcopenia and physical inactivity.

Methods: This observational study explored the relationship of serum irisin with cardiovascular outcome in 79 patients with stage 3-5 CKD.

Results: Serum irisin was significantly higher in healthy subjects (n=20) than CKD patients (7.2 ± 3.1 ± 0.9 µg/ml; p=0.0001) and was higher in patients with CKD stage 3 (3.2 ± 0.2 µg/ml) compared with patients at stage 4 and 5 taken together (n=36, 2.6 ± 0.7 µg/ml; p=0.05). Patients in the lowest serum irisin tertile had lower serum 1,25(OH)D levels (21.6±11.8 pg/ml) than patients in the middle (30.2±13 pg/ml; p=0.005) and the highest tertile (27±14 pg/ml; p=0.047). Patients in the highest irisin tertile had lower Kauppila score (10.6±6.9) than patients in the middle (11.8±5.5; p=0.007) and the lowest tertile (6.9±6.8; p=0.03). Twenty patients suffered from cardiovascular events during a 3-year follow-up. A Cox regression model using age, body weight, presence of diabetes mellitus, gender, Kauppila calcification score, serum values of FGF23 (as logarithm), phosphate, sclerostin, albumin and cholesterol, eGFR and serum irisin tertiles as covariates showed that patients in the highest tertile of serum irisin had a lower cardiovascular risk than patients in the middle tertile (B 1.61, OR 5.1, 95% CI 1.09-22.83; p=0.038).

Conclusions: These findings suggest that serum irisin may be a marker of cardiovascular outcome in CKD patients.

PO1746
Deoxycholic Acid (DCA) and Cognitive Impairment and Decline in the Chronic Renal Insufficiency Cohort (CRIC) Study
Kristen L. Nowak,1 Makoto Miyazaki,2 Michel Chonchol,3 Anand Srivastava,2 Michael J. Fischer,4 Ana C. Ricardo,5 Jiang He,4 Katherine T. Mills,4 Katherine L. Wolfrum,5 Amanda H. Anderson,2 Manjula Kurella Tamura,5 Harold I. Feldman,5 Tamara Isakova,2 Anna Jovanovich,2 1University of Colorado Health, Aurora, CO; 2Northwestern University Feinberg School of Medicine, Chicago, IL; 3University of Illinois at Chicago, Chicago, IL; 4Tulane University, New Orleans, LA; 5University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; 6Standford University, Palo Alto, CA; 7VA Eastern Colorado Health Care System, Aurora, CO.

Background: Cognitive impairment is common in chronic kidney disease (CKD). The secondary bile acid, DCA, is associated with endothelial dysfunction and oxidative stress, characteristics of cognitive impairment. DCA is also associated with cognitive impairment and risk of Alzheimer’s dementia among older adults without CKD. Whether DCA is associated with cognitive impairment in CKD is unknown.

Methods: We used multivariable-adjusted regression models to cross-sectionally and longitudinally evaluate the association between fasting serum DCA levels measured at visit 5 (considered baseline) and cognitive impairment. Among 2836 CRIC Study participants, cognitive impairment was assessed by the Mini-mental State Exam (MMSE). Among 698 participants enrolled in the CRIC Cognitive (COG) Study, cognitive impairment was further assessed by Trails A&B, Category Fluency, Buschke Recall, and Boston Naming tests. Cognitive impairment was defined by a test score ≥1 standard deviation (SD) worse than the test mean.

Results: Mean age was 59 ± 10 years, 45% were female, and 39% were black. In cross-sectional analyses, there was no association between DCA and cognitive impairment assessed by MMSE in the total cohort after adjustment for demographics and clinical factors (prevalence ratio per 1-SD increase ln DCA: 1.03, 95% CI 0.91-1.17). In longitudinal analyses, DCA was associated with progressive impairment (mean annual % change MMSE per 1-SD increase in DCA: -0.15, 95% CI -0.34 - -0.02), but not with incident impairment. Among CRIC COG Study participants, cross-sectional analyses DCA was associated with cognitive impairment based on Category Fluency (prevalence ratio per 1-SD increase in DCA: 1.36, 95% CI 1.05-1.76) but not with other measures of impairment. In longitudinal analyses among CRIC COG Study participants, DCA was not associated with progressive or incident cognitive impairment.

Conclusions: Among individuals with CKD stages 2-4, higher DCA levels were independently associated with prevalent cognitive impairment in Category Fluency and progressive cognitive impairment assessed by MMSE.

Funding: NIDDK Support, Veterans Affairs Support

PO1747
The Association of Sodium Intake and Albuminuria According to Cotinine-Verified Smoking Status: Korean National Health Examination Survey (KoNHEs)
Young-Bin Sung, Tae-bum Kim, Hyeon-Jin Min, Jonghyun Lee, Jiyang Yoon, Myung-Gyu Son, Park Hyun-Kyung, Won-Young Cho, Sewon Oh. Division of Nephrology, Department of Internal Medicine, Korea University Annyang Medical Center Korea University Medical Center, Seoul, Republic of Korea.

Background: Smoking and high sodium intake are reported to be associated with chronic kidney disease. Smoking and sodium intake are modifiable risk factors and the implementation of life style changes in the broad population could have a beneficial effect on public health. We assessed the association of sodium intake and smoking on the presence of albuminuria.

Methods: An observational study from the Korean National Health and Nutrition Examination Survey (2008-2011, 2014-2018) was performed. We included 38,161 adults with eGFR≥60 ml/min/1.73m2 and had urine cotinine/creatinine ratio (UCot/Ucrea). Smoking status was assumed by Ucot/Ucrea. 24 hour sodium intake was estimated from spot urine sodium using Kawasaki formula. Albuminuria was defined as urine albumin creatinine ratio a 30mg/g.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only 
Underline represents presenting author.
Results: Ucot/Ucrea level was significantly higher in current smokers than those in ex-smokers or non-smokers (CA: 0.00; 0.01; 0.046; vs. 0.23; 0.01; P = 0.001). Ucot/Ucrea level was significantly associated with sodium intake. Sodium intake of 2nd and 3rd Ucot/Ucrea tertile were significantly higher than that of 1st Ucot/Ucrea tertile (4.15±1.31, 4.13±1.43 vs. 3.73±1.15 mg; P < 0.001). The quartile groups of sodium intake had a linear relationship with albuminuria (5.2, 5.8, 7.5, and 9.7%, P < 0.001). The highest quartile of sodium intake was significantly associated with risk of albuminuria (OR 1.43, 95% CI 1.05-1.93, P = 0.022). We evaluated the association of sodium intake with albuminuria according to smoking status estimated by Ucot/Ucrea. In the group with the highest Ucot/Ucrea level, the highest sodium intake was significantly associated with risk of albuminuria (OR 1.62, 95% CI 1.23-2.14, P = 0.001). The highest quartile of sodium intake was significantly higher than that of other quartiles 2nd, 3rd, and 4th were 0.83 (95% confidence interval [CI], 0.75-0.91), 0.76 (95% CI, 0.68-0.84) and 0.80 (95% CI, 0.72-0.88), respectively. Restricted cubic spline regression also found a U-shaped relationship between total body water and all-cause mortality. In the correlation analysis, as the water intake increased, the total body water amount measured by BIA increased. Additionally, participants showed lower mortality rates as the total amount of water in the body was higher (1st vs. 2nd aHR 0.928 [95% CI, 0.622-1.384] and 1st vs. 3rd aHR 0.542 [95% CI, 0.315-0.933]).

Conclusion: In the general population, too little water in the body and water intake are associated with increased mortality. It is important to maintain adequate hydration status through adequate water consumption.

PO1750

Serum Cystatin C-to-Creatinine Ratio Is a Potential Biomarker for Sarcopenia in Patients with Non-Dialysis-Dependent CKD

Ileen Cho, Yong Seon Choi, Jung Nam An, Sung gun Kim, Young rim Song, HaHyun University Sacred Heart Hospital, Anyang, Gyeonggi-do, Republic of Korea.

Background: Sarcopenia is a prevalent complication in patients with chronic kidney disease (CKD) and linked with quality of life, morbidity and mortality. Sarcopenia is defined as both a biological, functional and body composition parameters, although several candidate biomarkers for this condition have been evaluated. This study aimed to evaluate serum cystatin C to creatinine (Cr) ratio as a potential biomarker for sarcopenia in patients with non-dialysis-dependent CKD.

Methods: A total of 517 outpatients were enrolled in this observational cohort study. We measured the muscle mass (lean tissue index, LTI) using bioimpedance analysis and handgrip strength (HGS), and sarcopenia was defined as low HGS and low muscle mass.

Results: Sarcopenia was observed in 25.5% patients. The serum cystatin C/Cr ratio was significantly higher in patients with sarcopenia regardless of age, sex, eGFR, and BMI and showed a positive correlation with age and pulse pressure, but LTI, HGS, hemoglobin, and serum albumin level showed a negative correlation with serum cystatin C/Cr ratio. Especially in patients with eGFR ≥ 45 mL/min/1.73 m², serum cystatin C/Cr ratio showed high negative predictive value in predicting sarcopenia (90.5%) and low LTI (90.4%). As the serum cystatin C/Cr ratio increased by 1, the prevalence rate of sarcopenia and low LTI increased by about 5.8 times and about 9.9 times even after adjusting for sex, age, BMI, underlying disease, albumin, Hb, and eGFR. The association between serum cystatin C/Cr ratio and sarcopenia was maximized in patients with eGFR less than 30, resulting in an increased prevalence rate of about 22.7 times, and in the case of low LTI, an independent association was found in patients with eGFR less than 45, and among them, a 43.9-fold increase in risk was identified. However, there was also no significant result for low HGS.

Conclusions: Serum cystatin C/Cr ratio is inexpensive and easily, quickly, and repeatedly measured; therefore, quick screening and management of sarcopenia will be possible, which will be of great help in the treatment of CKD patients.

PO1751

Prevalence of Inflammation and Associated Healthcare Resource Utilization in Patients with CKD

Rachel Lai,1 Lynda Szczec,1 Sarah Clayton,2 Lewis Harrison,2 Mollie Lowe,2 James Jackson.2 Fibrogen Inc, San Francisco, CA; 2Adelphi Group Ltd, Bollington, United Kingdom.

Background: Many patients with chronic kidney disease (CKD) suffer from inflammation, which often increases as CKD progresses. Inflammation is a risk factor for cardiorenal complications and complications related to treatment of anemia, but CKD inflammation has been associated with reduced red blood cell and erythropoietin production, as well as increased hepcidin levels, which can lead to functional iron deficiency. Because data on the impact of inflammation on healthcare utilization (HCRU) in patients with CKD is limited, we aimed to assess HCRU in these patients.

Methods: Data were drawn from the Adelphi CKD Disease Specific Programme™, a point-in-time survey of physicians and their patients with CKD (stage 3–5D) collected in the United States in 2018. Physician and patient reported HCRU-related information, including the mean number of healthcare visits, tests conducted, and payments conducted to diagnose and monitor patients. Inflammation was defined as C-reactive protein ≥ 4 mg/L, ferritin ≥ 700 ng/mL, or albumin ≤ 3.6 g/L. Fisher’s exact and t-tests were conducted to assess differences in HCRU between patients with and without inflammation.

Results: There were 2,536 patients with CKD and of these, inflammation was present in 136/491 (28%) non-dialysis-dependent, and 91/212 (43%) dialysis-dependent patients. HCRU, including the mean number of healthcare visits, tests conducted, and hospitalizations in the last 12 months, number of pills and injections taken per day, and amount of missing data if requiring a carer were greater in patients with inflammation vs those without (all p < 0.05; Table 1).

Key: TH – Thursday; FR – Friday; SA – Saturday; OR – Oral; PO – Poster; PUB – Publication Only

Underline represents presenting author.
Conclusions: We found that inflammation was common in patients with CKD and associated with greater HCRU across multiple measures in a real-world setting. Novel treatment approaches in CKD that are effective in patients with inflammation may help to reduce HCRU.

Funding: Commercial Support - FibroGen Inc

Table 1: Comparison of HCRU between patients with and without microalbuminuria.

<table>
<thead>
<tr>
<th>Group</th>
<th>HCRU (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without MA</td>
<td>75</td>
</tr>
<tr>
<td>With MA</td>
<td>80</td>
</tr>
</tbody>
</table>

Methods: We identified patients with diabetes who initiated SGLT2i (n=925), GLP1RA (n=400), dipeptidyl peptidase-4 inhibitors (DPP4i, n=1190), or sulfonylureas (SU, n=3285) between 2015 and 2018 in Geisinger Health System. Outcomes were percent weight change per year among all patients within 1 year after medication initiation and time to first achieving 5% weight loss among patients with overweight/obesity at medication initiation. Inverse probability of treatment weighting (IPTW) based on multinomial propensity scores was used to account for differences in baseline patient characteristics by medication class.

Results: The mean (SD) age of the 6919 patients was 58 (14) years and 3381 (49%) were females. Compared with SU, SGLT2i, GLP1RA, and DPP4i were associated with significant weight loss, with stronger associations for SGLT2i and GLP1RA (Table). Similarly, SGLT2i, GLP1RA, and DPP4i users were more likely to achieve 5% weight loss compared with SU (HR [95% CI]: 1.47 [1.28, 1.69] for SGLT2i; HR: 1.55 [1.32,1.82] for GLP1; HR: 1.31 [1.19,1.44] for DPP4). The associations were consistent across CKD stages.

Conclusions: In patients with and without CKD, SGLT2i and GLP1RA were associated with significant weight loss compared with SU. These results may further motivate uptake of SGLT2i and GLP1RA, two classes of medications with proven renal benefits among patients with overweight or obesity.

Funding: NIDDK Support

Percent weight change (%/year) within 1 year associated with diabetes medications

Table 2: Effect of SGLT2i and GLP1RA on weight change.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Weight Change (%/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT2i</td>
<td>-3.2</td>
</tr>
<tr>
<td>GLP1RA</td>
<td>-2.9</td>
</tr>
</tbody>
</table>

PO1752

Effects of Home BP-Based Behavioral Guidance on Urinary Albumin Excretion in School Workers with Microalbuminuria - Masanori Karoshi

Background: Prevention of work-related cardiovascular events, or Karoshi is an important social issue in Japan. This study aimed to examine if home-BP based behavioral guidance is effective to reduce CV event risk in school staffs associated with microalbuminuria, a marker of endothelial damage.

Methods: Subjects were 3868 Miyagi prefectural school workers. Urinary albumin excretion adjusted for creatinine (UAE) and daily sodium intake based on Tanaka method was examined together with usual annual health check-up in 2019. Among them, 169 were diagnosed as having microalbuminuria (30-299.9mg/gCr). Ninety-one subjects agreed to receive the home-BP based health guidance. Guidance was given according to 5 days mean of home BP measurements, or encouraging medical consultation and lifestyle guidance for subjects with 125-134/80-84mmHg and adequate lifestyle guidance for subjects <125/80mmHg if necessary. Outcomes were UAE and frequency of microalbuminuria in the next year. Data were compared between guided and non-guided subjects. Subjects with menstruation were excluded from analysis. Final analysis number was 48 and 43 for guided and non-guided groups.

Results: Guided group demonstrated similar baseline data as compared with non-guided group for age, male gender, body mass index, cardiovascular risk factors and UAE level. Prescription rate for hypertension and diabetes also was similar between them. LogUAE was significantly and similarly decreased in both groups. One year later, microalbuminuria was present in 31.2% for guided group and 30.2% for non-guided group for age, male gender, body mass index, cardiovascular risk factors and UAE level.

Conclusions: Reduction in UAE did not differ between groups with or without home-BP based behavioral guidance. Our data suggest that notification of microalbuminuria per se have considerable degree of favorable behavioral effects in school workers with microalbuminuria.

Funding: Government Support - Non-U.S.

PO1753

Weight Changes Following Diabetes Medication: A Population-Based Study - Beini Lyu

Background: The majority of patients with type 2 diabetes are obese, with greater percentages in those with concomitant CKD. Clinical trials suggest that the newer glucose-lowering medications, including sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor antagonists (GLP1), provide an added benefit of weight loss in people with type 2 diabetes. We evaluated the magnitude of weight change associated with diabetes medication prescription in real-world practice in persons with and without CKD (eGFR <60 vs. ≥60 ml/kg/1.73 m²).

Methods: Of a cohort of 111 participants who were randomized, 99 had baseline ccf-mtDNA levels, and 92 completed the study. The median age was 57 years old, 44% were female, and 92% had diabetes. Plasma ccf-mtDNA median concentrations at baseline, two, and four months were 3.62, 3.08, 2.78 pm for the usual activity group, and 2.01, 2.20, 2.67 pm for the aerobic exercise group. There was a 16.1% increase per month in ccf-mtDNA in the aerobic exercise group compared to the usual activity group (p = 0.024), especially with the combination of aerobic exercise and caloric restriction (29.5% increase per month). After four months of intervention, ccf-mtDNA increased in the aerobic exercise group by 81.6% (95% confidence intervals [CI] 8.2-204.8; p = 0.024) compared to the usual activity group, but it was only observed in the aerobic exercise and caloric restriction group (181.7% increase, 95% CI 41.1-462.2; p = 0.003).

Conclusions: Our data suggest that aerobic exercise increases plasma ccf-mtDNA levels in patients with CKD stages 3-4, more profoundly in ones with a combination of caloric restriction.

Funding: NIDDK Support, Other NIH Support - NHLBI, NEIHS, NCATS

PO1754

Effects of Caloric Restriction and Aerobic Exercise on Circulating Cell-Free Mitochondrial DNA in Patients with Moderate-to-Severe CKD: A Pilot Study - Javier Jaramillo Morales

Background: Understanding mechanisms for increased oxidative stress and inflammation in patients with chronic kidney disease (CKD) is vital due to their role in the pathophysiology of this population. Circulating cell-free mitochondrial DNA (ccf-mtDNA) is released to the plasma as a damaged-associated molecular pattern. Previous studies suggested that in patients with kidney disease, ccf-mtDNA increases and may induce inflammation. Past investigations in patients with CKD have found that aerobic exercise decreases inflammation. We hypothesized that in patients with moderate to severe CKD, aerobic exercise would reduce plasma levels of ccf-mtDNA.

Methods: We performed a post hoc analysis of a multi-center pilot randomized trial of aerobic exercise and caloric restriction (NCT01150851). We measured ccf-mtDNA in plasma at baseline and two and four months after four interventions (aerobic exercise (EX), caloric restriction (CR), EX + CR, usual activity and usual diet). A multivariable model adjusted for age, race, sex, systolic BP, BMI, diabetes, and eGFR was done.

Results: Of a cohort of 111 participants who were randomized, 99 had baseline ccf-mtDNA levels, and 92 completed the study. The median age was 57 years old, 44% were female, and 92% had diabetes. Plasma ccf-mtDNA median concentrations at baseline, two, and four months were 3.62, 3.08, 2.78 pm for the usual activity group, and 2.01, 2.20, 2.67 pm for the aerobic exercise group. There was a 16.1% increase per month in ccf-mtDNA in the aerobic exercise group compared to the usual activity group (p = 0.024), especially with the combination of aerobic exercise and caloric restriction (29.5% increase per month). After four months of intervention, ccf-mtDNA increased in the aerobic exercise group by 81.6% (95% confidence intervals [CI] 8.2-204.8; p = 0.024) compared to the usual activity group, but it was only observed in the aerobic exercise and caloric restriction group (181.7% increase, 95% CI 41.1-462.2; p = 0.003).

Conclusions: Our data suggest that aerobic exercise increases plasma ccf-mtDNA levels in patients with CKD stages 3-4, more profoundly in ones with a combination of caloric restriction.

Funding: NIDDK Support, Other NIH Support - NHLBI, NEIHS, NCATS
PO1756

Physical Activity Scores in Hemodialysis Patients with Thyroid Dysfunction: A Substudy of the NIH THYROID-HD Trial
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Background: Low physical activity is common in hemodialysis (HD) patients and is associated with adverse outcomes in this population (poor health-related quality of life, cardiovascular [CV] disease, death). Prior studies show that hypothyroidism is highly prevalent in HD patients, and is associated with worse self-reported physical function.

Methods: In a substudy of the ongoing multi-center NIH THYROID-HD Trial, we examined baseline physical activity scores determined by the Human Activity Profile (HAP), a validated 94-item instrument assessing daily activities across a wide range of energy expenditures, in HD patients with TSH levels in the high-normal (TSH >3-5 mIU/L) and subclinical hypothyroid range (TSH >5-10 mIU/L). The HAP was used to derive the Maximum Activity Score (MAS) and Adjusted Activity Score (AAS), representing greatest and mean estimated energy expenditures, respectively (range 0-94, segmented to low [<52], moderate [54-73], and high [>74] scores).

Results: Among 57 HD patients who underwent baseline HAP assessment, the mean±SD MAS and AAS scores were 52±21 and 26±27, respectively; median (IQR) MAS and AAS scores were 52 (40, 68) and 22 (0, 49), respectively. In the overall cohort, 79% had low, 14% moderate, and 7% high AAS scores. MAS scores were lower in patients who were older (>65 yrs), female, White, Hispanic, of longer (>1 yr) vintage, diabetic, or with underlying CV disease. A similar trend was observed for AAS scores.

Conclusions: In this substudy of the NIH THYROID-HD Trial, HAP scores in HD patients with high-normal and subclinical hypothyroid range TSH levels were lower than observed in prior historical dialysis cohorts that did not have underlying thyroid dysfunction. Further research is needed to determine the impact of thyroid hormone replacement on improving physical activity and function in this population.

Funding: NIDDK Support

PO1757

In Vivo Muscle Mitochondrial Function Is Associated with Exercise Capacity and Efficiency in CKD
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Background: CKD is associated with skeletal muscle dysfunction increasing risk for frailty. Muscle mitochondrial dysfunction may underlie impaired physical performance. The associations of in vivo muscle mitochondrial function with exercise capacity and efficiency in CKD is unknown.

Methods: We recruited 8 diabetic and 6 non-diabetic patients with CKD. Leg muscle mitochondrial oxidative capacity was measured by exercise recovery kinetics of [PCr] using 31P Magnetic Resonance Spectroscopy (31P MRS). Cardiorespiratory fitness (CRF, VO2 peak), total work, and work efficiency (total work/VO2peak) were assessed by cycle ergometry. We tested associations of 31P MRS measures with endpoints using Pearson correlations.

Results: Participants had a mean age was 61±10yrs, eGFR of 35±12ml/min with 43% females. Faster PCr recovery rate correlated with VO2 peak (r=0.58, p=0.03), total work (r=0.70, p=0.03) and work efficiency (r=0.59, p=0.03) (Figure). Associations of PCr recovery with work and work efficiency were independent of age, sex, and weight (both p>0.03).

Conclusions: Muscle mitochondrial oxidative capacity is a major determinant of exercise efficiency and capacity. Therapeutics targeting muscle mitochondrial function in CKD may improve physical performance and CRF.

Funding: NIDDK Support, Other NIH Support - DCI - Dialysis Clinics Incorporated
PO1758
Comparisons of In-Clinic and Free-Living Measures of Physical Function in Predicting Hospitalization in Patients with CKD
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Background: Physical function is associated with risk of hospitalization; however, comparisons of in-clinic and free-living measures of physical function and their associations with risk of hospitalization has not been well established.

Methods: In this secondary analysis of the Sit Less, Interact, Move More (SLIMM) pilot study, we compared in clinic and free-living measures using accelerometry data. Participants with CKD were randomized to the SLIMM intervention or standard of care and asked to wear a thigh worn accelerometer 7 days before a visit to capture their physical activity. In clinic measures of physical function like 6-minute walk distance were performed during visits. Free-living measures were determined from accelerometry.

Results: 106 participants were randomized, the mean age was 69 ± 12 and 69 ± 14, baseline eGFR was 44 ± 12 and 45 ± 14, and 48% and 37% were female for the standard of care and SLIMM groups respectively. When adjusted for covariates, both in clinic and free-living 6-minute walk distance and steps respectively were associated with hospitalizations (table). In comparisons between in clinic and free-living measures, in clinic measures were not significantly associated with hospitalizations while free-living measures were (table).

Conclusions: Both in clinic and free-living measures of physical function were predictors of hospitalization in patients with CKD.

Funding: NIDDK Support, Other NIH Support - NHLBI, Veterans Affairs Support

Adjusted cox proportional hazard model for hospitalization in in clinic and free-living 6-minute walk.

PO1759
Blood Pressure Trends in a Cohort of 9- and 10-Year-Old Children in Iceland: A 10-Year Follow-Up Study
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Background: Although there is significant evidence for an association between childhood and adult office blood pressure (BP), data on the correlation of childhood BP and ambulatory BP (ABP) in young adults are missing. The aim of this study was to examine the association between childhood office BP and both ABP and office BP indices in young adults.

Methods: Subjects were recruited from a cohort of 970 young adults aged 20-21 years who participated in a population-based study of BP in 9-10-year-old Icelandic school children. All participants underwent a minimum of 4 resting BP measurements at the childhood BP screening. A total of 121 individuals have completed their participation in the follow-up study, which included office and ambulatory BP measurements. Pearson correlation and linear regression analysis were used to examine the relationship between childhood and follow-up BP.

Results: A significant positive correlation was observed between childhood mean systolic BP (SBP) and systolic office and ambulatory BP at follow-up (r = 0.386, p < 0.001 and r = 0.370, p < 0.001, respectively). The correlation between mean childhood mean systolic office BP and follow-up mean systolic office BP was stronger for males (r = 0.50, p < 0.001) than for females (r = 0.298, p = 0.012), and the same applied for mean systolic ABP (r = 0.491, p < 0.001 and r = 0.323, p = 0.006, respectively). The correlation of mean childhood diastolic office BP and follow-up with mean DBP was insigniﬁcant for males (office DBP: r = 0.278, p = 0.055) but remained signiﬁcant for females (office DBP: r = 0.355, p = 0.0026; ABP: r = 0.449, p = 0.001). In adjusted analysis, childhood mean office SBP signiﬁcantly associated with mean ofﬁce SBP at follow-up in both males (beta = 0.69, p < 0.001) and females (beta = 0.26, p < 0.001). Each mmHg increment in mean childhood SBP predicted an increase of mean ambulatory SBP by 0.52 mmHg (p < 0.001), unaffected by sex. Childhood DBP did not significantly predict office or ambulatory BP at follow-up in adjusted analysis.

Conclusions: These preliminary results indicate that childhood SBP significantly predicts both systolic office and ambulatory SBP in young adults and these associations are stronger in males.

Funding: Government Support - Non-U.S.
PO1762
Clinical Event Reductions in Hypertension Patients with and Without CKD Treated with Renal Denervation: A Model-Based Estimate Based on Data from the Global SYMPLECTIC Registry

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Background: Estimates of clinical event reductions following renal denervation (RDN) were modelled for patients with and without chronic kidney disease (CKD) based on the RDN study data of the Global SYMPLECTIC Registry (GSR). Methods: GSR had 1,860 patients, 630 of whom had G3a CKD (eGFR<60 ml/min/1.73m²; n=630) and No CKD (eGFR ≥ 60 ml/min/1.73m²; n=1,860) cohorts of the GSR were analyzed. Reductions in office systolic blood pressure (oSBP) at 6, 12, 24, and 36 months follow-up were averaged and relative risks (RR) for death, cardiovascular (CV) death, myocardial infarction (MI), stroke, and new-onset end-stage renal disease (ESRD) were obtained from published meta-regression analysis of randomized trials of blood pressure lowering in hypertensive patients. Using the derived RRs, clinical event estimates for maintained baseline oSBP were calculated, facilitating estimation of 36-month absolute event reductions and resulting numbers needed to treat (NNT) for the individual endpoints. Results: Baseline oSBP and oSBP reductions for the CKD and No CKD cohorts were 163.6 ± 25.7, 11.1 and 166.7 ± 24.6; 135.2 mmHg, respectively. RR from 0.6% for death to 0.9 to 0.9 for death in the CKD cohort. The stroke, a numerically higher absolute reduction in major adverse cardiovascular events (MACE: composite of CV death, MI and stroke) within 3 years of RDN treatment in the CKD vs. No CKD patients (4.0% vs. 3.2%, p=0.12), in part due to higher overall 3-year MACCE rates observed in CKD patients (18.8% vs. 11.7%, p<0.001) (Table).

Conclusions: Model-based projections provide a directional estimate of the potential clinical event reductions following RDN treatment and suggest clinically meaningful risk reduction in patients with and without CKD.

Funding: Commercial Support - Medtronic

 Observed and projected events for the CKD and No CKD cohorts

BL: baseline; 36M: 36 months

PO1763
Achievement of Blood Pressure Target and Risk of Major Adverse Cardiovascular and Cerebrovascular Events in Patients with Metabolic Syndrome

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Background: Metabolic syndrome (MetS) is closely related to adversely cardiovascular morbidities and mortality. Among the components of MetS, controlling the hypertension might provide the highest yield in reducing major cerebro- and cardiovascular events (MACCE). Hence, we aimed to investigate the impact of control of hypertension on the development of MACCE and all-cause mortality according to the presence of MetS.

Methods: We performed a nationwide population-based study using the national health insurance database of South Korea. Among 2,998,127 subjects with hypertension who received more than 3 times national health screenings 2003 to 2011, a total of 1,920,601 subjects were included in the study. The study group was divided by the presence of the MetS and the degree of control of blood pressure (BP), 1) intensive well-controlled (well-C) (SBP <120 and DBP <70), 2) standard well-controlled (SBP 120-130 and DBP 80-89), 3) uncontrolled subgroup 1 (U-S1) (SBP 130-159 or DBP 80-99), and 4) uncontrolled subgroup 2 (U-S2) (SBP ≥ 160 or DBP ≥100). The main study outcome was all-cause mortality and composite MACCE. The study outcomes were investigated using multivariable Cox-regression analysis after adjusting for clinical variables.

Results: There were 945,243 (49.2%) subjects with 2 or more components of MetS. Among them, 142,991, 179,041, 562,725, and 60,486 subjects were grouped in the well-C intensive, well-C standard, U-S1, and U-S2, respectively. Compared to the well-C standard group, both intensively controlled group (hazard ratio [HR]: 1.123, 95% confidence interval [95% CI]: 1.062-1.186) and uncontrolled group (HR: 1.106; 95% CI: 1.015-1.216) in U-S2 group was associated with increased risk of composite MACCE. In addition, the risk of all-cause mortality in subjects with MetS was increased in well-C intensive group (HR: 1.197; 95% CI: 1.143-1.254) and U-S2 group (HR: 1.211; 95% CI: 1.121-1.386), compared to the well-C standard group.

Conclusions: Uncontrolled hypertension increased risk for MACCE and all-cause mortality in patients with or without MetS, whereas intensive control of BP also increased risk. Therefore, proper targeting the blood pressure is important to reduce the risk of major clinical outcomes irrespective of the presence of MetS.

Funding: Veterans Affairs Support

PO1765
Vascular Function Indices Are Strong Predictors of the Severity and Characteristics of Carotid Atherosclerosis

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Background: Vascular functional indices strongly predict adverse cardiac outcomes in CKD. However, few have examined the link between vascular function and the severity and characteristics of carotid atherosclerosis in CKD. Management of Cardiovascular disease in CKD is closely related to adversely vascular dysfunction and carotid atherosclerosis in Veterans with high-CV risk CKD. Analyzing the baseline parameters of enrollees, we aim to evaluate the predictors of carotid atherosclerosis in CKD patients.

Methods: All randomized participants of MaCK study underwent detailed clinical and laboratory evaluations, including evaluation of inflammation (hsCRP), vascular function (central aortic pressure(CAP), augmentation index(AI) and aorta pulse wave velocity(APWV) by sphygmocon® XCEL) and detailed evaluation of carotid atherosclerosis 15 mm around bifurcation (total plaque volume (TPV), lipid-rich necrosis, calcification, fibrous cap, and intraplaque hemorrhage by 3T MRI analyzed with Piaqiview® software).

Results: Initial 17 randomized participants (age 73±4years, all male, 41% with pre-existing CVD and 88% on statins, with eGFR 40±20, median of WC of the total study population.

Conclusions: Non-invasively measured central aortic pressure and aortic pulse wave velocity are strong predictors of carotid atherosclerosis and unstable plaques.

Funding: Veterans Affairs Support
**PO1766**

**Framingham Risk Score and ACC/AHA Pooled Cohort Equation for Prediction of Atherosclerotic Cardiovascular Events in CKD**

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**Background:** The Framingham Risk Score and the ACC/AHA Pooled Cohort Equation are used clinically to identify patients at high risk for atherosclerotic cardiovascular disease (ASCVD). The performance of these equations (alone or with clinically available cardiac biomarkers) is unclear in patients with chronic kidney disease (CKD), particularly at more advanced stages. We tested the discrimination of these risk scores and cardiac biomarkers to predict ASCVD in CKD.

**Methods:** We studied 1027 participants in the Chronic Renal Insufficiency Cohort without ASCVD who were not taking aspirin or statins. Framingham Risk Score, Pooled Cohort Equation, N-terminal pro-brain type natriuretic peptide (NT-proBNP), and high-sensitivity troponin T (HsTnT) were measured at baseline. Outcomes were the composite of fatal and non-fatal myocardial infarction (MI) and cardiac death, with or without stroke, over 10 years. We estimated internally valid C-indices using 10-fold cross validation for each risk score and cardiac risk marker overall, and across categories of eGFR.

**Results:** Among 1027 participants, the mean age was 52 years, and the mean eGFR was 48 mL/min/1.73 m². The C-index (95% CI) was 0.74 (0.69, 0.79) for the Framingham Risk Score, and 0.72 (0.67, 0.78) for the Pooled Cohort Equation. Both risk scores had better discrimination for predicting ASCVD at eGFR >60 mL/min/1.73 m² compared with lower eGFR. HsTnT had comparable discrimination to both risk scores overall. HsTnT alone had comparable discrimination across the spectrum of CKD severity (difference in C-index for lowest vs highest eGFR category for ASCVD -0.04; 95% CI -0.21, 0.14) (Table).

**Conclusions:** The Framingham Risk Score and Pooled Cohort Equation had moderate discrimination for prediction of ASCVD in CKD and performed better at eGFRs >60 versus <60 mL/min/1.73 m². HsTnT alone had discrimination comparable to each risk score overall, and comparable discrimination across the spectrum of CKD severity. Further work is needed to develop novel risk scores including cardiac biomarkers specifically for use in CKD.

**Funding:** NIDDK Support

**PO1768**

**Nondipping Heart Rate in Patients with CKD**

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**Background:** A decrease in the nocturnal heart rate (HR) decline, nondipping HR (NHR), was reported to be 14% in the general population and related to cardiovascular events and all-cause mortality; however, the clinicopathological features of chronic kidney disease (CKD) patients with NHR is still unclear. Previous studies have reported that interstitial and/or tubular atrophy (IFTA) was significantly associated with both daytime and nighttime hypertrophy observed with ambulatory blood pressure monitoring (ABPM). We aimed to investigate the clinicopathological findings associated with NHR status in patients with CKD.

**Methods:** We retrospectively identified 135 subjects who underwent ABPM and kidney biopsy simultaneously at our institution, from 2016 to 2019. We excluded patients with age <20 years, end-stage kidney disease, less than 5 glomeruli in the kidney biopsy, and patients taking β-blockers. NHR status was defined as (daytime HR – nighttime HR)/daytime HR <0.1. The percentage of global glomerulosclerosis (GS%), IFTA, and the severity of arteriosclerosis were scored semi-quantitatively according to the Mayo Clinic/Renal Pathology Society Chronicity Score (CS).

**Results:** Our median age was 51 years (interquartile range: 35–63), 54.0% of which were male, and the median eGFR was 53.0 [30.0–75.0] mL/min/1.73m². NHR status was found in 39 out of 135 patients (28.9%). Patients with NHR were older and had worse renal function, higher blood pressure, lower hemoglobin level, and a larger amount of urinary protein excretion than patients with dipping HR. In terms of histopathological parameters, patients with NHR had more severe GS%, IFTA, and arteriosclerosis, and higher CS (Table 1). In multivariable analysis, GS% was established as an independent determinant of NHR status after its adjustment according to age, sex, and other statistically significant parameters (β = 1.03 [1.00–1.05], P = 0.02).

**Conclusions:** NHR status was observed in 28.9% of CKD patients. This study indicates that GS% is the most relevant histopathological parameter associated with NHR in this population.

**Funding:** Other NIH Support - Medical Research Council (UK)

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

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**Table 1:** Data are presented as mean ± SD

<table>
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<th>Parameter</th>
<th>Mean ± SD</th>
<th>Median</th>
<th>Range</th>
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</thead>
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<td>eGFR (mL/min/1.73m²)</td>
<td>53.0 ± 25.0</td>
<td>51.0</td>
<td>30.0–75.0</td>
</tr>
</tbody>
</table>

**Figure 1:** Cox regression for MACE. *Adjusted for age, sex, smoking, deprivation, eGFR & cholesterol
Turning the Page on Page Kidney with Dual RAAS Blockade
William J. Assante,1,2 Jennifer Griffiths,1,2 Aromma Kapoor,1,2 1Westchester Medical Center Health Network, Valhalla, NY; 2New York Medical College, Valhalla, NY.

Introduction: Page kidney is a rare form of secondary hypertension from activation of the renin-angiotensin-aldosterone (RAAS) axis by compression of renal parenchyma. It can occur with blunt abdominal trauma/procedures, but it can occur spontaneously. Initial treatment is an ACE inhibitor (ACE) or angiotensin receptor blocker (ARB). Surgical intervention is usually a last resort after more conservative measures fail. Procedures carry their own intrinsic risk for morbidity and mortality, particularly in the setting of uncontrolled hypertension. This report details the case of a patient with Page kidney responsive to an unconventional conservative management approach: dual RAAS blockade with ACE + ARB to achieve normotensive control.

Case Description: The patient is a 55M with a history of end stage renal disease (ESRD). On admission, he was hypertensive with a blood pressure of 160/110 mmHg. A CT scan of the abdomen showed a 16.5cm right retroperitoneal hematoma adjacent to the right kidney with anterior dislocation of the kidney. A CT angiogram showed active extravasation within the hematoma. Coumadin was held and a dose of Vitamin K was given to reverse the patient's INR. Lisinopril 20mg PO daily was added and increased to maximum tolerated dose. Hemoglobin was stable therafter.

The patient soon developed hypertensive urgency with a rise in blood pressure to 180/120 mmHg. The patient was dyspneic and weak with right flank pain. He denied headaches, visual disturbances, and other symptoms of critical illness. He was hypotensive with systolic blood pressure of 120s, and was immediately admitted to the ICU. The patient was started on 120mmHg target blood pressure. The patient's blood pressure normalized with average in 120s systolic by 72 hrs post admission. No intervention was needed for bleeding control or surgical evacuation of the hematoma. The patient was discharged with lisinopril 40mg PO daily, and was followed with a nephrology consult.

Discussion: Page kidney is a rare but serious form of secondary hypertension from RAAS activation from renal parenchymal compression. Historically, a trial of either an ACE or ARB is indicated, with refractory cases being managed surgically. In this case, dual RAAS blockade was required for blood pressure control, which allowed surgical interventions, and their associated risk of morbidity and mortality, to be avoided.

ESRD Risk Predicting Using Cumulative Hypertension Burden
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Background: Hypertension is the leading risk factor for end-stage renal disease (ESRD). However, the association between sustained exposure of increased blood pressure (BP) and ESRD is not well-established. This study investigated whether the cumulative hypertension burden is a substantial risk factor for ESRD.

Methods: The incidence of ESRD among 2,144,801 participants identified from the Korean National Health Insurance Service database, who had documented BP assessments for annual health checkup data between 2006 and 2010, was determined. Over a median follow-up of 7.2 years, ESRD was identified in 1,758 participants. Hypertension burden was defined as the cumulative exposure of hypertension (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg) during 4 consecutive follow up period, and scaled 0 to 4.

Results: Hypertension burden was as follows: 0 (n = 1,164,488), 77.6%; 1 (n = 292,377), 13.6%; 2 (n = 114,397), 5.3%; 3 (n = 52,671), 2.5%; and 4 (n = 26,886), 1.0%. Compared to the hypertension burden of 0, adjusted hazard ratio for ESRD was increased to 1.43, 1.74, 1.85, and 2.70 in hypertension burden of 1, 2, 3, and 4, respectively. A positive dose-dependent relationship between the hypertension burdens and ESRD was found (P for interaction < 0.001). This association was maintained for the sustained exposure of both systolic and diastolic hypertension burden. In conclusion, hypertension burden increases the risk of ESRD.

Conclusions: Our study underlines the usefulness of a new assessment of the hypertension burden over a certain period for predicting the risk of ESRD from a large population-based cohort.
PO1772
Perseverance of Uncontrolled Hypertension Among Older Women Post Implementation of Hypertension Improvement Program
Emily Walsh,1 Olivia Myers,2 Talar Markossian,2 Holly J. Kramer,2 Katherine Habicht,1 Beatrice D. Probst,1 Loyola University Chicago Stritch School of Medicine, Maywood, IL; 1Parkinson School of Health Sciences & Public Health, Loyola University Chicago, Maywood, IL; 2Loyola University Medical Center, Maywood, IL.

Background: Age-dependent sex differences in hypertension control have been demonstrated in multiple populations. Four large primary care (PC) practices at Loyola adopted the Target:BP hypertension improvement program in 2018; hypertension control rates increased after adoption. Our study evaluated the impact of the Target:BP program on hypertension control by sex and by age group.

Methods: Analysis used data from 21,864 patients age ≥18 years with a hypertension diagnosis and ≥1 outpatient visit in 2019 to a PC clinic enrolled in Target:BP program. Uncontrolled hypertension was defined as blood pressure ≥140/90 mmHg based on last visit. Mixed effects models were used to calculate adjusted odds of uncontrolled hypertension after adjustment for demographics and co-morbidities. Interaction term of sex*age group (≥65, 66-75, >75 years) in fully adjusted mixed effects models was significant (P < 0.001) so adjusted odds of uncontrolled hypertension were calculated by sex and by age group. Adjusted proportion of patients with uncontrolled hypertension by sex and by age group was calculated using marginal effects.

Results: Mean age of patients with hypertension was 64.8 ± 12.7 years; 56.3% were female, 66.6% were White, 21.4% were Black and 11.0% were of Hispanic ethnicity. Among the 5973 (27.3%) with uncontrolled hypertension, 54.7% were female; mean age was 65.2 ± 12.9 years. Adjusted odds of uncontrolled hypertension was significantly higher among women vs. men age 66-75 years (OR 1.33; 95% CI 1.30, 2.28) and age 76+ years (OR 1.73; 95% CI 1.31, 2.28) vs. age ≤65 years. Figure 1 shows the adjusted proportion of patients with uncontrolled hypertension by sex and by age group.

Conclusions: Despite implementation of a hypertension improvement program, sex disparities in hypertension control persist among older adults.

PO1773
Influence of Biological Sex on Brachial Cuff Blood Pressure Accuracy
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Background: Females have higher risks of cardiovascular events compared to males with similar BP. Our objective was to assess if the accuracy of brachial cuff and central BP measurements towards intra-aortic BP is influenced by biological sex.

Methods: We enrolled 500 patients undergoing coronary angiography for simultaneous measurements of invasive aortic BP with brachial cuff and central BP (Mobi-o-Graph device). Acceptable accuracy was defined as a mean difference between non-invasive and aortic BPs ≤5 ± 8 mmHg. Linear regression and mediation analyses were used to adjust for potential confounders in the relationship between biological sex and BP accuracy.

Results: Of 500 participants, 145 were females. Several characteristics were different in males and females (Table). Brachial cuff systolic BP (SBP) was identical in both groups whereas aortic SBP was 6.2 mmHg higher in females (p=0.001). As such, the brachial cuff SBP was appreciably underestimated the aortic SBP in females but not in males. Type II central SBP was the most accurate BP in females, whereas it was brachial cuff SBP in males. In an adjusted linear regression model, only height and pulse pressure were independently associated with the accuracy of brachial cuff SBP. This effect of sex on accuracy was mostly mediated by height (3.5 mmHg; 95% CI 1.4 to 5.6; 57% mediation) to an extent that the direct effect of sex became non-significant (2.9 mmHg; 95% CI -0.3 to 6.2).

Conclusions: High potassium intake is associated with lower blood pressure and lower risk of cardiovascular disease. Whether these associations differ between men and women and whether they depend on daily sodium intake is unknown.

Methods: We performed an analysis in 11,267 men and 13,696 women from the Epic-Norfolk cohort. Daily sodium and potassium consumption was estimated from sodium and potassium concentration in spot urine samples by using the Kawasaki formula. Linear and Cox regression were used to explore the association between potassium intake, systolic blood pressure and cardiovascular events (defined as hospitalization or death due to cardiac disease).

Results: After adjustment for confounders, interaction between potassium intake and sex was significantly associated with systolic blood pressure (p=0.001) and cardiovascular events (p=0.035). In women, but not in men, the inverse slope between potassium intake and systolic blood pressure was steeper in those within the highest quintile compared to the lowest quintile of sodium intake (p=0.001 for interaction). In women within the highest quintile of sodium intake, every 1-gram increase in potassium intake was associated with a 2.9 mmHg lower systolic blood pressure. These associations were paralleled with lower risk of cardiovascular disease in women (highest vs. lowest potassium intake tertile: HR 0.88, 95% CI 0.93-0.94). Conversely, in men, the inverse association between potassium intake and cardiovascular disease was not statistically significant (highest vs. lowest potassium intake tertile: HR 0.94, 95% CI 0.88-1.01).

Conclusions: Females have higher aortic SBPs than males with identical brachial SBP, which is mostly mediated by a lower height. This could partly explain why females are at higher risk of cardiovascular diseases than males at similar brachial cuff SBP levels.
Background: Inflammation and oxidative stress contribute to the increased cardiovascular disease (CVD) burden in CKD patients. Altered tryptophan catabolism via the kynurenine pathway associates with CVD, but the ability of these specific metabolites to act as biomarkers of CVD risk in CKD warrants further research.

Methods: We measured tryptophan metabolites using targeted mass spectrometry in moderate to severe CKD patients (n=325; median follow-up 3 years). Vascular calcification at the coronary artery and aorta was measured using a 4-slice LightSpeed QXI and reported as Agatston scores. Incident CVD events included myocardial infarction, coronary revascularization procedures, stroke, transient ischemic attack, new-onset heart failure, sudden cardiac death, and peripheral vascular disease requiring revascularization or amputation. Multiple linear regression and Cox proportional hazard analyses assessed the relationship of tryptophan metabolites to subclinical markers of CVD and CVD events.

Results: We found that lower baseline tryptophan levels predicted increased aortic calcification in a fully adjusted model controlling for demographics, CVD history, traditional risk factors, renal function, CRP, and serum albumin (p<0.006). Higher baseline levels of anthranilic acid and hydroxanthranilic acid predicted increased coronary calcification and higher total Agatston score, respectively, in the fully adjusted model (p=0.03 and p=0.03). One unit decrease in serum tryptophan at baseline is associated with 70% decrease in time to incident CVD event when adjusting for demographics, CVD history, risk factors, and renal function (HR: 0.31, p<0.04). Increased anthranilic acid and quinolinic acid independently reduced time to incident CVD event (HR: 1.88, p=0.02; HR: 0.62, p=0.007, respectively), but were not significant in the fully adjusted model.

Conclusions: Lower tryptophan levels are associated with increased aortic calcification and decreased time to incident CVD events. Higher levels of anthranilic acid, hydroxanthranilic acid, and quinolinic acid are associated with subclinical CVD. Together, these data suggest that catabolism of tryptophan via the kynurenine pathway is associated with subclinical CVD and predicts cardiovascular events in CKD.

Funding: Other NIH Support - U01TR002240 NCATS

PO1775
Tryptophan Metabolites Associate with Subclinical and Incident Cardiovascular Disease in CKD
Trista M. Benitez, Elizabeth Vanderwoude, Yun Han, Jaeman Byun, Vetali K. Cheofor, Brenda W. Gillespie, Rajiv Saran, Anna V. Mathew. University of Michigan, Ann Arbor, MI.

PO1776
Abstract Withdrawn

PO1777
High Level of Uromodulin Increases the Risk of Hypertension: A Mendelian Randomization Study
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Background: The association of uromodulin and hypertension was clinically observed, but not proved as a causal relationship. We conducted a two-sample Mendelian randomization analysis to investigate the causal relationship between uromodulin and blood pressure based on the public datasets.

Methods: We selected two SNPs for the uUMOD exposure from the Genome-Wide Association Studies (GWAS) meta-analysis study(N=10884) and sixteen SNPs for uUMOD. These data demonstrate that catabolism of uromodulin(uUMOD) in the kidney results in increased blood pressure

Results: We found that lower baseline tryptophan levels predicted increased aortic calcification in a fully adjusted model controlling for demographics, CVD history, traditional risk factors, renal function, CRP, and serum albumin (p<0.006). Higher baseline levels of anthranilic acid and hydroxanthranilic acid predicted increased coronary calcification and higher total Agatston score, respectively, in the fully adjusted model (p=0.03 and p=0.03). One unit decrease in serum tryptophan at baseline is associated with 70% decrease in time to incident CVD event when adjusting for demographics, CVD history, risk factors, and renal function (HR: 0.31, p<0.04). Increased anthranilic acid and quinolinic acid independently reduced time to incident CVD event (HR: 1.88, p=0.02; HR: 0.62, p=0.007, respectively), but were not significant in the fully adjusted model.

Conclusions: Lower tryptophan levels are associated with increased aortic calcification and decreased time to incident CVD events. Higher levels of anthranilic acid, hydroxanthranilic acid, and quinolinic acid are associated with subclinical CVD. Together, these data suggest that catabolism of tryptophan via the kynurenine pathway is associated with subclinical CVD and predicts cardiovascular events in CKD.

Funding: Other NIH Support - U01TR002240 NCATS

PO1778
Follistatin Is a Potential Novel Therapeutic Agent for Essential Hypertension
Ann Kuganathan, Marcos S. Leal, Chao Lu, Bo Gao, Jeffrey G. Dickhout, Joan C. Krepinsky. McMaster University Faculty of Health Sciences, Hamilton, ON, Canada.

Background: Follistatin (FST) is an inhibitor of several members of the proline-rich TGFβ superfamily. It is highly effective at neutralizing activins, without activity against TGFβ itself. Activins are known to induce inflammation, oxidative stress and fibrosis, all of which contribute to the vascular dysfunction characteristic of hypertension (HTN). We previously showed that FST inhibits kidney fibrosis, improves kidney function and lowers blood pressure (BP) in a hypertensive chronic kidney disease mouse model. While this is a model of secondary HTN, here we seek to analyze the efficacy of FST in improving BP and vascular structure and function in a model of essential HTN.

Methods: Telemeters were implanted in the abdominal aorta of spontaneously hypertensive rats (SHR), a model of essential HTN, and normotensive control Wistar Kyoto (WKY) rats for wireless BP monitoring. Rats were treated with 0.075mg/kg FST or vehicle IP every other day from 12-20 weeks of age (8 weeks). BP was recorded weekly. First branch mesenteric arteries were harvested for analysis of vascular function using myography, assessed for oxidative stress by DHE, or formalin fixed for IHC.

Results: By the end of the study, FST significantly lowered both systolic and diastolic BP in SHRs (208 +/- 9 over 132 +/- 4 mmHg in control and 189 +/- 2 over 123 +/- 2 mmHg in FST-treated SHRs, P < 0.04 and P < 0.03 respectively). SHR vessels showed increased contractility with the α1 adrenergic agonist phenylephrine, which was attenuated by FST. Post streptozotocin (STZ) injection-induced relaxation in SHR vessels was also improved by FST. Structurally, FST-treated vessels had less collagen deposition, assessed by Trichrome, which was accompanied by a reduction in medial thickness. Increased oxidative stress seen in SHR vessels was inhibited by FST.

Conclusions: FST lowers BP in SHR with established HTN, at least in part by reducing vascular oxidative stress and medial thickening. This manifests as improved vascular function, with decreased hypersensitivity to contractile agents and improved endothelial function. Future work will identify the effects of FST on inflammation, and the role of specific activins in essential HTN.

Funding: Private Foundation Support

PO1779
Age and Sex Disparities in Hypertension Treatment Inertia After Implementation of Target: BP
Olivia Myers, Talar Markossian, Beatrice D. Probst, Katherine Habich, Holly J. Kramer. Loyola University Chicago, Chicago, IL; Loyola University Health System, Maywood, IL.

Background: Blood pressure (BP) control decreases with advancing age among women but not men, but reasons for sex disparities remain uncertain. Our institution enrolled four large outpatient primary care clinics in the Target:BP hypertension improvement program in 2018. This hypertension improvement program included audit and feedback of physician prescribing practices of BP lowering medications. We examined the adjusted association of medication escalation, a measure of treatment inertia, with age group among adults with uncontrolled hypertension and determined whether this association is modified by sex. We hypothesized that medication escalation for BP control differs by age group and by sex.

Methods: Adults aged 18 years with uncontrolled hypertension (BP ≥ 140/90 mmHg at last visit) receiving primary care at a clinic enrolled in Target:BP and a 1 primary care visit during 2019 were included. Medication escalation was defined as a change in BP lowering medication class or dose during a visit when hypertension was uncontrolled. Mixed effects models were used to calculate adjusted odds of medication escalation by age group (≤ 65, 66-75, ≥ 76 years) after adjustment for demographics and co-morbidities. Interaction term of sex* age group was then fitted in fully adjusted mixed effects models and was significant (P < 0.001). Adjusted odds of medication escalation were then calculated by sex and by age group and adjusted prevalence of medication escalation by age group and by sex was calculated using marginal effects.

Results: Mean age of 5973 adults with uncontrolled hypertension was 65.2 (SD 18) years; 54.7% were women; 64.7% were White, 24.0% were Black and 9.9% were Hispanic ethnicity. Figure (left panel) shows that adjusted prevalence of medication escalation declined with advancing age group among men and women combined. Right panel shows the decline in medication escalation with advancing age group differed by sex until age 76 years.

Conclusions: Medication escalation for uncontrolled hypertension declines with advancing age and this age associated treatment inertia differs by sex.
Oscillometric vs. Auscultatory Blood Pressure Measurements and the Impact of Atrial Fibrillation
Ahmed Aburahma, Christopher B. McFadden. Cooper University Health Care, Camden, NJ.

Background: The Hypertension literature recognizes a difference in Oscillometric Blood pressures compared to Auscultatory Blood pressure measurements. These differences are small but increased in patients with Atrial fibrillation. This difference varies in previous studies. Again this Difference is larger in subjects with atrial fibrillation. Current Blood pressure measurement guidelines emphasize the use of an Auscultatory method or repeated oscillometric measures to measure blood pressure in patient with arrhythmias including atrial fibrillation. This recommendation is not consistently implemented in clinical medicine. We aim to quantify the differences in blood pressure readings between oscillometric and auscultatory method and correlate that to presence or absence of atrial fibrillation.

Methods: This is a retrospective study that involved adult patients seen in the outpatient nephrology clinic by one of the investigators (CM) between January 2016 and January 2020. Data collection included age, sex, BMI, atrial fibrillation (AF), CKD stage, diabetes mellitus, blood pressure readings (by both methods, which were done by the investigator (CM) in all antihypertensive patients) and number of blood pressure medications. Information on a total of 200 patients were collected. 100 of those had hypertension with AF while the other 100 had hypertension but no AF to achieve a power of 80% and P value of 0.05.

Results: After using Unpaired t test, the average difference between two methods in hypotensive patients (259 µmHg) was significantly lower than systolic blood pressure (P value of 0.9 and 95% CI from -5.5 to 6.12) and 5.39 mmHg in diastolic blood pressure (P value of 0.0068 and 95% CI from 1.5 to 9.24). On the other hand, the average difference between two methods in hypertensive patients with atrial fibrillation were 6.8 mmHg in systolic blood pressure (P value of 0.018 and 95% CI from 1.18 to 12.5) and 5.04 mmHg in diastolic blood pressure (P value of 0.002 and 95% CI from 1.87 to 8.21).

Conclusions: This study showed a statistical difference between the two methods in measuring the blood pressure of hypertensive patients with atrial fibrillation. A larger study is needed to show the difference between the two methods. For now we need to encourage the use of auscultatory method in measuring the Blood pressure in this group of patients.

Small Changes in eGFR Are Associated with Different Patterns of 24-Hour Ambulatory Blood Pressure Monitoring in the General Population
Sang Youn Han,1 Sanggon Yoon,2 Seung Ku Lee,2 Chol Shin.3 Inje University Ilsan Paik Hospital, Goyang, Republic of Korea; 3Korea University Ansan Hospital, Ansan, Gyeonggi-do, Republic of Korea.

Background: Alteration of circadian blood pressure (BP) rhythm such as non-dipper and reverse-dipper pattern is associated with cardiovascular diseases and chronic kidney disease (CKD). However, most studies did not control for kidney function even though kidney function is an important risk factor. In this study, we tried to show 24-h ambulatory blood pressure monitoring (ABPM) patterns based on an eGFR in patients without CKD.

Methods: This study was a cross-sectional study from the data of the Korean Genome and Epidemiology Study, which is ongoing prospective cohort study. A total of 1733 participants (60.0±7.00 years, 938 women) who had an eGFR > 60 ml/min/1.73m2 were included. Dipping status was stratified as reverse dipper (≥<10%), non-dipper (0% to <<10%), and dipper (≥10%) based on the night to day ratio of mean BP. They were divided into 4 groups based on quartile of an eGFR (Q4, 128.6-101.6 g, Q3, 101.5-95.7, Q2, 95.6-87.4, Q1, 87.3-60.5).

Results: The proportion of dipper was progressively decreased from the highest to the lowest eGFR whereas that of reverse dipper and non-dipper significantly increased. (P<0.001). We analyzed the data using logistic regression model in relation to dipper, non-dipper, reverse dipper, and non-plus reverse dipper according to the quartiles of an eGFR. The highest quartile group (Q4) was fixed as the reference. In univariate analyses, Q1 and Q2 groups were significantly associated with increased odds ratio (OR) with reverse dipper and reverse plus non-dipper plus reverse dipper. After full-adjustment with age, sex, hypertension, diabetes, body mass index, smoking status, exercise, and alcohol consumption, the lowest eGFR group was significantly associated with reverse dippers and non-dipper plus reverse dippers compared to the highest eGFR group (OR=1.689, 95% CI, 1.005-2.840, OR=1.427, 95% CI, 1.027-1.855, respectively). The significant linear trend of non-dipper plus reverse dipper with a decrease in eGFR was confirmed with the test for trend (P=0.024).

Conclusions: Small changes in eGFR are associated with different pattern of 24-h ABPM in general population. ABPM could be useful tool to detect patients with non-dipper in this population.

Small Changes in eGFR Are Associated with Different Patterns of 24-Hour Ambulatory Blood Pressure Monitoring in the General Population
Sang Youn Han,1 Sanggon Yoon,2 Seung Ku Lee,2 Chol Shin.3 Inje University Ilsan Paik Hospital, Goyang, Republic of Korea; 3Korea University Ansan Hospital, Ansan, Gyeonggi-do, Republic of Korea.

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Results: The proportion of dipper was progressively decreased from the highest to the lowest eGFR whereas that of reverse dipper and non-dipper significantly increased. (P<0.001). We analyzed the data using logistic regression model in relation to dipper, non-dipper, reverse dipper, and non-plus reverse dipper according to the quartiles of an eGFR. The highest quartile group (Q4) was fixed as the reference. In univariate analyses, Q1 and Q2 groups were significantly associated with increased odds ratio (OR) with reverse dipper and reverse plus non-dipper plus reverse dipper. After full-adjustment with age, sex, hypertension, diabetes, body mass index, smoking status, exercise, and alcohol consumption, the lowest eGFR group was significantly associated with reverse dippers and non-dipper plus reverse dippers compared to the highest eGFR group (OR=1.689, 95% CI, 1.005-2.840, OR=1.427, 95% CI, 1.027-1.855, respectively). The significant linear trend of non-dipper plus reverse dipper with a decrease in eGFR was confirmed with the test for trend (P=0.024).

Conclusions: Small changes in eGFR are associated with different pattern of 24-h ABPM in general population. ABPM could be useful tool to detect patients with non-dipper in this population.
PO1784
Crit-Line Monitoring Effect on Blood Pressure Control in ESRD Patients Undergoing In-Center Hemodialysis
Washington University in St Louis, St Louis, MO.

Background: Patients with end stage renal disease (ESRD) are admitted to the hospital about twice per year, with a 35% readmission rate. Cardiovascular disease (CVD) makes up 28% of admissions; 38% of patients with CVD admissions have pulmonary edema. Fluid overload in ESRD increases morbidity and mortality. Fluid management improvements have potential to positively impact clinic outcomes in dialysis patients.

Methods: This was a prospective cohort study with adult patients at two outpatient dialysis facilities on the Washington University in St Louis Campus. Our inclusion criteria were patients with consistent 3x weekly in-center hemodialysis defined as 80% attendance in the 30 days prior to the study. A Critline protocol was implemented by the treatment team (Figure 1).

Results: Among 58 qualified patients, average age was 59. 77% were African American with male predominance (57%). Average BMI was 29. In the Critline cohort, systolic blood pressure trended down (Figure 2). In the initial 25 weeks, average number of antihypertensive medications per patient decreased from 2.6 to 1.8. The number of admissions for fluid overload stayed stable at 10, however readmissions decreased from 4 to 1.

Conclusions: Implementing a Critline protocol trended improvements in blood pressure and reduced number of antihypertensives medications. Our findings suggest that a protocolized approach to fluid management using critline will improve our patients outcomes.

Methods: We conducted a cross-sectional study of 241 CKD stage 5 patients from the Cardiopulmonary Exercise Testing in Renal Failure (CAPER) cohort. VO2peak (primary endpoint) was assessed by cardiopulmonary exercise testing (CPET) in parallel with transthoracic echocardiography.

Results: Of the 241 patients (mean age [SD] age, 48.9 [14.9] years; 154 [65.9%] males) 105 patients were pre-dialysis (mean eGFR [SD], 14 [3.4] ml/min/1.73m2). Major CVD was in tertile 1 of dialysis vintage (0-17 months), n=69 in tertile 2 (18-50 months) and n=64 in tertile 3 (>51 months). Predialysis patients had an impaired VO2peak of 22.7 [5.2] ml/min/kg, and this significantly declined to 18.5 [5.5] ml/min/kg in tertile 1 dialysis patients compared to the pre-dialysis group, tertile 1 dialysis patients exhibited reduced maximal workload (p=0.003), impaired maximal heart rate (p=0.02), increased LVMi (p=0.001) and markedly elevated FGF23 levels (p=0.01). On assessment of the effects of dialysis vintage, we found an incremental downward trend in VO2peak across the groups (4.5 [2.2] tertile 1, 18.4 [7.1] tertile 2, 16.9 [4.2] ml/min/kg) following exclusion of patients who had prior kidney transplants, however this did not reach statistical significance (p=0.2).

Conclusions: Initiating dialysis in advanced CKD patients is associated with impaired CFC comparable to declines seen in new onset heart failure, making this a critical time for these patients.

PO1786
Major Adverse Limb Events and Mortality After Peripheral Artery Revascularization in Hemodialysis Patients
Ting-yun Lin, Szu-Chun Hung. Taipei Tzu Chi Hospital, Taipei, Taiwan.

Background: Revascularization is important for symptom relief and limb salvage in peripheral artery disease, yet limited information exists on the prognosis of hemodialysis patients who receive the procedure. This study sought to determine the incidence and associated factors of major adverse limb events (MALE) after peripheral artery revascularization among hemodialysis patients.

Methods: Hemodialysis patients undergoing peripheral artery revascularization between July 1, 2005, and December 31, 2019, in the Taipei Tzu Chi Hospital were examined for the primary outcome of MALE, defined as severe limb ischemia leading to an intervention or amputation. The secondary outcomes included major adverse cardiovascular events (MACE) and all-cause mortality. Multivariable-adjusted Cox proportional hazards models were used to explore risk factors associated with development of MALE.

Results: A total of 402 hemodialysis patients were included in the final analysis. Overall, the mean age was 68 years, 56.5% (n = 227) were male, 83.3% (n = 335) had diabetes, and 58.0% (n = 233) had coronary artery disease. During a median follow-up of 2.2 years, 54.0% (n = 217) experienced a subsequent MALE. 33.6% (n = 136) had a MACE, and 54.5% (n = 219) died. Diabetes, coronary artery disease, current smoking, lower body mass index, and higher platelet count or total cholesterol were significantly associated with increased risk of post-procedure MALE.

Conclusions: A significant proportion of hemodialysis patients undergoing peripheral artery revascularization developed a subsequent MALE and MACE or died. Strategies that address risk factors for MALE should be evaluated to improve the outcomes of revascularized hemodialysis patients.

PO1785
Cardiovascular Functional Changes in Transplant Waitlist Dialysis Patients
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Background: The transition to dialysis is a crucial time in patients with advanced chronic kidney disease (CKD), conferred an increased risk for cardiovascular death. We recently showed that VO2peak, an index of cardiovascular functional capacity (CFC) significantly declined in advanced CKD patients following 1-year follow-up in the absence of changes in left ventricular mass index (LVMI). Herein, we hypothesized that initiating dialysis and continuing dialysis could worsen an individual’s CFC over time.

Conclusions: A protocolized approach to fluid management using critline will improve outcomes in dialysis patients.

Methods: This was a prospective cohort study with adult patients at two outpatient dialysis facilities on the Washington University in St Louis Campus. Our inclusion criteria were patients with consistent 3x weekly in-center hemodialysis defined as 80% attendance in the 30 days prior to the study. A Critline protocol was implemented by the treatment team (Figure 1).

Results: Among 58 qualified patients, average age was 59. 77% were African American with male predominance (57%). Average BMI was 29. In the Critline cohort, systolic blood pressure trended down (Figure 2). In the initial 25 weeks, average number of antihypertensive medications per patient decreased from 2.6 to 1.8. The number of admissions for fluid overload stayed stable at 10, however readmissions decreased from 4 to 1.

Conclusions: Implementing a Critline protocol trended improvements in blood pressure and reduced number of antihypertensives medications. Our findings suggest that a protocolized approach to fluid management using critline will improve our patients outcomes.

Conclusions: Initiating dialysis in advanced CKD patients is associated with impaired CFC comparable to declines seen in new onset heart failure, making this a critical time for these patients.

Conclusions: A significant proportion of hemodialysis patients undergoing peripheral artery revascularization developed a subsequent MALE and MACE or died. Strategies that address risk factors for MALE should be evaluated to improve the outcomes of revascularized hemodialysis patients.

PO1787
Central Blood Pressure Calibration Method and Cardiovascular Risk Prediction According to Sex
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Background: The accuracy of central BP is improved when calibrated on the mean BP and diastolic BP (CBSBP) compared to calibration on the systolic BP and diastolic BP (CBSBP). Furthermore, preliminary data suggest CBSBP may have the best accuracy in females. We aim to assess whether this enhanced accuracy translates into improved cardiovascular (CV) risk prediction when compared to brachial SBP (bsBP) and CBSBP in the general population and stratified by sex.

Methods: 12,927 participants exempt of known CV disease, with prospective follow-up from administrative databases and central BP measurements based on the SphygmoCor device was used to estimate CBSBP. CBSBP was derived from uncompensated radial pressure waveforms extracted from SphygmoCor output data, which was recalibrated with diastolic BP and 40% form factor derived mean BP. Participants with heart rate >60 were excluded due to incomplete waveform. Major CV events (MACE) comprised myocardial infarction, stroke, heart failure with hospitalization and CV death. Multivariable Cox regressions, differences in area under the curve, net reclassification index and integrated discrimination index were calculated comparing CBSBP to bsSBP and to CBSBP.

Results: Over a median follow-up of 10.1 years (IQR 9.9-10.3), there were 2125 MACE (723/7013 females and 860/5934 males). All BP parameters were significantly associated with MACE, regardless of sex. In the overall cohort, risk prediction metrics marginally favored CBSBP compared to bsSBP but were similar to CBSBP. No significant improvement of CV risk prediction was found in sex-stratified analyses (see Table).

Conclusions: CBSBP marginally improved CV risk prediction when compared to bsSBP but not CBSBP in the overall cohort only. All three BP parameters were similarly predictive in both sex, although this analysis possibly lacked power. This may be related to the FF-derived MAP (rather than oscillometric MAP), which is highly dependent on the brachial SBP.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
POI1788
Suppressed Renin Activity in CKD: Are We Missing Primary Hyperaldosteronism?
Mohammad D. D. El Shafie,1,2 Georges Nakhoul,3 Susana Arrigain,3 Jesse D. Schold,3 Jonathan J. Tailerisco,3 George Thomas,2 Ali Mehdi.2 1 Cleveland Clinic, Cleveland, OH; 2 Cleveland Clinic Glickman Urological and Kidney Institute, Cleveland, OH.

Background: Primary hyperaldosteronism (PA) is more prevalent than once thought and associated with adverse kidney and cardiovascular outcomes. A prior analysis of the CKD registry at the Cleveland Clinic in patients without a diagnosis of PA showed that the lowest quartile of plasma renin activity (PRA) (PRA ≤20 ng/ml/hr) had severe hypertension and faster eGFR decline. We hypothesized that some of these patients with suppressed PRA may have undiagnosed PA.

Methods: We reviewed patients in the Cleveland Clinic CKD registry with documented PRA and absolute plasma aldosterone concentration (PAC). Patients in the lowest PRA quartile were identified and stratified by PRA/PAC ratio. A cutoff ratio of ≥20 was considered suggestive of PA regardless of the PAC. Characteristics and outcomes of these two subgroups were compared using t-tests, chi-square tests, Kaplan-Meier analyses and Cox models.

Results: 576 patients were identified for this analysis. Median PRA and PAC were 0.5 μg/L/hr and 8.7 ng/dl respectively. 141 (51%) patients had a PAC/PRA ratio of ≥20 with a median PAC of 14.6 ng/dl in this subgroup. Patients with PAC>PRA of a ≥20 vs. <20 had significantly lower eGFR (mean: 50.7 vs. 55.4 mL/min/1.73 m²; p<0.009), more resistant hypertension (63.1% vs. 48.9%; p=0.044), lower serum potassium values (mean: 3.9 vs. 4.2 mmol/L; p<0.001), and higher serum bicarbonate levels (mean: 26.4 vs. 25.3 mmol/L; p=0.0001). With median follow up of 4.2 years, there was no difference in mortality between the two subgroups on adjusted cox model analysis (HR for ≥20 vs.<20: 0.83, 95%CI: 0.47,1.47). No difference in ESKD-free survival at 5 years was noted but the event rate was low (92.6 vs. 91.9 for ≥20 vs.<20; p=0.77).

Conclusions: Our analysis indicates that some CKD patients with suppressed PRA may have underlying PA. More than half of our suppressed PRA cohort had elevated PAC/PRA ratio of ≥20 suggestive of PA. The biochemical profile and severe hypertension further supports this diagnosis. We hypothesize that the diagnosis of PA was possibly ruled out because of the “not very high” PAC. Given the limitations of the spot PAC/PRA screen to diurnal PAC variations, a suppressed PRA should merit an in-depth evaluation for undiagnosed PA regardless of the PAC. Making this diagnosis is critical since it has significant therapeutic implications.

POI1790
Cardiovascular and Renal Outcomes of the New Intensive Blood Pressure Target in a CKD Population in Korea
Kyunghwan Jeong,1 Soo-Yoon Yoon,1 Ji Yoon Kong,2 Daeyoung Kim,1 Jongho Kim,1 Shinyeong Kang,1 Jin sug Kim,1 Heyeon Seok Hwang.1 Kyung Hee University Medical Center, Seoul, Republic of Korea; 2Kyung Hee University, Seoul, Republic of Korea.

Background: Hypertension is one of the most important modifiable risk factors of cardiovascular disease (CVD) including ischemic heart disease (IHD) and stroke. The 2021 kidney disease: improving global outcomes (KDIGO) clinical practice guideline for the management of blood pressure (BP) in CKD recommended a target systolic BP (SBP) <120 mmHg regarding of albuminuria, using standardized office BP measurement. We evaluated the prevalence of cardiovascular events and CVD progression to assess the adequacy of this intensive BP target for CKD patients in Korea.

Methods: The data of 166,397 adults whose baseline estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m² were extracted from the Korean national health insurance service database between 2009 and 2011. The data were adjusted for multiple factors such as age, sex, smoking, eGFR, and anti-hypertensive medications in multivariable Cox proportional hazards regression models. All patients were divided into four SBP categories (<120 mmHg, 120-129 mmHg, 130-139 mmHg, ≥140 mmHg). The primary outcome was CVD risk, and the secondary outcome was the risk of progression to end-stage renal disease (ESRD), especially in need of intermittent hemodialysis (HD).

Results: The mean ages of the each group of CKD patients were 45.1±15.7 years in SBP <120 mmHg group and 52.13±16.0 years in SBP 120-129 mmHg group, 11.1% in SBP ≥130 mmHg group and 24.6% in SBP 120-129 mmHg group of the participants were already taking anti-hypertensive medications. 112,012 patients (67.3%) had SBP ≥120 mmHg, and 78,119 patients (46.9%) had SBP ≥130 mmHg. Participants with SBP ≥120-129 mmHg exhibited a significantly high risk for IHD (hazard ratio (HR), 1.29; 95% confidence interval (CI), 1.03-1.61; P = 0.03) and stroke (HR, 1.57; 95% CI, 1.13-2.18; P <0.01) when compared with the participants with SBP <120 mmHg. Also, the risk of progression to ESRD was also higher (HR, 1.67; 95% CI, 1.46-1.91; P<0.001). Similar trend of findings were observed between the group with SBP<120 mmHg and the other groups.

Conclusions: Therefore, the new intensive BP target can be applied to the real clinical practice in CKD population with proper BP monitoring in Korea and it may eventually reduce the risk of CVD and progression to ESRD in a number of CKD patients.

POI1791
Intensive Blood Pressure Control, Age, and All-Cause Mortality in the US Veterans Health Administration
Masaaki Yamada,1,2 Benjamin R. Griffin,3,2 Jason Wachsmuth,2 Meenakshi Sambharia,1 Melissa L. Sweeney,3 Saket R. Girotra,2 Heather Reissinger,3 Brian C. Lund,2 Mary V. Sarrazin,2 Diana J. Jalal.1,2 The University of Iowa Roy J and Lucille A Carver College of Medicine, Iowa City, IA; 2Department of Research as & Development, Iowa City VA Medical Center, Iowa City, IA; 3Institute for Clinical and Translational Science, Iowa City, IA.

Background: Intensive blood pressure (BP) control has been shown to improve survival in large clinical trials. It is unknown if intensive BP control is associated with improved outcomes amongst older adults in the real-world setting. We examined the association of intensive BP control with all-cause mortality in U.S. Veterans.

Methods: This retrospective analysis of Veterans Health Administration (VHA) data included Veterans with ≥2 systolic blood pressure (SBP) readings between January 2016 and December 2017 excluding those with mean SBP <100 mmHg to minimize reverse causation. Prevalent hypertension was defined as diagnostic codes related to hypertension, prescribed antihypertensive drugs, or ≥2 office BP of ≥130/90 mmHg. The following SBP categories were investigated: SBP <120 mmHg, ≥120-129 mmHg, and ≥130 mmHg. A two-way interaction between SBP category and age was examined to assess if the effect of BP control on mortality differed by age category.

Results: We estimated the potential effect of SBP control on all-cause mortality and evaluated the potential interaction with age using a random-effect Cox regression model. Among the 1,959,003 Veterans, 18% had SBP <120 mmHg (n=352,684), 26% had SBP 120-129 mmHg (n=507,907), and 56% had SBP ≥130 mmHg (n=1,098,412). Mean SBP <120 and 120-129 mmHg associated significantly with mortality (the adjusted hazard ratio [aHR] was 1.30; 95% confidence interval [CI] 1.26-1.32 for SBP ≥120 mmHg and 1.03 [95% CI 1.01-1.04] for SBP 120-129 mmHg). There was a significant interaction between SBP category and age (p<0.01). Specifically, we observed a graded association of SBP <120 mmHg with all-cause mortality across increased age categories; this association was significant in the age categories 70 years (Figure 1).

Conclusions: Based on the analysis of real-world data of approximately 1.9 million Veterans, intensive BP control (SBP <120 mmHg) was associated with higher mortality specifically among older Veterans. These data have implications for BP management and suggest that intensive control of SBP may be harmful in older adults.

Funding: Veterans Affairs Support
Markers of Kidney Tubular Secretion and Risk of Cardiovascular Disease and Mortality in Persons with CKD in SPRINT

Simon Ascher,1,2 Ronit Katz,3 Rebecca Scherzer,1 Alexander Bullen,4,5
Cheng-Ta Lee,6 Jesse Stein,7 Simon Malhotra,4 Michelle Estrella,2 Jesse C. Seegmiller,1 Joachim H. Ix,3,7 Michael Shlipak,3 Pranav S. Garimella,1
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Background: Tubular secretion of organic solutes is essential to the clearance of many drugs, metabolites, and toxins. Whether novel measures of tubular secretion have prognostic value for cardiovascular and mortality risk among hypertensive, nondiabetic persons with CKD is uncertain.

Methods: In 2008 SPRINT (Systolic Blood Pressure Intervention Trial) participants with baseline eGFR <60 ml/min/1.73m2, we created a summary secretion score from 10 tubular secretion biomarkers by averaging across their urine-to-plasma ratios. We used multivariable Cox proportional hazards models to evaluate associations between secretion scores and risk of Cardiovascular disease (CVD) and all-cause mortality.

Results: Mean age at baseline was 73 ± 9 years and mean eGFR was 46 ± 11 ml/min/1.73m2. There were 272 CVD events and 144 deaths during a median follow-up of 3.26 years. Unadjusted analyses, a 1-SD higher secretion score was associated with a lower risk of CVD (hazard ratio [HR] per 1.73m2). There were 272 CVD events and 144 deaths during a median follow-up of 3.26 years. In adjusted analyses, a 1-SD higher secretion score was associated with a lower risk of CVD (HR: 0.87; 95% CI: 0.76, 0.99), but not all-cause mortality (HR: 1.12, 95% CI: 0.95, 1.33).

Conclusions: Among SPRINT participants with CKD, higher tubular secretion was not significantly associated with risk of CVD or mortality after adjustment for eGFR and albuminuria.

Funding: NIDDK Support

Table 1. Association of summary tubular secretion score* with a composite of adverse events in persons with CKD in SPRINT

<table>
<thead>
<tr>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event Rate</td>
<td>0.30</td>
<td>0.29</td>
<td>0.28</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00 (1.00, 1.00)</td>
<td>0.94 (0.87, 1.04)</td>
<td>0.87 (0.78, 0.96)</td>
</tr>
</tbody>
</table>

*Summary score calculated from averaging normalized urine-to-plasma ratios of all organic solutes.

MARKERS OF KIDNEY TUBULAR SECRETION AND RISK OF ADVERSE EVENTS IN PERSONS WITH CKD IN SPRINT

Simon Ascher,1,2 Rebecca Scherzer,1 Pranav S. Garimella,1 Ronit Katz,4 Stein I. Hallan,5 Vasanthan Jotwani,5 Rakesh Malhotra,5 Michelle M. Estrella,2 Jesse C. Seegmiller,1 Joachim H. Ix,3,7 Michael Shlipak,3 Alexander Bullen,2
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Background: Tubular secretion is an essential mechanism for the elimination of many drugs, metabolites, and toxins. Impaired tubular secretion may contribute to the high burden of adverse events (AEs) in persons with CKD. Whether novel measures of tubular secretion have prognostic value for AEs during hypertension treatment is unknown.

Methods: In 2008 SPRINT (Systolic Blood Pressure Intervention Trial) participants with baseline eGFR <60 ml/min/1.73m2, we created a summary secretion score from 10 tubular secretion biomarkers by averaging across their urine-to-plasma ratios. Multivariable Cox proportional hazards models were used to evaluate associations between secretion scores and risk of a composite of pre-specified serious AEs (hypertension, syncope, bradycardia, acute kidney injury, electrolyte abnormalities, and injurious falls) and two outpatient AEs (hyperkalemia and hypokalemia).

Results: Mean age was 73 ± 9 years and mean eGFR was 46 ± 11 ml/min/1.73m2. Overall, 30% of participants experienced at least one AE during a median follow-up of 3.2 years. The association between secretion score and composite AE risk followed a curvilinear pattern. Compared to the lowest secretion score quartile, the highest quartile was associated with reduced risk of the composite AE in analyses adjusting for demographics and clinical characteristics (hazard ratio [HR]: 0.63; 95% CI: 0.44, 0.91) (Table). After additionally adjusting for baseline eGFR and albuminuria, the association attenuated and was no longer significant (HR: 1.01, 95% CI: 0.67, 1.50). In multivariable analyses of the individual AEs, higher secretion was independently associated with higher risk of syncope or hypotension (HR per 1-SD higher secretion score: 1.30, 95% CI: 1.10, 1.54) and lower risk of ambulatory hyperkalemia (HR: 0.71, 95% CI: 0.54, 0.95).

Conclusions: Among SPRINT participants with CKD, higher tubular secretion was associated with lower AE risk, but this association was not independent of eGFR and albuminuria.

Funding: NIDDK Support

Table 2. Association of secretion score with serious adverse events in persons with CKD in SPRINT

<table>
<thead>
<tr>
<th>Event Rate</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite</td>
<td>0.87 (0.78, 0.96)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.63 (0.44, 0.91)</td>
</tr>
<tr>
<td>Syncope</td>
<td>0.68 (0.46, 1.01)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0.44 (0.08, 2.24)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>0.15 (0.01, 2.78)</td>
</tr>
<tr>
<td>Electrolyte abnormalities</td>
<td>0.63 (0.44, 0.91)</td>
</tr>
<tr>
<td>Injurious falls</td>
<td>0.63 (0.44, 0.91)</td>
</tr>
</tbody>
</table>

*Summary score calculated from averaging normalized urine-to-plasma ratios of all organic solutes.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

PO1794

Longitudinal Changes in FGF-23 and High-Sensitivity C-Reactive Protein with Incident CKD in the Accord-BP Trial

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Background: In adults over 50 with increased cardiovascular (CV) risk, intensive systolic blood pressure (SBP) lowering reduces the risk of death and major CV events, but increases the risk of incident CKD. Metabolic manifestations of incident CKD related to intensive SBP lowering are unknown. Here we explored the relation between incident CKD and FGF23, an early marker of bone and mineral metabolism, in participants enrolled in the ACCORD-BP trial.

Methods: We included 362 ACCORD BP participants with incident CKD during follow-up along with 359 control participants without any kidney events. Control participants were matched for age, sex, race/ethnicity, SBP intervention and glycemia treatment arms. Incident CKD was defined as a >30% decrease in eGFR to <60 ml/min/1.73m2. Serum concentrations of FGF23 and hs-CRP were measured using Meso Scale Discovery fluorescent immunoassays platform at baseline, month 24 and 48–close out. Differences from baseline were estimated for the average of month 24 and 48–close out using mixed effect models with fixed effects for group and visit.

Results: Mean age was 63±9 years, 55% women, and 30% non-white. Baseline duration of diabetes was 11±8 years; baseline eGFR, FGF23 and hs-CRP in the incident CKD and control groups were 87±17 and 92±19, 76(55,107) and 52(40,76) pg/ml and 3.2 (1.3,7.2) and 3.8(1.3,12.0) µm/ml, respectively. Longitudinal changes in these parameters are summarized in the Table and Figure.
POI1795

Carotid Plaque Characteristics and Incident Cognitive Impairment in Hypertensive Adults

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Background: Carotid atherosclerosis is associated with cognitive impairment. We investigated associations of plaque characteristics on carotid magnetic resonance imaging (MRI) with the development of mild cognitive impairment (MCI) or probable dementia.

Methods: In an ancillary study to the Systolic Blood Pressure Intervention Trial (SPRINT), carotid plaque was identified by MRI and characterized as having a lipid-rich necrotic core (NC) or calcification. In the parent study, adjudicated MCI and probable dementia were associated with both pre-event (odds ratio [OR], 2.04 [95% CI, 1.52–2.72]; P<0.001) and post-event dementia (hazard ratio [HR], 2.01 [95% CI, 1.65–2.44]; P<0.001) however, these associations attenuated and became non-significant after adjustment for the above covariates (OR=0.92 [0.65–1.31]; P=0.65 and HR=1.09 [0.85–1.39]; P=0.50). The results were similar when a competing risk model was used (subdistribution HR [SHR] =1.74 [1.43–2.12]; P<0.001, attenuating to 1.01 [0.78–1.33]; P=0.92 with complete adjustment). CKD was more strongly associated with late (>1 year) post-event dementia (SHR=2.32, 1.70–3.17; P<0.001), particularly in the minor events subgroup (SHR=3.08, 2.05–4.64; P<0.001), but not significantly so after complete adjustment (SHR=1.53, 0.90–2.60; P=0.12).

Results: Of 465 participants, 137 (29.5%) had NC plaque. Those with NC plaque were older and more likely to have cardiovascular disease than those without NC plaque. There were 38 MCI/probable dementia outcomes in the entire cohort over 2220 person-years of follow-up. The incidence (95% CI) of a composite outcome of MCI or probable dementia at 3 years of follow-up was 12.0% (7.5, 18.9) in the NC group and 7.0% (4.6, 10.4) in the no NC group with an absolute risk difference of 5.1% (95% CI -1.2, 11.3, P=0.11). With further adjustment, the absolute risk difference attenuated but the point estimate remained high (Figure). Results for the presence of any plaque or calcified plaque with MCI/probable dementia are also summarized in the Figure.

Conclusions: We observed large differences in risk for MCI/probable dementia associated with the presence vs. absence of NC plaques, but the significance of this finding was uncertain due to the small number of incident cases of cognitive impairment. Nonetheless, our observations indicate the need to study NC plaque as a novel and potentially more relevant marker of vascular health in future studies of cognitive impairment in hypertensive adults.

Funding: NIDDK Support, Veterans Affairs Support

POI1796

Associations of CKD with Dementia Before and After Transient Ischemic Attack and Stroke in a Population-Based Cohort Study


Background: Individuals with chronic kidney disease (CKD) appear to have a greater risk of developing cognitive disorders than the general population. Both vascular and neurodegenerative hypotheses have been proposed to underlie this cognitive burden.

To explore the vascular hypothesis further, we investigated the association between CKD and dementia before and after transient ischaemic attack (TIA) and stroke.

Methods: In a prospective, population-based cohort study of TIA and stroke (Oxford Vascular Study, 2002-2012), pre-event and new post-event dementia were ascertained through direct patient assessment and follow-up for 5 years, supplemented by review of hospital/primary care records. Associations between pre-dementia and CKD (defined as an estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m²) were examined using logistic regression, and between post-event dementia and CKD using both Cox and competing risk regression models, adjusted for age, sex, education, cerebrovascular burden (stroke severity, prior stroke, white matter disease), diabetes mellitus, and dyslipidaemia.

Results: Among 2305 TIA/stroke patients (median [IQR] age, 77 [67-84] years, 1174 [51%] male, 688 [30%] TIA), 1174 (50.9%) had CKD. CKD initially appeared to be associated with both pre-event (odds ratio [OR], 2.04 [95% CI, 1.52–2.72]; P<0.001) and post-event dementia (hazard ratio [HR], 2.01 [95% CI, 1.65–2.44]; P<0.001); however, these associations attenuated and became non-significant after adjustment for the above covariates (OR=0.92 [0.65–1.31]; P=0.65 and HR=1.09 [0.85–1.39]; P=0.50). The results were similar when a competing risk model was used (subdistribution HR [SHR] =1.74 [1.43–2.12]; P<0.001, attenuating to 1.01 [0.78–1.33]; P=0.92 with complete adjustment). CKD was more strongly associated with late (>1 year) post-event dementia (SHR=2.32, 1.70–3.17; P<0.001), particularly in the minor events subgroup (SHR=3.08, 2.05–4.64; P<0.001), but not significantly so after complete adjustment (SHR=1.53, 0.90–2.60; P=0.12).

Conclusions: In patients with TIA and stroke, CKD was not independently associated with either pre- or post-event dementia, suggesting that age, sex, education, and cerebrovascular burden may play a more important role in the relationship than renal-specific neurodegenerative mechanisms.

Funding: Other NIH Support - NIH National Heart, Lung, and Blood Institute, NIH RO1-HL134511
PO1798
Platelet Activity Mediates Enhanced Cardiovascular Risk in Patients with CKD and Peripheral Artery Disease

**Background:** Chronic kidney disease (CKD) is common in patients with peripheral artery disease (PAD), and both are associated with poor cardiovascular (CV) outcomes. Platelets drive PAD pathogenesis and mediate atherosclerosis. Platelet function in CKD and the related CV risk is unclear. We investigated relationships between CKD, platelet activity, and incident CV events in a cohort of patients with PAD.

**Methods:** The Platelet Activity and Cardiovascular Events (PACE) study enrolled 289 patients with PAD undergoing lower extremity revascularization (LER). CKD was defined as eGFR<60 mL/min/1.73m² by the CKD-EPI equation. We measured platelet activity via light transmission aggregometry (LTA) in response to submaximal ADP, collagen, serotonin, epinephrine, and arachidonic acid (AA) prior to LER, and followed patients for a median of 18 months. The primary clinical endpoints were myocardial infarction (MI) and a composite of major adverse CV events (MACE, MI, stroke, death).

**Results:** There were 113 (40%) patients with and 172 (60%) without CKD. Patients with CKD (vs. non-CKD) were older and more likely to be female, Hispanic, have diabetes, heart failure, and critical limb ischemia (P<0.05 for each). There were no significant differences in prevalent coronary artery disease or use of antithrombotic therapy between groups. Platelet aggregation in response to submaximal ADP, serotonin, epinephrine, and AA was elevated in the CKD group (Figure). After multivariable adjustment, patients with CKD were at greater risk of MI (aHR 2.2 [95% CI, 1.02-4.9]; P=0.045) and MACE (1.9 [1.2-3.3]; P=0.01) than those without CKD. Platelet aggregation in response to submaximal agonist stimulation had a 25% and 12% mediating effect on the association of CKD with PAD.

**Conclusions:** In patients with PAD, CKD was associated with increased platelet activity and CV events. Heightened platelet activity is an important mechanism underlying increased CV risk in CKD.

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PO1799
Circulating Vascular Adhesion Protein-1 Levels Predict Risk of Cardiovascular Events and Mortality in Hemodialysis Patients
Dae Kyu Kim,1 Yu ho Lee,2 Soo-Young Yoon,1 Jongho Kim,1 Jin sug Kim,1 Yang guyn Kim,1 So-young Lee,1 Shin-young Ahn,2 Shinyeong Kang,1 Dong-Young Lee,1 Kyung hwan Jeong,1 Ju young Moon,1 Hyeon Soek Hwang,1 Sangho Lee,1 Kyung Hee University Medical Center, Seoul, Republic of Korea; 2CHA Bundang Medical Center, Seongnam, Gyeonggi-do, Republic of Korea.

**Background:** Vascular adhesion protein-1 (VAP-1) is an oxidative enzyme of primary amnies that facilitates the transmigration of inflammatory cells. The oxidative and inflammatory effects of VAP-1 are prominently increased in pathological conditions such as metabolic, atherosclerotic, and cardiac diseases. However, the clinical significance of circulating VAP-1 levels in hemodialysis (HD) patients is unclear.

**Methods:** A total of 439 HD patients were enrolled from June 2016 to April 2019 as part of a prospective multicenter cohort study. Plasma VAP-1 levels were measured at the time of study data entry, and the primary endpoint was defined as a composite of cardiovascular (CV) events and cardiac events.

**Results:** Circulating VAP-1 levels were positively correlated with plasma levels of circulating VAP-1 levels in hemodialysis patients is unclear. Serum VAP-1 levels were positively correlated with ventricular (LV) mass index, LV end-systolic volume, and LV end-diastolic volume. Multivariate linear regression analysis revealed that VAP-1 levels was negatively correlated with LV ejection fraction (β = −2.14; p = 0.013). The cumulative event rate of the composite of CV events was significantly greater in VAP-1 tertile 3 (p = 0.049). VAP-1 tertile 3 was also associated with an increased cumulative event rate of cardiac events (p = 0.016). In Cox regression analysis, VAP-1 tertile 3 was associated with a 2.61-fold risk for the composite of CV events (95% confidence interval [CI], 1.37–4.97) and a 2.72-fold risk for cardiac events (95% CI, 1.33–5.56) after adjustment for multiple variables.

**Conclusions:** Higher circulating VAP-1 levels independently predicted the composite of CV events and cardiac events in HD patients. The results of this study suggest the importance of future studies on the effect of neprilysin inhibition in reducing CV events.

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PO1800
Circulating Neprilysin Level Predicts the Risk of Cardiovascular Events in Hemodialysis Patients
Hyeon Seok Hwang,1 Jin sug Kim,1 Yang guyn Kim,1 Yu ho Lee,2 Dong-Young Lee,1 Shin-young Ahn,2 Ju young Moon,1 Sangho Lee,1 Kyung hwan Jeong,1 Kyung Hee University Medical Center, Seoul, Republic of Korea; 2CHA Bundang Medical Center, Seongnam, Gyeonggi-do, Republic of Korea; 3Korea Veterans Health Service, Seoul, Republic of Korea; 4Korea University Medical Center, Seoul, Republic of Korea.

**Background:** Neprilysin inhibition has demonstrated impressive benefits in heart failure treatment, and is the current focus of interest in cardiovascular (CV) and kidney diseases. However, the role of circulating neprilysin as a biomarker for CV events is unclear in hemodialysis (HD) patients.

**Methods:** A total of 439 HD patients from the K-cohort were enrolled from June 2016 to April 2019. The plasma neprilysin level and echocardiographic findings at baseline were examined. The patients were prospectively followed up to assess the primary endpoint (composite of CV events and cardiac events).

**Results:** Plasma neprilysin level was positively correlated with ventricular (LV) mass index, LV end-systolic volume, and LV end-diastolic volume. Multivariate linear regression analysis revealed that neprilysin level was negatively correlated with LV ejection fraction (β = −2.14; p = 0.013). The cumulative event rate of the composite of CV events was significantly greater in neprilysin tertile 3 (p = 0.049). Neprilysin tertile 3 was also associated with an increased cumulative event rate of cardiac events (p = 0.016). In Cox regression analysis, neprilysin tertile 3 was associated with a 2.61-fold risk for the composite of CV events (95% confidence interval [CI], 1.37–4.97) and a 2.72-fold risk for cardiac events (95% CI, 1.33–5.56) after adjustment for multiple variables.

**Conclusions:** Higher circulating neprilysin levels independently predicted the composite of CV events and cardiac events in HD patients. The results of this study suggest the importance of future studies on the effect of neprilysin inhibition in reducing CV events.

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PO1801
Serum Cathepsin-S Concentration Is Not Related to Arterial Calcification Severity Among Hemodialysis Patients
Hao-Wei Ma,1 Chih-Ching Lin,2 Szu-Yuan Li. Taipei Veterans General Hospital, Taipei, Taiwan.

**Background:** Vascular calcification is prevalent among hemodialysis patients and is strongly correlated to their cardiovascular and total mortality. Cathepsin S, a lysosomal cysteine protease that is elevated in CKD patients, has shown its critical role of vascular calcification in cell culture experiments and in uremic animal model. To validate the relationship of Cathepsin S and vascular calcification in clinical practice, we conducted the current cross sectional study.

**Methods:** 88 patients on maintenance hemodialysis were enrolled and their serum Cathepsin S and its natural inhibitor Cystatin C were measured. Serum level of vascular calcification was semi-quantified by aortic arch calcification (AAC) score on chest X-rays. Patients were divided into groups according to their AAC score, and the serum Cathepsin S level, Cathepsin S / Cystatin C ratio and other factors were compared between groups.

**Results:** There was no significant difference in the level of Cathepsin S (p=0.778) or Cathepsin S to Cystatin C ratio (p=0.417) between patients with different aortic arch calcification score. Only age was associated with the severity of AAC score (p=0.014).

**Conclusions:** Despite a pre-clinical study supporting the role of Cathepsin S in the development of vascular calcification under uremic and phosphate-rich conditions, serum Cathepsin S was not found to be associated with vascular calcification severity among hemodialysis patients in this study. Serum cathepsin S is the strongest predicting factor for higher Cathepsin S levels in these patients. Further study is needed to confirm these findings using a different grading system.
Mean age and serum Cathepsin S with 95% confidence interval between groups of patients, categorized by their Aortic arch calcification (AAC) grade.

POI1802

Kidney Function Trajectory Following Left Ventricular Assist Device Implantation

Carl P. Walther, Julia Benoit, Harveen Lamba, Sankar D. Navaneethan.

Background: LVADs have variable effects on kidney function. Identification of distinctive eGFR trajectory groups after LVAD placement, by applying unsupervised techniques to longitudinal eGFR measures, may enable insights into diverse pathophysiology.

Methods: From a national cohort, we identified persons who underwent isolated, primary continuous flow LVAD implantation in the US, 2016-17. eGFR values from pre-LVAD implantation to 12 months post were used. Latent class mixed models using cubic splines were applied to derivation and validation subsets, and models with 2-9 distinct groups were evaluated to find the optimal number.

Results: In the cohort (3,461 in derivation subset, 1,154 in validation), we identified 5 distinct trajectory groups. The 2 largest groups (1,2) are similar to previously reported cohort averages, with early eGFR increase followed by decline, but differed by baseline eGFR. Three smaller groups (3-5, ~15% of the cohort) demonstrated novel trajectories: group 3 had early worsening with sustained low kidney function; 4 had early and sustained eGFR improvement, and 5 had substantial eGFR variation. These groups differed in baseline factors (groups 3 and 4 had the most pre-LVAD acute dialysis, 4 and 5 the most cardiogenic shock) and outcomes (groups 2 and 4 had the highest survival, 3 and 5 had the lowest).

Conclusions: Novel eGFR trajectories after LVAD implantation were identified in a national cohort. Group 4, with early and sustained increase in eGFR, may reflect type 1 cardiorenal syndrome. Group 3 may reflect chronic kidney disease with early complications, and group 5 may reflect intact kidney parenchyma but post-LVAD right ventricular failure. These results demonstrate the feasibility of identifying previously unobserved heterogeneity in kidney outcomes. The novel trajectory groups may reveal potential for tailored care, in addition to pathophysiologic insights.

Funding: NIDDK Support

POI1803

Which Loop Is Best? Comparing the Effect of Loop Diuretic Prescribing on Mortality and Heart Failure Readmission

Arti V. Virkud, Abhijit V. Kshirsagar, Patricia Chang, Michele Jonsson Funk, Jessica K. Edwards, Michael R. Kosorok, Emily Gower.

Background: Loop diuretics are a mainstay of heart failure (HF) management. While furosemide is most commonly prescribed, torsemide and bumetanide are increasingly being prescribed, possibly due to their superior bioavailability. Few trials or real-world evidence studies have compared the effectiveness of prescribing these loop diuretics while adequately addressing critical study design biases.

Methods: We identified beneficiaries initiating the study loop diuretics by using an active comparator, new-user cohort design and Medicare claims data from 2007-2017. We estimated 1-year risks of death and a composite outcome (HF readmission/death) using inverse probability of treatment weighting to adjust for relevant confounders. We calculated a dose equivalence based on furosemide to adjust for disease severity.

Results: We identified 45,310 furosemide, 1,148 torsemide, and 1,630 bumetanide new users. In the total weighted population, 24.3% had a reduced ejection fraction, 27.1% had CKD (≥ Stage 2), with a mean age of 80.1 years and a mean furosemide dose equivalent of 50.8 mg/mL. The 1-year risk of death across all study loop diuretics was similar (19.9%-20.6%), whereas the risk of the composite outcome was more varied (29.1%-32.0%). The 1-year risk difference (95% CI) of the composite outcome was -2.9% (-6.2, 0.4) for torsemide vs. furosemide and -1.1% (-3.8, 1.6) for bumetanide vs. furosemide.

Conclusions: Among Medicare beneficiaries, the risk of HF readmission/death varies meaningfully with torsemide having a reduced risk compared to other study loop diuretics. This study leverages claims data and causal methodology to generate a less biased and more generalizable estimate than previous studies. While additional trial and real-world evidence studies are needed, this study suggests initial loop diuretic prescription after HF hospitalization may produce long-term differences in risk of death and HF readmission.

Funding: NIDDK Support

POI1804

Diuretic Resistance in Acute Decompensated Heart Failure with Preserved vs. Reduced Ejection Fraction

Akash Sharma, Rahul Patel, Chakradhar Velagapudi, Shweta Bansal.

Background: Loop diuretic resistance (DR) is one of the common causes of inadequate decongestion in patients hospitalized with acute decompensated heart failure (ADHF). However, DR has not been characterized in patients with HF with preserved ejection fraction (HFpEF). We estimate 1-year risks of death and a composite outcome (HF readmission/death) among Medicare beneficiaries with HF hospitalization and initiating a loop diuretic (2007-2017).

Methods: We identified beneficiaries initiating the study loop diuretics by using an active comparator, new-user cohort design and Medicare claims data from 2007-2017. We estimated 1-year risks of death and a composite outcome (HF readmission/death) using inverse probability of treatment weighting to adjust for relevant confounders. We calculated a dose equivalence based on furosemide to adjust for disease severity.

Results: We identified 45,310 furosemide, 1,148 torsemide, and 1,630 bumetanide new users. In the total weighted population, 24.3% had a reduced ejection fraction, 27.1% had CKD (≥ Stage 2), with a mean age of 80.1 years and a mean furosemide dose equivalent of 50.8 mg/mL. The 1-year risk of death across all study loop diuretics was similar (19.9%-20.6%), whereas the risk of the composite outcome was more varied (29.1%-32.0%). The 1-year risk difference (95% CI) of the composite outcome was -2.9% (-6.2, 0.4) for torsemide vs. furosemide and -1.1% (-3.8, 1.6) for bumetanide vs. furosemide.

Conclusions: Among Medicare beneficiaries, the risk of HF readmission/death varies meaningfully with torsemide having a reduced risk compared to other study loop diuretics. This study leverages claims data and causal methodology to generate a less biased and more generalizable estimate than previous studies. While additional trial and real-world evidence studies are needed, this study suggests initial loop diuretic prescription after HF hospitalization may produce long-term differences in risk of death and HF readmission.

Funding: NIDDK Support
**Conclusions:** Although the comparisons were not statistically significant due to small sample size; the results suggest that DR is more prevalent in HFpEF. Despite similar clinical features of congestion and response to high-dose spironolactone, a state of reduced neurohormonal activation points that additional factors might be contributing to DR in HFpEF compared to HFrEF patients.

**Funding:** Commercial Support - Relypsa Education Grant

Table 1: Baseline characteristics of HFrEF vs. HFpEF patients

<table>
<thead>
<tr>
<th></th>
<th>RS=HFrEF (n=171)</th>
<th>DR=HFrEF (n=86)</th>
<th>Total=HFrEF (n=257)</th>
<th>RS=HFpEF (n=102)</th>
<th>DR=HFpEF (n=56)</th>
<th>Total=HFpEF (n=158)</th>
<th>p-value</th>
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<tr>
<td>Age (years)</td>
<td>55 (41.1)</td>
<td>55 (41.1)</td>
<td>55 (41.1)</td>
<td>55 (41.1)</td>
<td>55 (41.1)</td>
<td>55 (41.1)</td>
<td>0.39</td>
</tr>
<tr>
<td>Male (%)</td>
<td>68 (69.1)</td>
<td>65 (75.6)</td>
<td>68 (69.1)</td>
<td>58 (56.9)</td>
<td>54 (96.4)</td>
<td>60 (38.1)</td>
<td>0.55</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>28.7 (7.3)</td>
<td>28.7 (7.3)</td>
<td>28.7 (7.3)</td>
<td>30.3 (8.4)</td>
<td>32.9 (5.7)</td>
<td>31.2 (6.9)</td>
<td>0.06</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>120 (20.7)</td>
<td>120 (20.7)</td>
<td>120 (20.7)</td>
<td>120 (20.7)</td>
<td>120 (20.7)</td>
<td>120 (20.7)</td>
<td>0.26</td>
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<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>76 (14.3)</td>
<td>76 (14.3)</td>
<td>76 (14.3)</td>
<td>75 (14.3)</td>
<td>74 (14.3)</td>
<td>75 (14.3)</td>
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<tr>
<td>Pulmonary Edema (%)</td>
<td>64.7</td>
<td>90</td>
<td>82.9</td>
<td>90</td>
<td>90</td>
<td>90</td>
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<tr>
<td>Diuretics (mg/day)</td>
<td>57</td>
<td>57</td>
<td>57</td>
<td>57</td>
<td>57</td>
<td>57</td>
<td>0.3</td>
</tr>
<tr>
<td>eGFR at baseline (mL/min/1.73m²)</td>
<td>80 (22.3)</td>
<td>80 (22.3)</td>
<td>80 (22.3)</td>
<td>80 (22.3)</td>
<td>80 (22.3)</td>
<td>80 (22.3)</td>
<td>0.96</td>
</tr>
<tr>
<td>Plasma creatinine (mg/dL)</td>
<td>0.9 (0.4)</td>
<td>0.9 (0.4)</td>
<td>0.9 (0.4)</td>
<td>0.9 (0.4)</td>
<td>0.9 (0.4)</td>
<td>0.9 (0.4)</td>
<td>0.96</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>59.9 (9.9)</td>
<td>59.9 (9.9)</td>
<td>59.9 (9.9)</td>
<td>59.9 (9.9)</td>
<td>59.9 (9.9)</td>
<td>59.9 (9.9)</td>
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<td>NYHA functional class</td>
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<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>1.0</td>
</tr>
<tr>
<td>Brain natriuretic peptide (pg/mL)</td>
<td>16.1 (12.1)</td>
<td>16.1 (12.1)</td>
<td>16.1 (12.1)</td>
<td>16.1 (12.1)</td>
<td>16.1 (12.1)</td>
<td>16.1 (12.1)</td>
<td>0.12</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>123 (78.0)</td>
<td>123 (78.0)</td>
<td>123 (78.0)</td>
<td>123 (78.0)</td>
<td>123 (78.0)</td>
<td>123 (78.0)</td>
<td>0.96</td>
</tr>
<tr>
<td>Brain natriuretic peptide (pg/mL)</td>
<td>16.1 (12.1)</td>
<td>16.1 (12.1)</td>
<td>16.1 (12.1)</td>
<td>16.1 (12.1)</td>
<td>16.1 (12.1)</td>
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<td>0.12</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>123 (78.0)</td>
<td>123 (78.0)</td>
<td>123 (78.0)</td>
<td>123 (78.0)</td>
<td>123 (78.0)</td>
<td>123 (78.0)</td>
<td>0.96</td>
</tr>
<tr>
<td>Aldosterone (ng/mL)</td>
<td>46.4</td>
<td>46.4</td>
<td>46.4</td>
<td>46.4</td>
<td>46.4</td>
<td>46.4</td>
<td>0.96</td>
</tr>
<tr>
<td>Aldosterone (ng/mL)</td>
<td>46.4</td>
<td>46.4</td>
<td>46.4</td>
<td>46.4</td>
<td>46.4</td>
<td>46.4</td>
<td>0.96</td>
</tr>
<tr>
<td>Erythropeptide (pmol/L)</td>
<td>145</td>
<td>145</td>
<td>145</td>
<td>145</td>
<td>145</td>
<td>145</td>
<td>0.96</td>
</tr>
<tr>
<td>Erythropeptide (pmol/L)</td>
<td>145</td>
<td>145</td>
<td>145</td>
<td>145</td>
<td>145</td>
<td>145</td>
<td>0.96</td>
</tr>
<tr>
<td>Norepinephrine (pg/mL)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>0.96</td>
</tr>
<tr>
<td>Norepinephrine (pg/mL)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>0.96</td>
</tr>
</tbody>
</table>

RS=Responsive, DR=Diuretic Resistant

**PO1805**

Renal Outcomes and Safety of Angiotensin Receptor Neprilysin Inhibitors in Patients with Heart Failure: A Meta-Analysis

Rima N. Abou arkoub, Thomas Mavrokanas, Amy Bergeron, Abhinav Sharma, Ahsan Alam. 1McGill University Health Centre, Montreal, QC, Canada; 2McGill University Health Centre Glen Site McConnell Resource Centre Medical Library, Montreal, QC, Canada.

**Background:** Angiotensin receptor neprilysin inhibitors (ARNIs) are an effective treatment for heart failure. However, their safety profile compared with angiotensin converting enzyme-inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) with respect to renal outcomes has not been clearly established.

**Methods:** We conducted a literature search of MEDLINE, Cochrane library, Embase, and clinical trials registries using relevant search terms (last search date May 7, 2021). The primary renal outcome was kidney function decline and the safety outcome was hyperkalemia. Only studies with at least 12 weeks of follow up were included in the renal outcome analysis to better capture CKD.

**Results:** Ten randomized controlled trials were eligible for inclusion (n=22,174 participants). ARNIs were associated with a lower risk of kidney function decline compared with ACEIs or ARBs: RR 0.65 (95% CI 0.53-0.81). The risk of hyperkalemia was similar in both treatment groups: RR 0.96 (95% CI 0.81-1.13).

**Conclusions:** ARNI use in patients with heart failure is associated with a lower risk of kidney function decline and a similar risk of hyperkalemia compared to ACEIs or ARBs.
PO1806
Hydralazine-Isosorbide Dinitrate Associated with Reduced All-Cause and Cardiovascular Mortality in Patients on Dialysis with Heart Failure
Qandeel H. Soomo,1 Thomas Mavrakanas,2,3 David M. Charytan,1,4 1NYU Langone Health, New York, NY; 2McGill University, Montreal, QC, Canada; 3Brigham and Women’s Hospital, Boston, MA

Background: Heart failure (HF) is an important contributor to the increased cardiovascular (CV) mortality incidence in ESKD. Therapies targeting HF’s unique pathophysiology in ESKD are lacking. Hydralazine-isosorbide dinitrate (H-ISDN) targets reduced nitric oxide bioavailability and could improve CV mortality in ESKD

Methods: Adult patients with HF on maintenance dialysis between January 2011 and December 31, 2016 were identified using the United States Renal Data System. There were 6306 patients with at least one prescription for H-ISDN and 75,851 non-users. The primary outcome was death from any cause. Secondary outcomes included cardiovascular death and sudden death. Treatment effects were estimated using stabilized inverse probability weights in Cox proportional hazards regression. Because H-ISDN has been shown to improve outcomes in Black HF patients, we investigated effect modification by race

Results: Age was similar in H-ISDN users (66 ± 13 years) and non-users (69 ± 13 years) with 50% and 51% men, respectively. H-ISDN (51%) users were more likely to be of Black race than non-users (27%). Dialysis vintage was longer in H-ISDN (25 months) users compared with non-users (15 months). All characteristics were well balanced in weighted models. Risks of all-cause mortality, cardiovascular death, and sudden death were significantly reduced in H-ISDN users compared to non-users (Table). We did not identify significant effect modification by race (Figure)

Conclusions: To our knowledge, this is the first analysis of the impact of H-ISDN on mortality in ESKD. Our results suggest that combination H-ISDN improves survival in dialysis patients with HF

PO1807
Long-Term Outcomes After Renal Revascularization for Atherosclerotic Renovascular Disease in the ASTRAL Trial
Philip A. Kalra,1,2 Darren Green,1,2 Natalie Ives.1 The ASTRAL trial investigators 1Salford Royal Hospital, Salford, United Kingdom; 2The University of Manchester, Manchester, United Kingdom; 3University of Birmingham, Birmingham, United Kingdom

Background: The Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial randomized 806 patients with atherosclerotic renal artery stenosis (RAS) between 2000-2007, randomised 1:1 to medical therapy with or without renal artery stenting. The initial results were presented in 2009 at median follow-up 34.6 months when no benefit of revascularization to renal functional outcome or cardiovascular events (CVE) was evident. Surviving patients remained under follow up until 2014.

Methods: All available data were analysed to assess whether there was a later impact of revascularization on renal function, CVE and survival, including a composite outcome of renal and CV outcomes and death (as used in the CORAL trial). Pre-specified sub-group analyses of different categories of renal function, renal length, prior rapid deterioration in kidney function, and severity of RAS. Further post-hoc analysis of patients with severe RAS (defined as bilateral 70% or > 70% RAS in a solitary kidney – global renal ischemia), those with/without proteinuria and a per protocol analysis were performed.

Results: The mean age of the entry population was 70.5 years, mean eGFR 40 ml/min/1.73m², with mean RAS 76% and blood pressure 150/76 mmHg. 83% of the revascularization group underwent attempted stenting. Median follow-up was 56.4 months with 108 patients lost to follow up or withdrawn; 50% of the evaluable population had died, 14% had received RRT and 40% had suffered a 1° CVE. No benefit of revascularization was observed for any outcome in the intention to treat and per protocol analyses, either in the whole population or the pre-specified sub-groups. In the severe RAS sub-group (163 patients) revascularization was associated with a hazard ratio (HR) of 0.74 (0.54-1.01; p=0.062) for the composite renal and CV outcome and an HR of 0.70 (0.49-1.0) for death (p=0.051).

Conclusions: The long-term follow-up of the ASTRAL trial population showed no overall benefit of renal revascularization to renal and CV outcomes. It has been highlighted that a proportion of the population had lower risk mild-moderate RAS. The long-term outcomes in patients with severe RAS (global renal ischemia) point to a potential benefit of stenting that may be worthy of further study in a more selected population.

Funding: Government Support - Non-U.S.

PO1808
Revascularization in Atherosclerotic Bilateral Renal Artery Stenosis
Sana J. Shaikh, Bilal Al-Khalil, Ling Chen, Anitha Vijayan. Washington University in St Louis, St Louis, MO.

Background: Patients with B/L RAS, if found to have worsening renal failure, refractory HTN or recurrent CHF, are often referred for revascularization despite limited evidence. We hypothesized that revascularization plus medical management prevents adverse outcomes in patients with B/L RAS.

Methods: This was a retrospective single-center cohort study in patients with B/L RAS, RAS in a solitary kidney, U/L RAS with an atrophic or <1cm smaller contralateral kidney or, RAS in a U/L functioning kidney. We excluded patients with non-atherosclerotic RAS, renal artery dissection, atheroembolism and renal transplantation. The primary outcome was Major Adverse Kidney Events (MAKE) at 3 mo. Secondary outcomes were renal events, changes in BP, hospital admissions and all-cause mortality at 1 yr. We used the Chi-square test for the primary outcome and the Chi-square test or two-sample t-tests for the secondary outcomes.

Results: 153 patients were included in the study. There were no differences in the baseline characteristics of the intervention and control groups, except for higher number of smokers in the control cohort (Table 1). There was no difference in MAKE between the 2 groups at 3 mo. At 1 yr, there were fewer admissions for CHF in the intervention group (Table 2). There were no other major differences in secondary outcome measures.

Conclusions: Revascularization for B/L RAS does not improve renal outcomes, BP control or mortality, but may prevent admissions for CHF.

Table 1: Baseline characteristics
<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention Group (N=69)</th>
<th>Control Group (N=84)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>68 (98.6)</td>
<td>81 (96.4)</td>
<td>0.413</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>19 (27.5)</td>
<td>22 (26.2)</td>
<td>0.852</td>
</tr>
<tr>
<td>CKD stage 3 or more</td>
<td>39 (56.5)</td>
<td>42 (50.0)</td>
<td>0.421</td>
</tr>
<tr>
<td>TIA/CVA</td>
<td>11 (15.9)</td>
<td>13 (15.5)</td>
<td>0.937</td>
</tr>
<tr>
<td>ASCVD equivalent disease</td>
<td>34 (49.3)</td>
<td>46 (54.8)</td>
<td>0.499</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>29 (40.2)</td>
<td>43 (51.2)</td>
<td>0.259</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>22 (33.3)</td>
<td>21 (25.0)</td>
<td>0.037</td>
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<tr>
<td>Obesity</td>
<td>20 (29.0)</td>
<td>23 (27.8)</td>
<td>0.772</td>
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<tr>
<td>Dyslipidemia</td>
<td>36 (51.2)</td>
<td>62 (73.8)</td>
<td>0.529</td>
</tr>
<tr>
<td>History of smoking</td>
<td>36 (51.2)</td>
<td>61 (73.5)</td>
<td>0.020</td>
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</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Hypertension in a Young Female: A Common but an Intriguing Anecdote
Bailoo,1 Sohail Sabir.2 1Foundation University Medical College, Rawalpindi, Pakistan; 2National University of Medical Sciences, Rawalpindi, Pakistan

Introduction: Renal artery stenosis accounts for about 1-10% of the 50 million people worldwide with hypertension. All major trials conducted so far on RAS found no benefit with renal artery stenting. Here we report a case of resistant hypertension in a young female who subsequently found to have bilateral renal artery stenosis and ultimately benefited from unilateral stenting.

Case Description: A 35 yrs female, married, with no comorbidities, presented with 03 months history of intermittent episodes of throbbing headache along with dizziness, palpitations, fatigue. Examination revealed BP - 160/100 with no postural drop, and regular pulse with no radio-radial, radio-femoral delays. Her baseline investigations(including blood complete picture, LFTs, RFTs, urine routine examination, PTT:PTK were Normal. Hepatitis B and C serology were negative) USG abdomen showed right shrunken kidney with no renal artery flows on Doppler ultrasound. She was put on four different groups of anti hypertensives including a beta blocker, a calcium channel blocker, thiazide diuretic and an angiotensin receptor blocker but her blood pressure did not settle. Further investigations revealed raised ESR but other tests including autoimmune screening, 2DECHO all negative-CT aortogram revealed a non visualised shrunken right kidney. So based on renal imaging findings, a final diagnosis of bilateral renal artery stenosis was made. Percutaneous transluminal angioplasty with stenting to proximal left renal artery was done. She was given dual antiplatelets along with a statin post operatively and advised monthly follow up. Currently she is normotensive.

Long-Term Safety and Efficacy of Renal Denervation with the Symplicity Spyral Catheter in the Global SYMPLICITY Registry
Markus P. Schlaefer,1 Felix Mahfoud,2 Bryan Williams,3 Luis M. Ruijlope,4 Krzysztof Narkiewicz,2 Martin Faly,2 Giuseppe Mancia,2 Michael Böhnm,2 1The University of Western Australia, Perth, WA, Australia; 2Universitätsklinikum des Saarlandes und Medizinische Fakultät der Universität des Saarlandes, Homburg, Germany; 3University College London, London, United Kingdom; 4Hospital Universitario 12 de Octubre, Madrid, Spain; 5Gänsis Universitet Medyczny, Gdańsk, Poland; 6Università degli Studi di Milano-Bicocca, Milano, Italy; 7Medtronic Inc, Minneapolis, MN.

Background: Catheter-based renal denervation (RDN) therapy targets overactivity of the sympathetic nervous system to treat hypertension. Results from recent randomized sham-controlled clinical trials have demonstrated the safety and efficacy of RDN, but long-term safety and durability of the procedure in real-world patients is also important.

Methods: The Global SYMPLICITY Registry (GSR) is a prospective, international registry of patients who receive radiofrequency RDN treatment due to uncontrolled hypertension or conditions associated with excessive sympathetic nervous system activation. Office and ambulatory blood pressure (BP) levels were measured at baseline, 3, 6, 12, 24, and 36 months per standard of care. Adverse events were collected out to 3 years. In this analysis, we present safety and efficacy data for patients who received RDN with the multi-electrode Symplicity Spyral catheter in GSR.

Results: Currently there are 641 patients treated with the Symplicity Spyral catheter (baseline office BP 168±25 mmHg, 4.6±1.5 prescribed anti-hypertensive medication classes, mean age 60.5±12.5 years, 56.9% male, 42.5% history of cardiace disease, 37.2% type II diabetes mellitus, and 19.1% renal insuficiency with eGFR<60 ml/min/1.73m²).

At 1 year, there were no cases of new renal artery stenosis >70% or renal artery re-intervention. Rates of other adverse events at 3 years included new onset end stage renal disease (2.4%), cardiovascular death (1.6%) and myocardial infarction (0.8%). Mean change in eGFR from baseline to 3 years was -6.5±15.7 mL/min/1.73m². Changes in mean 24-hour and office BP from baseline to 6, 12, 24 and 36 months are shown in the Figure.

Conclusions: Office and 24-hour BP were significantly reduced from baseline at all follow up time-points after RDN with the Symplicity Spyral catheter, with no instances of renal artery re-intervention.

Funding: Commercial Support - Medtronic

Endovascular Renal Denervation Efficacy in a Five-Year Follow-Up
João Carvalho,1 Patricia Q. Branco,2 Catarina Mateus,2 Pedro Gonçalves,2 Manuel D. Almeida,3 Maria augusta C. Gaspar,2 1Servico de Saúde da Regiao Autonoma da Madeira, Funchal, Portugal; 2Centro Hospitalar de Lisboa Ocidental EPE Hospital da Santa Cruz, Carnaxide, Portugal.

Background: Endovascular renal denervation (ERD) is a minimally invasive procedure that uses radiofrequency ablation to burn the nerves in the renal arteries. Renal sympathetic nerves can modulate sympathetic activity at the whole body level, playing an important role in essential hypertension. This study aims to evaluate ERD efficacy in the treatment of essential hypertension in a five-year follow-up.

Methods: We conducted a prospective study including 41 patients with essential hypertension. ERD was performed using Simplicity Probe or Spyral. Blood pressure (BP) was evaluated using 24-hour ambulatory BP monitoring. Echocardiography was performed using HDI 5000. Clinical and biochemical variables were explored.

Results: A total of 41 patients were included. Overall, 53.7% (n=22) were females with a mean age of 63.6 ± 7.5 years, BMI 30.8 ± 5.2 Kg/m², 17.1% (n=7) had an estimated glomerular filtration rate (eGFR) < 60ml/min/1.73m² and 68.3% (n=28) had diabetes. Proteinuria (>300mg/g) was found in 24.4% (n=10) of the patients. A significant reduction in the number of antihypertensive drugs being taken was found after 5 years’ follow-up (p<0.001). Despite this reduction, a significant reduction in diastolic blood pressure.
(DBP) (p = 0.001) was found, but not in systolic blood pressure (SBP) (p = 0.08). Also left ventricle mass index (LVMi) reduced significantly (p = 0.0001) and a reduction of acute elevation of left ventricle filling pressure (LVFP) was detected using E’/E (p = 0.0001). There was a worsening of eGFR (p = 0.0001) as expected by the progressive worsening of kidney function. We have found a non significant reduction in proteinuria (p = 0.07). In female patients with a reduction in proteinuria, it was not associated with BP and an overall reduction in proteinuria when using multivariate analysis. In a multivariate analysis, the reduction in the number of antihypertensive drugs, of the LVMi, SBP and DBP were not related with age, gender, body mass index and proteinuria.

From our observation, we managed to reduce the number of antihypertensive drugs and still patients DBP with RDN. Also RDN showed benefits in reducing LVMi and LVFP. Reduction of proteinuria, when present, was independent of BP and an overall LVMi. There was a worsening of kidney function as expected in a long term follow-up. RDN has been shown to be an effective mean of treating essential hypertension.

**PO1812**
Potential Benefits of Asymptomatic Hyperuricemia Treatment: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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**Background:** Asymptomatic hyperuricemia is strongly associated with an increased risk for chronic kidney disease and cardiovascular conditions. However, many current guidelines suggest no medical treatment for patients with asymptomatic hyperuricemia. We aim to systematically analyze randomized control trials with serum uric acid-lowering medication in the treatment of patients with asymptomatic hyperuricemia.

**Methods:** A literature review of seven medical databases (Scopus, Clinical Gov, Pubmed, Web of Science, Google Scholar, VHL, and GHL) for randomized controlled trials related to the treatment of asymptomatic hyperuricemia was conducted. Bias was evaluated using the Cochrane Risk of Bias 2 tool. Standard differences of means of variables of interest were combined across studies to compare the effects of uric acid lowering treatment versus control. Using the Comprehensive Meta-Analysis Program, fixed-effects and random heterogeneity model, forest plots were created for each variable of interest.

**Results:** Analysis of eleven studies showed significant decreases in creatinine [0.302 (95% CI: -0.599, 0.005)], systolic blood pressure [-0.277 (95% CI: -0.5, -0.055)], and serum uric acid [-1.972 (95% CI: -2.145, -1.800)] in the treatment versus control group. Furthermore, significant increases in estimated glomerular filtration rate (eGFR) after analysis sensitivity [0.228 (95% CI: 0.027, 0.428)], and high sensitivity-C reactive protein [0.588 (95% CI: 0.205, 0.971)] were observed in the treatment versus control group. Lastly, non-significant increases in creatinine [0.087 (95% CI: -0.269, 0.042)], and diastolic blood pressure [-0.312 (95% CI: -0.638, 0.013)], while non-significant increases in hemoglobin A1C [0.394 (95% CI: -0.026, 0.813)] and fasting glucose level [0.117 (95% CI: -0.145, 0.380)] were found in the treatment versus control group.

**Conclusions:** This study showed that uric acid lowering treatment of patients with asymptomatic hyperuricemia may be beneficial in those with elevated creatinine and blood pressure, and decreased eGFR.

**PO1813**
Urinary Glycogen Synthase Kinase 3β Level Predicts the Progression of Hypertensive Nephrosclerosis

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**Background:** Hypertensive nephrosclerosis (HTN) is a serious consequence of end-stage kidney disease. Recently, emerging evidence suggests that glycogen synthase kinase (GSK) 3β is a key factor in the progression of diabetic kidney disease (DKD). However, it remains uncertain whether the role of GSK3β is specific for DKD or a generic mediator of renal damage irrespective to the underlying cause. We aim to 1. identify patients with biopsy-confirmed HTN patients. Their GSK3β 3 level in urinary supernatant was measured by conventional ELISA, and GSK3β mRNA level in urinary sediment was measured by quantitative polymerase chain reaction. The results were compared to the baseline kidney function and the subsequent risk of renal function deterioration. 2. The results: average GSK3β 3 level was 212.67 ± 47.74 nL/g by conventional ELISA, which closely correlated with its mRNA level in urinary sediment (r = 0.821, P = 0.0001). Urinary GSK3β level significantly correlated with baseline glomerular filtration rate (GFR) (r = 0.337, P = 0.010) and the slope of GFR decline (r = 0.397, P = 0.033). Patients with a high urinary GSK3β level has a higher risk of developing 40% kidney function loss and progressing to dialysis-dependent kidney failure than those with a low GSK3β level. 3. GSK3β 3 mRNA level also significantly correlated with baseline GFR (r = 0.582, P < 0.0001) and the slope of GFR decline (r = -0.402, P = 0.022). Patients with a high urinary GSK3β mRNA level has a higher risk of developing 40% kidney function loss and progressing to dialysis-dependent kidney failure than those with a low GSK3β level (p = 0.022 and p = 0.004, respectively).

**Conclusions:** These results demonstrated that urinary GSK3β level correlates with the rate of kidney function loss in patients with biopsy-confirmed HTN, and urinary sediment GSK3β level appears to be a better prognostic marker than urinary GSK3β level by ELISA. Our results suggest that GSK3β is a generic mediator for the progression of chronic kidney disease and is not specific for DKD.

**Funding:** Clinical Research Support, Government Support - Non-U.S.
**Conclusions:** These observations are compatible with a sexual dimorphism in the NKA via mechanism of regulation of NHE3 and Na+ transport in the RPT. This study highlights the importance of improving our understanding of the natriuretic mechanism of NKA signaling in the RPT and its potential impact on sex-based differences in renal physiology and pathophysiology.

**Funding:** Private Foundation Support

**POI1816**

Sex-Dependent Regulation of the WNK-NCC Pathway via Ubiquitination in Response to Dietary High Salt Intake in Young Sprague-Dawley Rats

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**Background:** The thiazide-sensitive Na+-Cl–cotransporter (NCC), located in the thick ascending limb of distal convoluted tubule, fine-tunes sodium reabsorption and regulates blood pressure. The NCC is downregulated by high salt intake in normotensive salt resistant rats. These studies investigated the potential mechanistic pathways by which NCC is degraded in response to high salt intake in male and female Sprague-Dawley (SD) rats.

**Methods:** 3-month-old normotensive male and female SD rats were fed a normal salt (NS; 0.6% NaCl) or HS (4% NaCl) diet for 21 days. On day 21, the kidneys were collected and ~200 mg of the renal cortex was used to measure the expression of total NCC, WNK1, WNK4, Nedd4-2, Sortilin, KLHL3, and calcineurin via immunoblotting (N=5–6/group).

**Results:** A 21-day HS diet evokes the suppression of total NCC protein expression in young normotensive male and female SD rats. A HS diet downregulated WNK1 in male but not female SD rats. HS diet suppressed the expression of the full-length and short WNK4 variants in female SD rats only. There was a trend for HS to increase Nedd4-2 expression in male SD rats (P=0.06), in contrast female rats downregulated Nedd4-2 in response to HS. The expression of sortilin, KLHL3, and calcineurin was suppressed by a HS diet in female SD rats.

**Conclusions:** These data suggest that in response to a HS diet young female SD rats exhibit greater ubiquitin-dependent proteolytic and lysosomal degradation of the NCC with young male SD rats to regulate sodium homeostasis and blood pressure via a WNK-dependent signaling pathway.

**Table 1:** NS, 0.6% NaCl; HS, 4% NaCl. *P*<0.05 vs. respective NS Group.
Conclusions: Thus far, we report a shift in the histaminergic tone toward less histamine production and increased NO production, which led to a reduced HS diet. Dahl SS rats are associated with HT2 blocker exhibit lower water consumption, reduced diuresis, and increased urinary osmolality.

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PO1820 Salt-Induced Blood Pressure Elevation in Females Is Associated with Increased Arachidonic Acid Metabolites
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Background: Excess dietary sodium (Na+) intake is a major risk factor for salt-sensitive hypertension and cardiovascular disease. Several clinical trials have found that women are more salt-sensitive than men, but the contributing sex-specific mechanisms are poorly understood. Arachidonic acid (AA) and its metabolites play a role in the pathophysiology of hypertension. We hypothesized that women have greater blood pressure (BP) elevation in response to Na+ intake that is associated with higher AA metabolites than men.

Methods: Plasma AA metabolites were measured via a metabolomics analysis in volunteers who completed a validated 3-day food record to estimate dietary Na+ intake before the study visit where BP was measured. Based on the recommendations by the American Heart Association, we classified daily Na+ intake <2.3g as normal salt, and high salt for subjects consuming a 2.3g Na+. Spearman correlation was used to assess the relationship between AA metabolites and SBP/DBP, and sex differences in BP response.

Results: Women (n=81) displayed a stronger relationship between BP and Na+ intake than men (n=49) (r=0.372; p=0.001 vs. r=0.317; p=0.026). The relationship between Na+ intake and BP was stronger in white (n=46, r=0.4172; p=0.004) than in black (n=22, r=0.338; p=0.124) women and conversely stronger in black (n=7, r=0.70; p=0.034) than white (n=32, r=0.251; p=0.166). We measured plasma levels of palmitate and linoleate, both upstream of AA synthesis, AA, and 12-Hydroxyeicosatetraenoic acid (12-HETE) an AA metabolite. In subjects consuming a high Na+ diet (women 28, men 25) levels of linoleate (1.211 ± 0.330 vs. 0.869 ± 0.170, p<0.001), palmitate (1.155 ± 0.292 vs. 0.924 ± 0.233; p= 0.003), AA (1.119 ± 0.242 vs. 0.965 ± 0.201; p=0.015) and 12-HETE (1.329 ± 0.925 vs. 0.92 ± 0.52; p=0.0469) were higher in women. In contrast, no sex differences in any of these parameters were observed between men and women consuming a normal salt diet.

Conclusions: Our findings suggest that AA and its metabolites may account for sex and perhaps also racial differences in salt sensitivity of BP. Further study of AA and its metabolites may shed light on the mechanisms of the sex differences in salt sensitivity.

Funding: Other NIH Support - NHLBI

PO1821 Gstm1 Genotype Affects Metabolic Response in Hypertension
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Background: Glutathione S-transferases (GSTs) are a family of enzymes that detoxify electrophilic compounds and products of oxidative stress. In humans, GST μ- (GSTM1) has a common null allele variant, GSTM1/0, which has been linked to elevated oxidative stress in pathophysiological conditions and increased risk and/or accelerated progression of a variety of diseases. Recently, we reported that Gstm1 knockout (KO) mice had increased oxidant stress and augmented kidney injury in angiotensin II (Ang II)-induced hypertension (HTN).

Methods: Kidney tissue was obtained from 12-20 week old male wild-type (WT) and Gstm1 knockout (KO) mice at either baseline (no treatment) or following 4 weeks of Ang II- induced HTN via mini-osmotic pump at 1000 ng/kg/min. For each animal, a kidney was excised and snap frozen. For qPCR, mRNA was extracted from an homogenized kidney and used to create cDNA, followed by probing for a panel of 18 Gt genes. For metabolomics, frozen tissue was ground to a fine powder and sent to Metabolon (Morrisville, NC) to obtain a global metabolic profile.

Results: Analysis of qPCR results showed no significant alternations in the expression of Gt genes between WT and KO mice, except for the expected loss of Gstm1 in KO mice. Metabolomics analysis yielded data for 926 metabolites, with expected significant increases in compounds with known pro-inflammatory effects and a further 131 (14%) displayed an interaction between genotype and treatment. Comparing Ang II-treated KO and WT mice, there was a significant increase in metabolite abundance in the methionine and glutathione pathways, including the transulfuration pathway linking them. Furthermore, there was an increase in carnitine and anserine and a decrease in several lipid peroxidation markers.

Conclusions: The loss of GSTM1 in Ang II-induced HTN did not elicit a significant compensatory upregulation of mRNA of other GSTs. It is likely other antioxidant pathways are upregulated based on the altered metabolite abundances. However, based on previous results in treated KO mice, any compensatory mechanism is insufficient to protect against the oxidative stress-induced kidney damage. Further research should be pursued to elucidate the oxidative stress-related specific substrates of GSTM1 that are not detected by other pathways.

Funding: NIDDK Support

PO1822 HMGB-1 Activates Mineralocorticoid Receptor-Dependent Endothelial Cell Injury via Receptor for Advanced Glycation End Products
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Background: Endothelial dysfunction plays a central role in the pathogenesis of cardio-renal syndrome. High mobility group box-1 (HMGB-1) is a protein with various roles in different cellular compartments, and indirectly regulates the activity of transcription and DNA repair in the nucleus. On the other hand, during tissue damage, it is released into the extracellular environment as damage-associated molecular patterns (DAMPs). HMGB-1 has been shown to be elevated in CKD patients and be involved in endothelial dysfunction through binding to toll like receptor (TLR) and receptor for advanced glycation end products (RAGE). In addition, we recently demonstrated that RAGE-mediated Rac1 activated mineralocorticoid receptor (MR) and resulted in podocytes damage. In the present study, we hypothesized that crosstalk between HMGB-1/ RAGE and Rac1-MR pathways could contribute to endothelial dysfunction in kidney diseases.

Methods: In the present study, we investigated whether HMGB-1 could activate Rac1-MR axis and induce endothelial injury in cultured umbilical vein endothelial cells (HUVECs) by assessing expression levels of genes for MCP-1 and cell adhesion factors (ICAM-1, VCAM-1) with or without administration of RAGE antagonist or MR blocker (exsrenorenne, 1uM).

Results: HMGB-1 supplementation significantly increased GTP-bound Rac1 and enhanced MR transcription into the nucleus in HUVECs. We also found that RAGE expression was enhanced by HMGB-1 and RAGE antagonist completely abolished Rac1 activation and MR translocation observed in HMGB-1 exposed HUVECs. HMGB-1 also upregulated MCP-1, ICAM-1, and VCAM-1 in HUVECs, all of which were significantly blocked by pretreatment of Rac1 antagonist as well as MR blocker.

Conclusions: These results suggest that there may be a close relationship between HMGB-1/ RAGE axis and Rac1/ MR activation, thus contributing endothelial injury. Using RAGE antagonist or MR blocker could be novel therapeutic strategies against endothelial dysfunction in patients with kidney diseases.

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PO1824

Effect of Tochu Extract and Its Component Geniposidic Acid on Renal Hemodynamics and Hypertensive Renal Damage
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Background: Aqueous extract of Eucommia ulmoides (Tochu) leaf is used as Tochu tea in Japan and has the effect of lowering blood pressure. We investigated the effects of Tochu extract and its component geniposidic acid on renal hemodynamics and hypertensive renal damage in Dahl salt-sensitive hypertensive rats (DS).

Methods: DS rats received 1% saline solution from 4 weeks of age. After the blood pressure reached 150 mmHg or higher at 9 weeks of age, the rats were treated with 1% saline solution (DSHS), or 1% saline added 0.5% Tochu extract (DSHS + T) or, 1% saline added 0.2% geniposidic acid (DSHS + G) for another 4 weeks. RS rats fed with tap water were used as controls (DSLS). At 13 weeks, renal plasma flow (RPF) was measured by renal clearance study, and immunostaining and PCR of NADPH oxidase, eNOS, sodium transporters and fibrinectin factors were performed.

Results: Blood pressure was significantly increased in DS rats compared to DSLS rats (196 vs.144 mmHg, p<0.01), which was significantly decreased in DS + T rats (158 mmHg) and DS + G rats (162 mmHg). Vascular resistance of afferent arterioles was significantly increased in DS + G rats compared to DSLS rats, and was decreased in both DS + T and DS + G rats. RPF was significantly higher in DS + T rats than in DSLS rats associated with reduced renal vascular resistance (p <0.05). In DSLS rats, NADPH oxidase expression and superoxide production were increased, with increased TGF-beta, procollagen 1, fibronectin and renal fibrosis. These were suppressed in DS + T and DS + G rats. NO production by eNOS was decreased in DSLS rats, but the treatment groups increased eNOS expression and NO production in the vascular endothelium, resulting in decreased renal vascular resistance and improved renal blood flow. Urinary sodium excretion was significantly higher in DSLS rats than in DS + T rats with increased sodium chloride co-transporter (NCC). However, there was no further change in NCC or other sodium transporters in the treatment groups, and the high urinary Na excretion in the treatment groups was due to the increased RPF.

Conclusions: Tochu and geniposidic acid suppressed NADPH oxidase and increased eNOS in DS rats, resulting in improved blood pressure, renal hemodynamics and renal damage.

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PO1825

Effect of Uremia on Endothelial Cell Damage Is Mediated by Excessive Neutrophil Extracellular Trap Formation
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Background: Uremia is a clinical syndrome characterized by accumulation of various uremic toxins and associated metabolic abnormalities in chronic kidney disease (CKD). Patients with CKD are at increased risk for cardiovascular (CV) disease and death, and endothelial dysfunction may be a key uremia-specific risk factor. However, the mechanism by which uremia influences endothelial dysfunction is still unclear. We report a role for excessive neutrophil extracellular trap (NET) formation induced by uremic serum on endothelial cell (EC) injury.

Methods: Plasma nucleosome and myeloperoxidase-DNA, representative markers of in vivo NETs, and the intracellular adhesion molecule (ICAM)-1 level were measured in incident hemodialysis (HD) patients and healthy volunteer (HV), and their prognostic role was evaluated. For in vitro study, we differentiated HL-60 cells into neutrophil-like cells (dHL-60) by applying retinoic acid, and the effect of uremic serum on dHL-60 and ECs were determined.

Results: The amount of in vivo NETs were significantly higher in incident HD patients compared to HV, and the markers were strongly associated with ICAM-1 levels. In particular, nucleosome and ICAM-1 levels were independent predictors of a composite endpoint, all-cause mortality or vascular access failure. In vitro, uremic serum derived from HD patients showed significantly increased NETs formation from dHL-60, and these NETs significantly decreased EC viability and induced apoptosis. In addition, the ICAM-1 level in HUVEC supernatant was significantly increased by uremic serum-induced NETs compared to control serum-induced NETs.

Conclusions: Dysregulated neutrophil activities in the uremic milieu may play a key role in endothelial damage and vascular inflammatory responses.

PO1826

Contributions of Obesity and Hypertension to Progression of Cardiovascular Disease
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Background: Obesity and hypertension are highly prevalent in patients with cardiorenal syndrome (CRS). Insight in how these comorbidities individually contribute to disease progression is required to improve treatment strategy. We dissected the separate contribution of obesity and worsening hypertension by deoxycorticosterone acetate (DOCA) plus high salt diet in the obese female ZSF1 rat, a model of metabolic CRS in the absence of diabetes [Nguyen, PLoS One 2020]. We hypothesize that in obese non-diabetic female ZSF1 rats obesity has a profound effect on functional progression of CRS while hypertension mainly affects fibrosis and inflammation.

Methods: Systolic blood pressure (SBP), renal and cardiac function were assessed biweekly in lean and obese female ZSF1 rats from 12 to 26 weeks of age. From 19 weeks, rats were implanted with either a DOCA pellet and fed a high salt (6% w/w) diet or with a placebo pellet and fed a normal salt diet. At 26 weeks of age, glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were assessed under isoflurane anesthesia. Subsequently, rats were sacrificed and tissues processed for analysis of renal and cardiac damage and inflammation.

Results: Obese versus lean placebo rats showed elevated E/e' ratio from 12 weeks, indicative of diastolic dysfunction. From 24 weeks obese compared to lean placebo rats developed proteinuria with lower GFR at 26 weeks of age. DOCA-salt markedly increased SBP in obese but not lean rats, despite similarly high natriuresis compared to placebo rats. ERPF was increased by DOCA-salt in lean but not obese rats. DOCA-salt worsened proteinuria and glomerulosclerosis in obese rats. Cardiac fibrosis and glomerular hypertrophy, present in obese rats, were not aggravated by DOCA-salt.

Conclusions: DOCA-salt increased the number of macrophages in heart, but not in glomeruli of obese ZSF1 rats.

Funding: Private Foundation Support

PO1827

Association Between Kidney Function and Lipid Levels in Older Adults
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Background: The associations between kidney function and lipid levels in older adults have not been well characterized. Moreover, it is unknown whether residual atherosclerotic cardiovascular disease (ASCVD) risk after statin use differs by lipid levels other than total cholesterol (TC) or low-density lipoprotein cholesterol (LDL-C), such as triglyceride (TG).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: We conducted a cross-sectional study of older adults (≥65 years) using visit 5 data (2011-2013) of the Atherosclerosis Risk in Communities study. Multivariable linear and logistic regression was used to examine the eGFR-lipid level associations, stratified by statin use. Among statin users without ASCVD who had LDL-C levels ≥100 mg/dL, we predicted 10-year ASCVD risk after statin use by TG levels (<150 mg/dL vs. ≥150 mg/dL) across eGFR levels.

Results: The mean age of the study population (n=4965) was 75 (SD 5) years, 58% were female, and 22% were Black. The mean eGFR was 63 (SD 18) ml/min/1.73 m² and 52% were on statins. In both statin users and non-users, there were no associations between eGFR and total TG or LDL-C. Low eGFR was associated with low high-density lipoprotein cholesterol (HDL-C) and high TG (Figure). Among statin non-users, eGFR <45 (vs. ≥60) was independently associated with low HDL-C (<50 mg/dL) (prevalence 95% CI: 1.86; 96% CI: 1.38-2.51) and high TG (≥150 mg/dL) (31% vs. 20%; 1.15; 1.01-1.30). The results were similar among statin users. Among statin users with LDL-C ≥100 mg/dL, the prevalence of high predicted ASCVD risk (risk ≥20%) was greater among those with vs. without high TG across all eGFR categories (eGFR ≥60, 66% vs. 59%; 45-59, 78% vs. 73%; eGFR <45, 90% vs. 79%).

Conclusions: We found that low eGFR was associated with low HDL-C and high TG levels, regardless of statin use. Among statin users who achieved adequate LDL-C control, ASCVD risk was still higher among those with high TG compared to those without high TG.

Funding: NIDDK Support

Adjusted associations between eGFR and lipid levels in older adults

POI1829
Cerebrovascular Dysfunction in CKD
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Background: Cerebrovascular dysfunction, characterized by reduced cerebrovascular reactivity, cerebral hypoperfusion, and increased pulsatile flow within the brain precedes the onset of dementia and is linked to cognitive dysfunction. While large-artery vascular dysfunction is prevalent in chronic kidney disease (CKD), cerebrovascular function has not been well characterized to date in moderate-to-severe CKD.

Methods: Using transcranial Doppler, we compared middle cerebral artery (MCA) blood flow-velocity response to hypercapnia (normalized for blood pressure and end-tidal CO₂) in a measure of cerebrovascular reactivity) and MCA pulsatility (a measure of cerebrovascular stiffness) in patients with stage 3-4 CKD vs. age-matched healthy controls using an independent samples t-test. We also administered the trail making test (parts A and B) as an index of processing speed and measured carotid-femoral pulse-wave velocity (CFPWV) as an index of aortic stiffness.

Results: Seven participants with CKD (2F, 68±3 yrs [means±SEM]), estimated glomerular filtration rate [eGFR]: 38±5 ml/min/1.73m²) were compared to 8 healthy controls (1F, 63±2 yrs, eGFR: 83±5 ml/min/1.73m²). MCA pulsatility index was greater (1.08±0.10 vs. 0.85±0.04 A.U.; p=0.05) and normalized MCA blood flow-velocity response to hypercapnia tended to be lower (6.3±4.0 vs. 11.6±7.3 %; p=0.06) in CKD as compared to healthy controls. Trail making part A time was slower (A: 31.8±3.3 s vs. 20.2±1.6 s; p<0.01); part B time tended to be slower (longer time to complete): 71.7±13.6 s vs. 42.7±6.7 s; p=0.07) and CFPWV was greater (1122±115 vs. 811±88 cm/sec; p=0.05) in CKD vs. control. Greater MCA pulsatility index correlated with worse cerebrovascular reactivity (r = −0.63, p=0.01), greater CFPWV (r = 0.65, p<0.01), slower trail making part B time (r = 0.59, p<0.05), and lower eGFR (r = −0.53, p=0.09).

Conclusions: Impaired cerebrovascular function is evident in patients with moderate-to-severe CKD. Increased cerebrovascular stiffness is associated with reduced kidney function, increased aortic stiffness, impaired processing speed, and worse cerebrovascular reactivity.

POI1830
Circadian Clock Provides Beneficial Effects Against Endothelial Dysfunction by Regulating Heme Synthesis and Heme Oxygenase 1 Expression
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Background: The circadian clock is a molecular mechanism that confers 24 hours variations in gene expression and function to regulate number of physiological functions in humans. Chronic circadian clock disruption is associated with vascular stiffness and dysfunction in endothelial signaling and responses. 5-Aminolevulinic acid (ALA) is the common precursor of heme. The iron ion is inserted into PPIX to form heme in the mitochondrion and incorporated into hemoproteins. Heme is a ligand of REV-ERBα and REV-ERβ which modulate circadian rhythms by binding to the ROR region of CLOCK or BMAL1 to suppress the expression of these genes. Heme oxygenase-1 (HO-1) is an intracellular enzyme which catalyzes the oxidation of heme to generate ferrous iron, carbon monoxide, and biliverdin, which is subsequently converted to bilirubin. These products have anti-inflammatory, anti-apoptotic and anti-thrombotic properties. In this study, we observed if the deletion of Bmal1, a critical component of the circadian clock, can influence HO-1 which play an important part in the protection of vascular diseases.

Methods: Congenic 12- to 16-week-old male, wild-type and Bmal1-KO littermate mice were generated from heterozygote breedings to be used for these studies. We also knocked down Bmal1 in different cell lines to evaluate the protein levels of HO-1 expression in the knocked down cells. To synchronize circadian rhythms, serum stimulations were performed. Cells were also pre-incubated with or without 1 mM ALA and 0.5 mM sodium ferrous citrate (SFC).

Results: In aorta from Bmal1 KO mice, there was a reduction in HO-1 expression in mice with a dysfunctional circadian rhythm. Bmal1 KO mice display pre-mature aging to have a dramatic prothrombotic phenotype. This phenotype is linked to the regulation of key regulators for cardiovascular disease. These include HO-1 which is significantly reduced in Bmal1 KO mice. ALA/SFC co-incubation affected the oscillation and phase variation in gene expression and function to regulate number of physiological functions in humans. Chronic circadian clock disruption is associated with vascular stiffness and dysfunction in endothelial signaling and responses. 5-Aminolevulinic acid (ALA) is the common precursor of heme. The iron ion is inserted into PPIX to form heme in the mitochondrion and incorporated into hemoproteins. Heme is a ligand of REV-ERBα and REV-ERβ which modulate circadian rhythms by binding to the ROR region of CLOCK or BMAL1 to suppress the expression of these genes. Heme oxygenase-1 (HO-1) is an intracellular enzyme which catalyzes the oxidation of heme to generate ferrous iron, carbon monoxide, and biliverdin, which is subsequently converted to bilirubin. These products have anti-inflammatory, anti-apoptotic and anti-thrombotic properties. In this study, we observed if the deletion of Bmal1, a critical component of the circadian clock, can influence HO-1 which play an important part in the protection of vascular diseases.

Conclusions: These findings indicate that circadian clock provides beneficial effects against the endothelial dysfunction to promote atherothrombosis by regulating Heme synthesis and HO-1 expression. This study establishes a mechanistic connection between Bmal1 and cardiovascular phenotype.

Funding: Government Support - Non-U.S.
PO1831
Bradykinin Reduces Long-Lasting TRPV1-Mediated Inward Currents in Afferent Nonfiring Renal Neurons
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Background: Bradykinin has been reported to be sympathoexcitatory via renal afferent nerves. Hence we tested the hypothesis that bradykinin directly stimulates cultivated renal neurons with afferent axons.

Methods: Dorsal root ganglion neurons (Th11-L2) of rats were investigated in voltage clamp mode to assess inward currents and current clamp mode to assess action potential (AP) generation [neurons classified as tonic (high AP generation upon stimulation), phasic (AP ≤ 5 upon stimulation) or no firing]. Stimulation of TRPV1 receptors by protons (pH 6) with and without the addition of bradykinin (1, 10, 100 µM). 111 DRG renal neurons retrogradely stained with Dil for investigation.

Results: Bradykinin (BK) alone did not induce inward currents nor APs. Proton stimulation (pH 6) of TRPV1 significantly augmented long-term inward currents (baseline -0.36 ± 0.09 nA vs. -1.39 ± 0.34 nA, p < 0.05, mean±SEM) and increased action potential generation in tonic neurons (0 APs/10s vs. 9.57 ± 1.89 APs/10s, p < 0.05, mean±SEM). However, the co-stimulation of renal neurons with protons and BK had any effect only in one specific subgroup of renal neurons: it significantly decreased long-lasting currents in non firing neurons (AD stimulation with 100µM BK+HCl: -0.12 ± 0.62 nA, 10µM BK+HCl: -0.11 ± 0.07 nA; 1µM BK+HCl: -0.06 ± 0.02 nA versus pH 6: -0.32 ± 0.06 nA*, **p < 0.05, mean±SEM).

Conclusions: Bradykinin was only able to reduce long-lasting, TRPV1 dependent inward currents in non-firing renal neurons. Alterations of inward currents are likely involved in the release of neurogenic proinflammatory peptides (SP, CGRP). Hence, bradykinin might impair the release of neuropetides from intraretal axons of a specific subgroup of renal afferent neurons.

PO1832
The Impact of rs2254524 LSS Polymorphism on Blood Pressure in a New Mouse Model
Sipontina Paolo,
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Background: Bradykinin was only able to reduce long-lasting, TRPV1 dependent inward currents in non-firing renal neurons. Alterations of inward currents are likely involved in the release of neurogenic proinflammatory peptides (SP, CGRP). Hence, bradykinin might impair the release of neuropetides from intraretal axons of a specific subgroup of renal afferent neurons.

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T Lymphocytes in Human Hypertension
Ghalz Z. Quinn,1 Xin Sheng,1 Amin Abedini,1 Lynda Vuong,2 Briania G. Nixon,2 Jonathan Hill,2 Steven S. Pullen,1 Myung Shin,3 Ming Li,4 A. A. Hakimi,1 Katalin Suzsak,1 University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; 2Memorial Sloan Kettering Cancer Center, New York, NY; 3Bristol-Myers Squibb, Inc., Ridgefield, CT; 4Merck & Co Inc, Kenilworth, NJ.

Background: Mouse models have shown that T lymphocytes are required for hypertension (HTN) development and accumulate in the vasculature and kidneys. The role of immune cells, including T lymphocytes, remains poorly understood in patients with HTN. Here, we analyzed immune cells in human kidney tissue samples in patients with HTN.

Methods: Human kidney tissue was obtained from the unaffected portions of 631 tumor nephrectomies and included clinical, histological and follow-up tissue data. Tissue was microdissected into glomerular and tubular compartments for RNA-sequencing. In silico deconvolution of each kidney sample was performed using the CIBERSORTx method to enumerate relative cell type fractions. Flow cytometry was used for validation analyses using cell type specific antibodies in another set of 58 human kidney tissue samples. Regression analyses were used to determine the associations of renal immune cells and clinical parameters. Linear mixed modeling was used to assess longitudinal data.

Results: CD4 and CD8 T-cells were increased in patients with HTN (p=0.05) while T regulatory cells (Tregs) were decreased (0.4% vs. 0.6%, p=0.022). In adjusted models, HTN was associated with older age, Black race, diabetes, decreasing eGFR, and lower Tregs and natural killer T-cells and higher CD4 T-cells were associated with HTN, independent of baseline eGFR or the degree of renal fibrosis (p<0.01). We observed that 3.8mM BGP decreased fibronectin expression (p<0.01), but did not significantly change trimeric collagen I (COL1) expression. Additionally, 3.8mM BGP decreased fibronectin expression (p<0.01), but did not significantly change trimeric collagen I (COL1) expression. In vitro studies involving treatment of human ventricular cardiac fibroblast models were also conducted.

Results: Hearts from HD donors exhibited significant myofibrosis (p<0.01) compared to HTN and control. HD and HTN hearts had higher heart weights (p<0.01) and greater LV wall thickness (p<0.01) compared to control hearts. RNA-sequencing revealed that the focal adhesion pathway was one of the most perturbed pathways in HD hearts compared to control. FAK mRNA and protein expression was significantly upregulated (p<0.05), and major cytoskeletal proteins associated with the focal adhesion pathway, including β-actin (p<0.01), β-tubulin (p<0.01), vinculin (p<0.05), and vimentin (p<0.01) were significantly dysregulated in HD hearts compared to control. Uremic mineral stressors (high phosphate and high calcium) decreased FAK expression as well as β-tubulin (p<0.05) and vimentin, and promoted cleavage of FAK and vimentin, in vitro. Concurrent FAK sRNA transfection and mineral stress significantly decreased both full-length and cleaved FAK expression (p<0.05) and further dysregulated vimentin (p<0.05) and vinculin (p<0.05) expression, in vitro.

Conclusions: FAK and the focal adhesion pathway plays a central role in the development of CKD-associated cardiomyopathy and appears to preserve the dynamic formation and turnover of cytoskeletal HD hearts. These findings suggest a potential therapeutic target for regulating the focal adhesion pathway in the management of cardiac remodeling in CKD.
Plasma Proteins Associated with eGFR and Incident Cardiovascular Events in the Cardiovascular Health Study Cohort

Christine P. Limonte,1 Pranav S. Garimella,2 Robert Gorszet,3 Diana I. Jalal,4 Michelle Odde,5 Michael Shlipak,6 Nisha Bansal,7 Thomas R. Austin,8 Ian H. de Boer,9 University of Washington, Seattle, WA; 10 The University of Iowa Hospitals and Clinics, Iowa City, IA; 11 University of California San Francisco, San Francisco, CA; 12 University of California San Diego, La Jolla, CA; 13 Beth Israel Deaconess Medical Center, Boston, MA; 14 Stanford University, Stanford, CA.

Background: Proteinomics may help identify mechanisms through which low estimated glomerular filtration rate (eGFR) increases risks of heart failure (HF), myocardial infarction (MI), and cardiovascular (CV) death. We investigated the changes in pendrin levels in urinary extravasal (uEV) and intracellular vesicles (eVs) from patients with aldosterone (PA) and in rats with aldosterone-induced hypertension.

Methods: We designed an aptamer-based assay to measure 1300 proteins among 3185 older adults in the Cardiovascular Health Study. Proteins associated with eGFR were identified using linear regression models. A Bonferroni-corrected p-value less than 7.6x10^-8 was used to account for multiple testing. Proteins significantly associated with eGFR were tested for associations with incident HF, MI, and CV death using Cox-proportional hazard regression adjusting for demographic and clinical variables. We evaluated whether proteins mediated associations between eGFR and incident CV events.

Results: The mean baseline eGFR was 70 ml/min/1.73m^2 and over a follow-up median of 13 years, there were 1033 incident HF, 555 incident MI, and 963 CV death events. 797 proteins were significantly associated with eGFR. Of these, 52, 0, and 22 proteins were associated with incident HF, MI, and CV death, respectively. All proteins associated with HF and CV death significantly mediated the effects between eGFR and incident CHF and CV death, respectively. The 10 proteins most strongly associated with both HF and CV are shown in Table.

Conclusions: eGFR is associated with a large number of plasma proteins. A subset of these proteins are also associated with incident HF and CV death and may reflect mechanisms through which reduced eGFR increases the risk of these outcomes.

Funding: Other NIH Support - NIH - NHLBI

Conclusions: This study included 30 patients who were diagnosed as having PA in Yokohama Rosai Hospital or in Teikyo University Hospital. The protocol was approved by the institutional review board. In animal experiments, SD rats received continuous infusion of aldosterone after uninephrectomy. Isolation of uEV was performed by the ultracentrifugation method in accordance with the previous report (Fernandez-Llama et al. JCI 2010).

Results: Western blot analysis revealed that pendrin is detected in dimeric and monomeric forms in uEVs in humans and in rats. In aldosterone-infused rats, pendrin levels in uEVs were highly correlated with the pendrin abundance in the kidney. We also found significant correlation between abundance in uEVs and that in the kidney for Na-CI cotransporter and epithelial Na channel in this model. In PA patients, pendrin levels in uEVs were reduced by 49% from the baseline by adenectomy or pharmacological MR blockade. Correlation analysis revealed that the magnitude of pendrin reduction after treatment significantly correlated with the baseline aldosterone-renin ratio (ARR), and tended to inversely correlate with serum K+ levels. Furthermore, a cross-sectional analysis in PA patients confirmed a significant correlation between ARR and pendrin levels in uEVs.

Conclusions: These data are consistent with experimental studies demonstrating the role of pendrin in aldosterone-induced hypertension, and suggest that pendrin analysis in uEVs may also be useful to understand the pathophysiology of human hypertension.

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PO1843
Correlations of Creatinine with Biomarkers of Tubular Injury and Secretory Function in Patients Admitted with Heart Failure
Alexander J. Kula,1,2 David K. Prince,2 Kevin D. O’Brien,2 Bryan R. Kestenbaum,2 Song Li,2 Nisha Bansal,2 Seattle Children’s Hospital, Seattle, WA;1University of Washington, Seattle, WA.

Background: Serum creatinine values during hospitalization for decompensated heart failure (ADHF) may not comprehensively capture kidney function. The aim of this pilot study was to evaluate correlations of traditional markers of filtration (serum creatinine) with novel measures of tubular injury and tubular secretion in patients admitted with ADHF.

Methods: Biospecimens were obtained within 24 hours of admission in 61 patients admitted with ADHF at a University of Washington hospital. We measured serum creatinine, urine tubular injury markers (urine NGAL, KIM-1, II-18 and TIMP2 standardized to urine creatinine) and proximal tubular secretory function ([urine concentration]/[plasma concentration] normalized to U). We calculated spearman correlations of each kidney measure with each other and admission serum brain natriuretic peptide (BNP).

Results: Serum creatinine poorly correlated to biomarkers of tubular injury (Table 1). Higher serum creatinine was significantly correlated with lower clearance of all secretory biomarkers aside from cinnamoylglycine. Admission BNP did not correlate with serum creatinine or injury biomarkers but had a consistent inverse relationship with secretory biomarkers aside from cinnamoylglycine. Admission BNP poorly correlated to biomarkers of tubular injury (Table 1).

Conclusions: The results from this pilot study demonstrate that serum creatinine poorly correlates with biomarkers of tubular injury and inversely correlates with tubular secretory clearance in patients admitted for ADHF. More research is needed to understand how filtration, tubular injury, and secretory clearance relate to clinical outcomes and response to treatment in patients with ADHF.

Funding: NIDDK Support

Table 1: Correlation matrix of biomarkers on admission for ADHF

PO1844
RAAS vs. COVID: Case of an 18-Year-Old with New-Onset Hypertension
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Introduction: It has been increasingly known that SARS-CoV-2 causes an imbalance in the Renin-Angiotensin-Aldosterone System (RAAS). Here we present an interesting case of a young man, who presented with new onset of HTN and elevated renin and aldosterone levels with a history of COVID-19.

Case Description: An 18-year-old Caucasian man with a remote history of asthma initially presented to his primary care physician with new onset of headaches. He was noted to have an elevated blood pressure, but otherwise a benign physical examination. A workup for secondary HTN revealed an elevated renin (8.7 ng/mL/hr), aldosterone levels (42 ng/dL) and otherwise unremarkable. He was started on Enalapril 5mg daily. A workup including CT and MRI of the brain, were unremarkable. He was referred to nephrology for the new diagnosis of HTN and elevated renin and aldosterone levels with a history of COVID-19.

During the initial renal evaluation, patient was asymptomatic and his BP was well controlled on the Enalapril. Renin and aldosterone levels were repeated, about 8 weeks after the cessation of Enalapril. Patient’s blood pressure remained well controlled and didn’t require any medications. Since the diagnosis of HTN, the patient maintained a strict low salt diet. He always had good fluid intake. At a follow up visit, patient continued to remain asymptomatic and with good blood pressure control without needing medications. Repeat renin (1.9 ng/mL/hr) and aldosterone (16.8 ng/dL), as well as aldosterone/renin levels were resulted within normal limits. Later patient admitted that he was diagnosed with COVID-19 a month prior to his onset of headaches.

Discussion: SARS-CoV-2, which causes COVID-19, is known to hijack the RAAS cascade and use ACE2 enzyme to make human cell entry. Studies have demonstrated the possible correlation between COVID severity and comorbidities such as HTN (potentially involving the RAAS). Current recommendations are to continue the use of ACE Inhibitors (ACEI) and Angiotensin Receptor Blockers (ARB) in COVID-19 patients. Our case, not only supports the above findings, but also demonstrates how RAAS is vulnerable to SARS-CoV-2, can manifest with new onset HTN and other complications. It is also interesting to see, how ACEIs and ARBs should be utilized as first line agents for BP control and to improve outcomes. To much relief, the effect on RAAS by the SARS-CoV-2 seems to be transient and short lived.
Page Kidney and Uncontrolled Hypertension: Rare Complication Post Kidney Biopsy

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Introduction: Page kidney is a rare phenomenon defined as an external compression of the renal parenchyma that can lead to hypertension and acute kidney injury. Compression of the renal parenchyma can occur from the formation of a subcapsular hematoma of traumatic or non-traumatic origin. This phenomenon can be seen as a rare cause of hypoperfusion related to subcapsular hematoma formation following kidney biopsy. We report a case of a 34-year-old male with chronic kidney disease who developed abdominal pain and uncontrolled hypertension within 24 hours of kidney biopsy, found to have imaging findings consistent with Page kidney as a complication of the procedure.

Case Description: A 34-year-old male patient with a history of HTN, CAD, and stage 3B CKD presented to the ER with left flank pain and hypertensive urgency with SBP > 200 mmHg one day following a native kidney biopsy. He underwent a kidney biopsy for evaluation of sub-nephrotic range proteinuria and unclear etiology of CKD. CT abdomen/pelvis with contrast demonstrated a new 3.5 cm left subcapsular hematoma with perinephric and retroperitoneal extension. Abdominal pain worsened and repeat imaging showed expansion of the hematoma up to 24.5 cm. Before, during, and after kidney biopsy, the patient had well-controlled HTN with SBP range in the 130-140 mmHg. The day following the biopsy, SBP had risen to over 200 mmHg. Given his recent biopsy, significant HTN, and expansion of subcapsular hematoma on imaging, Page kidney was identified as the culprit leading to uncontrolled HTN. He was admitted to the ICU and started on a nicardipine drip with improvement in BP. Interventional radiology was consulted, and the patient underwent a left renal angiogram showing active extravasation at the hematoma site, which was then embolized. The patient achieved adequate BP control and the nicardipine drip was successfully weaned off. He was then transitioned back to his home oral antihypertensives.

Discussion: Page kidney refers to a condition in which there is an external force compressing the kidney resulting in decreased kidney perfusion manifesting in a state of ischemia. This activates the RAAS system leading to secondary hypertension. Although many cases have previously been reported, Page kidney remains an uncommon cause, especially over recent years, of uncontrolled secondary hypertension and acute kidney injury.

Non-suppressed Plasma Renin Activity in Primary Aldosteronism with Hypertensive Kidney Disease

Hazem Ayesh. University of Toledo - Health Science Campus, Toledo, OH.

Introduction: Primary aldosteronism (PA) prevalence has been estimated at 4.7–25.5% of all hypertensive patients. Renin aldosterone ratio (ARR) serves as a widely used screening test. Elevated ARR with suppressed plasma renin activity (PRA) is considered a positive screening test which should be followed by confirmatory testing. There are cases when PA is associated with non-suppressed PRA as in our case.

Case Description: A 37-year-old African American female patient with a past medical history of chronic kidney disease stage 4 presented to the hospital with a complaint of severe headache for 2 days associated with nausea and vomiting. Physical exam was remarkable for tachycardia and elevated blood pressure at 190/101 mmHg. Notable labs include low potassium at 3.4 [3.5 – 5.0 mmol/L], elevated creatinine at 4.84 [0.40 – 1.00 mg/dL] with a baseline creatinine of 2.36 mg/dL, urinalysis was positive for proteinuria. Secondary hypertension workup showed unremarkable renal duplex ultrasound, unremarkable thyroid function test, normal free plasma metanephrine, unremarkable urine drug screen. Screening for Cushing’s syndrome wasn’t performed given there were no supporting clinical manifestations. Plasma aldosterone concentration (PAC) elevated at 64.1 [3.1 – 35.4 ng/dL] with normal PRA at 1.7 ng/mL-hour. Calculated ARR was elevated at 37.7 ng/dL per ng/mL-hour, which raised the suspicion for primary aldosteronism (PA). Saline infusion test (SIT) showed elevated post-infusion PAC at 78.1 ng/dL which confirmed the diagnosis of PA.

Discussion: There are reports in literature that PA is more common than initially thought and has adverse effects on cardiovascular and renal systems independent of hypertension. So early diagnosis and management are highly recommended. The initial finding of non-suppressed PRA despite elevated ARR complicated diagnostic process. Multiple case studies reported non-suppressed PRA in patients with PA, especially when associated with hypertensive kidney disease and arteriosclerosis. In our case, kidney biopsy showed glomerulosclerosis with arteriopathy consistent with hypertensive kidney disease. We suggest focusing on ARR as a reliable screening for PA and not solely depend on the fact that PA is associated with suppressed PRA, especially in these cases. Another important point is to consider lowering ARR cutoff for diagnosis of PA since PRA isn’t completely suppressed in these cases.

Abiraterone-Induced Mineralocorticoid Excess Despite Concurrent Prednisone in Setting of Drug-Induced Liver Injury (DILI)

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Introduction: Abiraterone, a CYP17A inhibitor used in the treatment of castration-resistant prostate cancer (CRPC), is prescribed with concurrent glucocorticoids (GC) to prevent secondary mineralocorticoid excess (SME). We hereby describe a case of refractory hypokalemia in setting of abiraterone-induced SME despite prophylactic GC.

Case Description: A 70-year-old male with CRPC on abiraterone 1g and prednisone 5mg daily, presented with jaundice, fatigue, and hypertension. Workup revealed hyperbilirubinemia, transaminitis and profound hypokalemia. Liver biopsy demonstrated DILI. Abiraterone was thus discontinued. Hypokalemia persisted despite aggressive repletion with up to 320mEq KCl daily. Deoxycorticosterone elevation confirmed abiraterone-induced SME. Increased dosage of prednisone to 40mg daily and addition of eplerenone led to prompt normalization of potassium and blood pressure. Darolutamide was started after DILI resolution for CRPC treatment.

Discussion: Abiraterone’s antitumor effect lies in reduction of androgen production by CYP17 inhibition. Excessive deoxycorticosterone/corticosterone accumulation, driven by reactive rise in corticotropin, may manifest as hypokalemia, hypertension or fluid retention. GC coadministration serves to mitigate SME. SME in this case may be explained by 1) Liver injury: Pharmacokinetic studies have shown increased systemic abiraterone exposure in liver impairment up to 3.6 folds, necessitating dose reduction or drug discontinuation. Severe liver impairment causing decreased availability of hepatic 11β-hydroxylase (11β-HSD1) may also partially contribute to its active form prednisolone, removing negative feedback to corticotropin. 2) Prednisone 5mg BID or dexamethasone 0.5mg daily has shown superiority to prednisone 5mg daily (in this case) for SME prevention, at expense of greater weight gain and insulin resistance. Eplerenone can be used in addition to GC in SME treatment and may be noninferior to GC as steroid sparing preventive option. Spironolactone should be avoided due to its affinity to androgen receptor. It is prudent to monitor for medication adjustment as SME resolves.

Non-suppressed Plasma Renin Activity in Primary Aldosteronism with Hypertensive Kidney Disease

Suramath Isaranuwatchai. Chulabhorn Hospital, Bangkok, Thailand.

Background: Hypertonatremia is the most common electrolyte disorder in cancer patients and associated with poor prognosis in several types of cancer. Severe hyponatremia (serum sodium less than 120 mmol/L) is linked to increased hospital length. We conducted this retrospective study to evaluate for clinical and laboratory characteristics of cancer patients with severe hyponatremia.

Methods: Medical records from previous 2 years at Chulabhorn hospital were reviewed. Cancer patients who had serum sodium less than 120 mmol/L were included. Clinical data, including symptoms, causes of hyponatremia, treatments, response to treatments and survival rate, were recorded.

Results: A total of 154 patients with cancer and severe hyponatremia were identified. 147 patients (95.5%) had solid malignancy. Only 7 patients (4.5%) had hematologic malignancy, all of which were lymphoma. The most common solid malignancy was hepatocellular carcinoma (14.9%), followed by lung cancer (14.3%) and pancreatic cancer (10.4%). Interestingly, 36.3% of patients were asymptomatic despite severe hyponatremia. Of 98 patients that were diagnosed with symptomatic hyponatremia, the most common symptom was fatigue (30.5%), followed by nausea/vomiting (26.0%) and alteration of consciousness (19.5%). Seizures were present in only 3 patients (1.9%). The most common cause of hyponatremia was volume depletion (83.8%), which was mostly due to poor intake. Syndrome of inappropriate antidiuresis (SIAD) was the cause of severe hyponatremia in only 7 patients (4.5%). Most of our patients (76.0%) were treated with isotonic saline infusion and 83.8% of which responded with significant improvement in serum sodium level. Hypertonic saline infusion was given in only 27 patients (17.5%). Survival rate at 30 days was 46.1% and survival rate at 6 months was 26.4%.

Conclusions: Our data demonstrated that the most common cause of severe hyponatremia in cancer patients was volume depletion from poor intake, in contrast to SIAD which was suggested by other previous studies. In addition, most patients in our cohort responded to isotonic saline infusion. Fluid restriction and diuretic/aquaretic drug administration, presuming that patients have SIAD, may worsen the serum sodium level in these hyponovolemic cancer patients. This study emphasized the importance of clinical evaluation and investigation for cancer patients with severe hyponatremia to achieve the correct diagnosis and provide proper management.
PO1850
Novel Use of Daratumumab for Post-Hematopoietic Cell Transplant Membranous Nephropathy
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Introduction: Membranous nephropathy (MN) is the most common cause of glomerulopathy after hematopoietic cell transplantation (HCT), usually seen with graft versus host disease (GVHD). Although remission frequently occurs upon immunosuppression, 20% of patients fail to respond and may progress to end stage renal disease. Here we report the rapid remission of a treatment resistant patient with daratumumab (Dmab).

Case Description: A 16 year old female 1 year post-HCT for beta thalassemia major was started on rituximab for oral GVHD. Three months later, she developed nephrotic syndrome. Renal biopsy showed MN. Serum and renal tissue were negative for PLA2R antibody. Rituximab was changed to rituximab in case MN was medication induced. She was treated with tacrolimus (tough 3 – 8 ng/mL), prednisone, losartan, atorvastatin, and 4 weekly rituximab infusions. Eight months into therapy, she failed to meet criteria for even partial remission. The toxicity of additional steroids and or cyclophosphamide was undesirable. With 0% CD19 cells, rituximab was not indicated. Thus, plasma cell dyscrasia was treated with tacrolimus (trough 3 – 8 ng/mL), prednisone, losartan, atorvastatin, and 4 weekly rituximab infusions. Eight months into therapy, she failed to meet criteria for even partial remission. The toxicity of additional steroids and or cyclophosphamide was undesirable. With 0% CD19 cells, rituximab was not indicated. Thus, plasma cell dyscrasia was started on ruxolitinib for oral GVHD. Three months later, she developed nephrotic syndrome resolved and her serum albumin was greater than 3.0 g/dL by week 10. She weaned off of steroids and tacrolimus by week 16, at which time she had near-complete remission of her renal disease. Trialed off of losartan week 16 – 17, but protein excretion increased, so it was restarted. Time course and biomarkers of MN are in Figure 1.

Discussion: The mechanism of HCT-associated MN is incompletely understood. Its association with GVHD and often successful treatment with rituximab have implicated direct or indirect humoral activation as potential pathogenic mechanisms. The success of CD38 depletion with Dmab may imply omalizumab production by resident plasma cells as a driver of refractory disease. Dmab may be a novel therapeutic option for HCT patients who are not responsive to traditional MN therapy.

Figure 1: Time course and biomarkers of MN after Dmab. *Urinary collection 15 hours

PO1852

Background: the prevalence of chronic kidney disease is high among kidney neoplasm patients because of the overlapping risk factors. We aim to identify risk factors of eGFR decline in kidney cancer survivors post partial nephrectomy (nx).

Methods: All partial nx patients with neoplasm at Northwell Health were included (2018/7-2020/5, n=187). Clinical and histology parameters, including neoplastic and non-neoplastic pathology, were analyzed. Non-neoplastic assessment includes glomerulosclerosis(GS), interstitial fibrosis and tubular atrophy(IFPA), and a semi-quantitative estimate of the severity of arterial and arteriolar sclerosis (AAS). Multivariate linear mixed model was performed. Independent variables included age, sex, hypertension, diabetes, baseline eGFR, tumor diagnosis, proteinuria, G5%, IFTA%, and AAS.

Results: The median follow-up time is 147d. In all patients, independent risk factors of post-nx decreased eGFR were female(p=0.02), age(p<0.01), overweight(p<0.001), eGFR<90 at the time of nephrectomy(p<0.001), severe AAS(p<0.01), and prolonged follow-up. In the ones with baseline eGFR≥90(n=61), proteinuria(p<0.001) and the non-cancer kidney organoids for cancer invasion assay. The CL experiment showed that M2-like macrophage depletion from the IRI-kidney cortex inhibited tumor progression and increased tumor infiltrated CD8 T cell. And CD8 efficacy in reduction or inhibition of the invasion.

Results: Kidney cancer on IRI kidneys (IRI-KC) was more progressive than that on non-cancer kidneys. AAS. (p=0.02), GS%>25%(p=0.02) and overweight (p=0.03) were independent risk factors of decreased post-nx eGFR. eGFR time trend of patients with and without these risk factors is shown in the figure.

Conclusions: We propose a minimum workup for this population to include eGFR, urinalysis, and non-neoplastic pathology evaluation. The time of kidney cancer treatment may be a unique opportunity for these patients to be identified and directed to early interventions, including nephrology consults and patient education on nutrition and weight control.

PO1853
Development of 3D Renal Cell Carcinoma Organoids and Cancer Invasion Assay Nathan Lee,1 Shun-Yang Cheng,1,2 Joseph V. Bonventre.1 1Brigham and Women’s Hospital, Boston, MA; 1University of Southern California, Los Angeles, CA.

Background: Recent advances in in vitro 3D culture technologies, such as organoids, derived from hPSCs, have opened new avenues for development of human disease models. Modeling cancer by utilizing cancer organoids provides advantages as they maintain 3D cell-cell interactions, heterogeneity, microenvironment, and drug response of the sample they originate from. Such preclinical models are essential for more efficient translation of cancer research into novel treatment regimens for patients. 5-year survival rate at advanced stage IV RCC is 17% less than 10%, as RCC is also notorious for resistance to chemotherapy and radiation therapy. Therefore, development of effective tools for better understanding and drug screening for RCC are needed. Kidney cancer organoids and novel assays such as cancer invasion assays can be useful tools to personalize potential therapeutics.

Methods: Primary kidney cancer cell lines were generated from patient biopsy samples. 3D kidney cancer organoids and non-cancer kidney organoids for cancer invasion assay were generated from primary kidney cancer cell lines and hPSCs, respectively, by modifications of our laboratory’s prior published kidney organoids techniques. Organoids were characterized by immunostaining. Upon maturation, organoids were added onto the non-cancer kidney organoids and incubated together for the invasion assay with or without treatment with drugs. Frozen sections and imaging were utilized to examine the cancer invasion. Kidney cancer organoids were treated with various drugs to investigate efficacy in reduction or inhibition of the invasion.

Results: RCC cancer organoids showed significantly better expression of kidney cancer markers such as KIM-1, HIF-1α, HIF-2α, and CAIX compared to 2D primary RCC cells. Addition of the cancer organoids to normal kidney organoids within 3 days. Treatment of the cancer organoids by the receptor tyrosine kinase inhibitor, sunitinib or the histone acetyltransferase inhibitor (A-485) showed reduction in efficacy of cancer invasion.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author. 571
Conclusions: Development and use of cancer invasion assay for renal cell carcinoma utilizing kidney cancer patient derived kidney organoids could lead to better understanding of cancer invasion and provide the capability to screen and profile for identification of potential treatment options in renal cell carcinoma.

Funding: NIDDK Support, Other NIH Support - NCAATS, T32

PO1854

Multi-Omics Approach to Uncover Underlying Biology of Low-Risk Clear Cell Renal Cell Carcinoma Patients with Progressive Disease

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Background: Renal Cell Carcinoma (RCC) constitutes approximately 3 % of all cancers and its incidence is rising worldwide, especially in Western countries. In the last two decades, enormous advances have been made in the development and implementation of medical therapies for metastatic ccRCC, however, surgery still represents the only curative option. One of the issues in developing a curative medical therapy lies in the high degree of inter- and intra tumor heterogeneity. We believe that by applying multi-omics technology to highly specific subgroups and comparing them to closely matched controls we can mitigate the heterogeneity issue and deepen our understanding one step and subgroup at the time.

Methods: We assembled a cohort of ccRCC patients (n=443) and identified all “low-risk” patients which later developed progressing tumours (n=8). Subsequently we performed genome-wide expression profiling, miRNA profiling and proteomics profiling from formalin-fixed samples obtained at initial surgery from these “low-risk” patients and 16 matched patients not progressing to recurrence with metastasis. The patients were matched for Leibovich risk score, age, sex, tumor size and tumor stage.

Results: Pathway analysis yielded differences between progressive and non-progressive patients in categories such as Molecular Mechanisms of Cancer, B Cell Receptor Signaling in mRNA data and Acute Phase Response Signaling and FXR/RXR Activation in proteomics data. By integrating our three -omics analysis we revealed that acute Phase Response Signaling also plays a role on all three levels. Additionally, we developed a 14-component classifier, drawing from both mRNA, miRNA and protein-based data that reliably differentiated the different subgroups. We further examined the correlations between each of the components and uncovered a dense network of interactions.

Conclusions: Multi-omics methods represent an important tool in furthering our understanding renal cancer biology in the pursuit of medical therapies.

PO1855

TME2M7 Expression and Clinical Characteristics and Survival in Clear Cell Renal Cell Carcinoma

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Background: Transmembrane protein 27 (TME2M7/collectrin), a glycoprotein and homolog of angiogenic matricellular enzyme 2 (ACE2), is a regulator of renal amino acid uptake in the proximal tubule and may have a protective role in hypertension. Two previous reports have shown that the absence of TME2M7 expression in clear cell renal cell carcinoma (ccRCC) correlates with poorer cancer-related survival. Here we report our findings of TME2M7 expression in ccRCC and clinical outcomes.

Methods: We conducted a retrospective analysis to identify all cases of ccRCC diagnosed between 2010 and 2015 at the University of Rochester Medical Center. The intensity of TME2M7 immunostaining on tumor tissue was semi-quantitatively graded on a scale of 0, 0.5, 1, 1.5, 2, 2.5, and 3 by a single pathologist, and correlated with tumor characteristics and survival.

Results: There were 321 cases of ccRCC. There was evidence of metastasis at time of nephrectomy in 36 (11.2%), and at the latest follow up in 70 (21.8%), and 82 (25.5%) of patients.

Conclusions: The absence of TME2M7 expression is associated with more aggressive tumor characteristics and poorer all-cause mortality in ccRCC. TME2M7 may be a useful biomarker to assess cancer prognosis. Further studies are needed to better assess if TME2M7 is protective in RCC.

Table 1: Correlation between TME2M7 Staining and Clinical Characteristics

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TME2M7 Staining (0–3)</td>
<td>&lt;=0.001</td>
</tr>
<tr>
<td>ECOG score</td>
<td>&gt;=0.05</td>
</tr>
<tr>
<td>Tumor stage (T1,T2)</td>
<td>&lt;=0.05</td>
</tr>
<tr>
<td>TNM (stage)</td>
<td>&lt;=0.05</td>
</tr>
<tr>
<td>Tumor grade</td>
<td>&lt;=0.05</td>
</tr>
<tr>
<td>Prognostic grade</td>
<td>&lt;=0.05</td>
</tr>
<tr>
<td>Sarcopenia (muscle present)</td>
<td>&lt;=0.05</td>
</tr>
<tr>
<td>Left renal vein invasion</td>
<td>&lt;=0.05</td>
</tr>
<tr>
<td>Hypertension</td>
<td>&lt;=0.05</td>
</tr>
<tr>
<td>Metastasis at time of nephrectomy</td>
<td>&lt;=0.05</td>
</tr>
<tr>
<td>Mortality at 5 year</td>
<td>&lt;=0.05</td>
</tr>
</tbody>
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PO1856

Role of miR-23b and miR-133a in Apoptosis Control Induced by TRAIL in Lung Adenocarcinoma and Kidney Carcinoma Cell Lines

Denise Leite, Edgar Maquigussa, Mirian A. Boim. Universidade Federal de Sao Paulo Escola Paulista de Medicina, Sao Paulo, Brazil.

Background: Lung and kidney cancer are often diagnosed as advanced disease and frequently become resistant to systemic therapies. Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) binds to TRAIL receptor 1 and 2 (TRAIL-R1/R2) on the cell surface to stimulate apoptosis, making TRAIL apoptotic pathway a promising target for cancer therapy. Cullin-3 ubiquitination is essential to TRAIL receptors activation. However, resistance to TRAIL is an obstacle to achieve an effective anti-tumoral therapy. One of the mechanisms that lead to TRAIL resistance appears to be dependent on translocation, mediated by clathrin (CLTA), of TRAIL receptors to the nucleus. MicroRNAs (miRs)-23b and -133a may have relevant role in TRAIL resistance.

Methods: A549 and CaKi-2 cell lines and their respective controls (MRC-5 and HK2) were used. mRNA expressions of miR-23b, miR-133a, TRAIL-R1/R2, CLT3, CLAIPaf-1 and KPNA-1 were estimated by RT-qPCR. MTT assay was used to evaluate the effect of TRAIL-induced cytotoxicity. TRAIL receptors cellular distribution was determined by western blot.

Results: Both cell lines were TRAIL resistant on MTT. TRAIL-R1 and TRAIL-R2 were predominantly located in nuclear compartment of A549 cells. TargetScan showed that miR-23b targets CLT3, Apaf-1 and KPNA-1 and miR-133a targets CLTA. MiR-23b expression was upregulated in A549 and CaKi-2 cells. MiR-23b inhibition upregulated CLT3 expression in A549 cells. In contrast, miR-133a was undetectable in both cell lines. TargetScan was used to determine potential mRNA targets for miR-23b and miR-133a.

Conclusions: MiR-23b expression was upregulated in A549 and CaKi-2 cells. However, supposed miR-23a target mRNAs were unchanged suggesting no relationship between miR-23a and those molecules. MiR-23b inhibition upregulated CLT3 expression in A549 cells, which could enhance TRAIL receptors activation and sensitivity- this will be investigated in next step. In contrast, miR-133a was undetectable raising the hypothesis of an increased capacity of cells to translocate TRAIL receptors to the nucleus via clathrin and thus be resistant to TRAIL. The possible miR-133a ability to reduce clathrin expression may represent a novel approach for control of TRAIL apoptotic pathway and must be further investigated as a TRAIL sensitizing mechanism.

PO1857

Recapitulating Kidney Angiomyolipoma with Renal Organoids

Generated from Tuberous Sclerosis Complex Patient-Derived Induced Pluripotent Stem Cells

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Background: Angiomyolipomas (AMLs) constitute 80% of the renal lesions found in patients with Tuberous Sclerosis Complex. AML can cause kidney failure and lead to premature death due to the formation of vascular aneurysms that are prone to spontaneous bleeding. Key aspects of the pathology of AMLs, and most remarkably the cell(s) type(s) and developmental mechanisms that give raise to the lesions, remain unknown. Previous efforts to recapitulate AML experimentally using transgenic mice have failed to produce reliable models of AMLs, precluding our ability to study tumor mechanisms and develop novel therapies.

Methods: We directed the nephric differentiation of a series of TSC patient-derived iPSC lines that included a line carrying a heterozygous microdeletion in the TSC2 locus (TSC2-/-), a TALEN-engineered isogenic cell line carrying microdeletions in both TSC2 alleles (TSC2-/-) and a cell line in which the original mutation present in the patient was corrected using CRISPR-Cas9 (TSC2-/-).

Results: We derived renal organoids from isogenic TSC2-/-, TSC2-/- and TSC2-/- iPSCs. Flow cytometry analysis of kidney organoids derived from TSC2-/- iPSCs but not from isogenic TSC2-/- or TSC2-/- iPSCs were enriched in ACTA2 cells, a percentage of which (~24%) co-expressed melanocytic markers including prelaminar protein (PMEL), melanin A (MLANA) and cathepsin K (CTSK) indicative of a myomelanocytic phenotype that is a hallmark of kidney AMLs. Morphologically, ACTA2 cells found in TSC2-/- organoids had a plump myoid morphology that matched the well-characterized morphology of kidney AML cells. Whole transcriptome RNA sequencing (RNA-seq) of TSC2-/-, TSC2-/- and TSC2-/- organoids identified MLANA, PMEL, GPNMB, MITF, CTSK and ACTA2 as genes that were exclusively upregulated in TSC2-/- organoids, confirming the myomelanocytic phenotype of TSC2-/- AML organoids. Hallmark gene sets enriched in TSC2-/- renal organoids in each comparison included IL-6-JAK-STAT3 signaling, adipogenesis, angiogenesis, fatty acid metabolism, KRAS signaling and estrogen response, as major pathways shared with kidney AMLs.

Conclusions: Collectively, our findings support the notion that AMLs originate from cells of the renal lineage and suggest a central role for TSC2 loss-of-heterozygosity (LOH) genetic mechanisms in the etiology of AML.

Funding: NIDDK Support
**PO1858**

**Characterization of Wilms Tumor and Human Fetal Kidney Using Spatial Transcriptomics**

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**Background:** Growing evidence links Wilms tumor (WT) to aberrant nephrogenesis. Studies highlighted the genetic complexity of WT, but little is known about the molecular mechanisms that regulate WT development. Using Spatial transcriptomics (ST), which allows analysis of the gene expression based on morphological context, we showed important differences between WT subtypes and defined the interactive gene networks involved in WT development using human fetal kidney (hFK) as reference.

**Methods:** Using Visium 10X Genomics, we generated spatial maps of gene expression in human fetal kidney (hFK) and/or unfavorable (stage III) and unfavorable (stage I) WTs. Data were analyzed using Space Ranger software v.1.0. Seurat v.3.2, Panther V14, and Loupe Cell Browser and further analyzed against our previously generated bulk/sc-RNA seq data on the same samples.

**Results:** ST identified specific clusters in hFK that closely recapitulated the developmental stages of normal nephrogenesis (nephrogenic zone, glomeruli, tubules, and stroma). Unfavorable WT and favorable WT clusters showed heterogeneity of the tumor landscape (blastosoma, epithelium, and stroma and non-renal phenotypes). Blastosma in WT favorable vs. WT unfavorable, though histologically identical, presented different transcriptomics profiles. WTs also showed gene expression typical of muscle tissue (or other non-renal phenotypes) rather than mature kidney structures, which correlated with the histologic absence of mature tubules and glomeruli. Comparative RNA-seq analysis identified cells expressing SIX2 and CITED1 as the root cells of the origin of the WT. Unfavorable WT expressed a higher level of CITED1 in blastema foci and higher expression of uncommitted genes and modulation of inductive nephrogenic signals like WNT and FGF. We also identified genes expressed specifically in WT subtypes and performed a preliminary characterization of the immune milieu of WT.

**Conclusions:** The spatiotemporal mapping combined with different transcriptomic data highlighted the heterogeneity of the WT subtypes confirming uncommitted nephron progenitors as driving the development of WT. We identified genes that may allow for better stratification of WT and potential therapeutic targets for distinct WT subtypes.

**Funding:** Private Foundation Support

**PO1859**

**Recurrent Renal Cell Carcinoma Post Renal Transplantation**

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**Introduction:** Renal Cell Carcinoma (RCC) can occur in renal transplant recipients (RTR). RCC recurrence post nephrectomy occurs in 20-40% of non-transplant (Tx) patients and in less than 15% of RTR. The median survival for patients with metastasis is 6-12 months with 5 year survival less than 10%. We present 3 RTR who developed recurrent RCC post-Tx.

**Case Description:** RTR1 was 61 years old and received a deceased donor kidney Tx (DDKTx) for IgA nephropathy. He was induced with thymoglobulin. Immunosuppression (IS) included Mycophenolate Mofetil (MMF), Tacrolimus (FK), and steroids (S). 8 years pre-Tx, a 2.5cm RCC lesion was found in the R native kidney, and he underwent nephrectomy. 1 year later, he developed BK viremia, and IS was changed to Everolimus and S. 2 years post-Tx, RCC metastasis was detected only in the pancreas head and tail. Treatment involved tyrosine kinase inhibitors (TKI) and VEGF inhibitors without resolution; he died within 2 years of RCC recurrence with a functioning allograft. RTR2 was 56 years old and received a DDKTx, secondary to ADPKD. IS involved MMF, Cyclosporine, and S. History was significant for L nephrectomy 3 years pre-Tx for RCC. Both lesions were small and recently limited. 10 years post-Tx, she presented with recurrent RCC in the pancreas and thyroid. Treatment involved change in IS to Sirolimus and Azathioprine. No other treatment was taken by the patient. She died 4 years later with a functioning allograft. RTR3 is a 54 year-old who received a living related renal Tx for CKD stage 5. IS included MMF, FK, and S. 8 years post-Tx, he was diagnosed with an 8cm RCC lesion of the L native kidney and underwent nephrectomy. After a 6 year tumor free interval, RCC recurred only in the lungs and lymph nodes. He received IS reduction and TKI with progression of disease to bone metastasis. His current treatment involves TKI with Denosumab, and he still has a functioning allograft.

**Discussion:** Our cases demonstrate that RCC recurrence occurs at variable time points post-Tx and can present aggressively in RTR with poor outcomes. We suspect that recurrent disease arises from micrometastatic tumor cells that escape immune surveillance. RTR with a history of RCC prior to Tx should be monitored closely for metastatic recurrence post-Tx.

**PO1860**

**Impact of ESKD on Overall and Cancer-Specific Mortality in Patients with Localized Prostate Cancer (PCa): A Retrospective Cohort Study of SEER-Medicare**

Nagaratna Sarabu,1 University Hospitals, Cleveland, OH.

**Background:** Our objective was to compare overall and PCA specific mortality between ESKD and non-ESKD patients with localized PCa.

**Methods:** Study participants were male patients, who were diagnosed with localized PCa between January 1st 2004 and September 30, 2015 (last day of International Classification of Diseases-9-Clinical Modification (ICD-9-CM) use) and were 40 years or older at the time of diagnosis. ESKD status, further stratified into dialysis and kidney transplant (KT) was determined using ICD-9-CM codes. Time to death from any cause was modeled using Cox regression and time to PCA specific death using Fine and Gray competing risk model.

**Results:** At a median follow up of 6.2 years, 3.5 years and 5.0 years for non-ESKD (N=186,482), dialysis (N=970) and KT (N=413), overall mortality rates were 1.8%, 8.5%, and 4.8% at 1-year, 7.7%, 31.5% and 13.5% at 3-years and 15.2%, 50.8% and 27.9% at 5-years respectively (P-Value: <0.001). Figure 1. In multivariate model, dialysis status was associated with 2.9 times higher hazard of death (HR: 2.9, 95% CI: 2.0, 3.0) compared to non-ESKD group. Rates of PCA specific mortality were 0.4%, 1.1%, and 0.7% at 1-year, 1.6%, 3.1%, and 1.5% at 3-years and 3%, 4.8%, and 2.2% at 5-years for non-ESKD, dialysis, and transplant groups respectively (P-value: 0.04). In multivariate model, dialysis status and transplant status were associated with similar risks for PCa specific death to non-ESKD group. Figure 2.

**Conclusions:** ESKD patients have excess relative overall mortality but similar PCa specific mortality compared to non-ESKD patients with localized PCas.

Variable Incidence Curves

Hazard Ratios for Mortality

**PO1861**

**Case of Spontaneous Tumor Lysis Syndrome in Metastatic Prostate Cancer**

Mohammad Al-Hasan,1 Mauricio Monroy,2 Albany Medical Center, Albany, NY.

**Introduction:** Tumor lysis syndrome has been described in hematological malignancies mainly where there is a large tumor burden that lyse in relatively short period of time causing a large burden of metabolites that causes AKI. In this case, we will present a case of spontaneous tumor lysis syndrome caused by widespread metastatic cancer prostrate which is an unusual cancer to cause such syndrome. That metastasis was mainly to the bone marrow causing a picture of pancytopenia, which also raises the possibility that the tumor lysis syndrome could be due to the breakdown of the cells of the bone marrow rather than the lysis of the prostate cancer cells.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Case Description: 65-year-old male patient presented with altered mental status upper quadrant abdominal pain, and fever. He weighed 182.2, severe anemia with hemoglobin of 8.8 gm/dL, a creatinine of 7.32 and BUN of 181, calcium 9.3, phosphorus 7.4, uric acid 41.5, bilirubin of 2.9 and LDH was high at 789, alkaline phosphatase was 345, patient had severe anaemia with hemoglobin of 2.6, white count 12,600 and thrombocytopenia with platelet count of 6600. Urine analysis showed uric acid crystals. Flow cytometry analysis of peripheral blood did not reveal a clonal population of cells or expanded population of blasts. CT scan chest abdomen pelvis suggested diffuse osseous lytic and blastic metastatic lesions. Serum immuno-electrophoresis was negative. PSA level of more than 1400.

Diagnosis: The patient along with severely elevated serum uric acid level, and presence of uric acid crystals in the urine sediment, made it highly likely the diagnosis of TLS. The presence of diffuse osseous lesions and a PSA above the level that can be measured were consistent with metastatic prostate cancer as the underlying malignancy. The new onset of patient's symptoms was TLS in solid malignancies, rare, especially without anti-neoplastic therapy. In this case, the presence of severe anaemia and thrombocytopenia were highly suspicious for bone marrow invasion, and possible contributor to TLS. Regrettfully, a bone marrow biopsy couldn’t be obtained before patient expired. Conclusion: Bone marrow extension with lysis of bone marrow cells may be a contributing factor.

PO1862
Overlooked and Unanticipated: Life-Threatening Hypocalcemia due to Denosumab in a Patient with Prostate Cancer

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Introduction: Denosumab is a monoclonal antibody that inhibits osteoclast-mediated bone resorption by binding to receptor activator of NF-kB ligand, which is upregulated by tumor cells. Despite FDA warning, insidious and severe onset hypocalcemia is a known complication in patients treated with this agent.

Case Description: A 77-year-old man with a history of prostate cancer and CKD stage 4 presented to the ED with tremors and numbness in both arms along with perioral dysesthesias. In addition to furousemide and metoprolol, he received his first dose of denosumab 2 weeks prior to presentation, indicated for bone metastasis. Physical examination was remarkable for the Chvostek sign and delayed reflexes in his upper and lower extremities. Lab results were as follows: Na 136 mEq/L, K 4.4 mEq/L, HCO3: 6.4 mEq/L, Cr: 4.8 mg/dL, PO4: 6.1 mg/dL, Ca: 4.8 mg/dL, Mg: 2.6 mg/dL & albumin: 3.5 g/dL. Further testing disclosed 25 hydroxy vitamin D (25(OH)D): 6.5 (<25 ng/mL), iPTH: 988 (10-55 pg/mL). Free FT3 and FT4 was normal, TSH slightly high. C-reactive protein was 167 (40-465 pg/mL), ALP: 243 (44-147 iU/L). Urine calcium-to-creatinine ratio was 0.04, suggestive of minimal calcium excretion. ECG showed prolonged QTc. Given the clinical evidence of severe hypocalcemia and ECG changes, the patient was started on peripheral calcium infusion with hourly iCa2+ measurements to maintain iCa >1 mmol/L and reversal of QTc prolongation. Concomitantly, the patient was treated with calcium carbonate 2500 mg TID, ergocalciferol 50,000 units weekly, and thrombocytopenia were highly suspicious for bone marrow invasion, and possible contributor to TLS. Regrettfully, a bone marrow biopsy couldn’t be obtained before patient expired. Conclusion: Bone marrow extension with lysis of bone marrow cells maybe a contributing factor.

PO1863
Impact of CKD on the Nutritional Status of Patients with Cancer

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Background: Cancer patients routinely live with impaired nutritional status and other comorbidities. There are few prospective data on the impact of chronic kidney disease (CKD) on the nutritional aspects of patients with cancer.

Methods: Patients with solid cancer, admitted for treatment at a cancer hospital in Brazil (Instituto de Câncer do Estado de Sao Paulo) were prospectively evaluated between April 2015 and October 2017. Patients underwent a nutritional evaluation including subjective global assessment produced by the patient (PG-SGA), anthropometry (Arm Muscle Area-AMB, weight, height) and electrical bioimpedance (BIA). sarcopenia was determined when the sum of three measures of BIA ≤17.4 kg/m2 for KM and ≤15 kg/m2 for FFM. Measurement of the glomerular filtration rate was determined through plasma clearance of 125I-EDTA (mGFR). CKD was classified according to the K/DOQI guidelines based on mGFR indexed for body surface area.

Results: Six hundred and ninety-six pts were enrolled. Patients were 60(51-67) years old, 51.9% male. The most common cancer sites were breast(26.3%), prostate(20%), and gastrointestinal(12.2%). A total of 14.7% had metastatic disease, 94.9% ECOG (0-1), median mGFR was 81(66.7-94.6), with 55.7%, 32.8% and 11.5% presenting mGFR G1, G2 and G3, respectively. When compared to patients with mGFR G1, patients with mGFR G2 and G3 had a higher frequency of malnutrition by PG-SGA and BMI, and higher proportion to AKI compared to AMB. In addition, fat free mass deficit, sarcopenia and lower phase angle values were more frequently observed in mGFR G2 and G3 according to the BIA data(Table1).

Conclusions: In patients with cancer admitted for treatment lower mGFR was associated with worse nutritional status. Therefore, nutritional monitoring in conjunction with the oncology, nephrology and nutritional team is necessary.

PO1864
The Impact of a Nutritional-Nephrological Combined Approach (NNCA) on the Metabolic Profile and Perceived Quality of Life of CKD Patients

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Background: Nutritional therapy (NT) based on controlled protein intake represents a cornerstone of the management of CKD. However there is not a precisely defined an adequate protein intake for onco-nephrological patients. Aim of our study is to investigate the impact of a low-normal protein diet on metabolic profile and quality of life in CKD pts affected (CS) or not (CT) by urological non-metastatic malignancies treated with a NNCA.

Methods: 103 pts were enrolled in the Urological Department at San Raffaele hospital between 2018 and 2020, screened for absence of malnutrition and administered a conventional CKD protein-controlled diet (0,7-1 g/Kg/die, 30-35 kcal/kg/die) including aprotic foods. Anthropometrical outcomes, lab test exams and clinical variables were examined at baseline and after 6 months. To evaluate the impact of the NNCA on perceived quality of life, a QoL-Short Form36 (SF36) questionnaire were administered to pts.

Results: The combined treatment produced eGFR improvement and urea parameters improvements (49% of pts improved eGFR, 65% uremia) without negatively altering the anthropometrical outcomes. The nutritional status was preserved in both groups and all pts had an improvement in BMI (CS: 2.8 kg/h; CT: 1.3 kg/h) PA* (CS: 2.8%; CT: 1.3%); ROH (CS: 1.3%; CT: 0.38) and FFM (h) (CS: 0.1; CT: 2) and a decrease of WC (CS: 1.3cm; CT: -1.65cm), and ECW/ICW (CS: 0.02; CT: 0.03). The SF36 questionnaire highlighted a good perceived quality of life in subjects treated with the NNCA, even if social activities were negatively affected.

Conclusions: Our study suggests that low-normal protein high calories diet ameliorates the nephrological scenario, the metabolic complications and the nutritional perspective in uro-oncological CKD pts. Following NNCA, perceived quality of life has been pushed towards high scores and does not appear to be influenced by physical health or emotional status. Monitoring and food choice limitations may have increased the perception of the pathological condition, thereby increasing the sense of responsibility in adhering to the NT. All this improves the physical health, but also demotivates pts and worsens their social attitudes.

PO1865
A Rare Case of Calcitriol-Mediated Hypercalcemia in Metastatic Gastrointestinal Stromal Tumor (GIST)

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Introduction: Hypercalcemia accompanies 10-30% of malignancies. Calcitriol production accounts for <1% cases, usually with lymphoma, but has been reported with solid tumors.

Case Description: A 62 year old male with GIST with liver involvement was admitted for an elevated calcium (Ca) of 13.9 mg/dL & AKI with creatinine (Cr) 2.2 mg/dL. Diagnosed with GIST 3 years prior, he was treated with imatinib & an investigational mitogen-activated protein kinase enzyme inhibitor. Due to disease progression, he was switched to sunitinib 1 week prior to admission and endorsed taking 100,000 IU of OTC vitamin D tablets daily for perceived immunologic benefits. Further workup showed bland urinalysis & fractional sodium excretion of 2.6%. Renal sonogram was normal. AKI was ascribed to hypercalcemia-mediated vasoconstriction & renal blood flow reduction. He had an ionized Calcium 6.6 mg/dL (nl: 4.8-5.3 mg/dL), appropriately low PTH & PTHrP 0.9 pmol/L (nl:4.2 pmol/L). The 25(OH) vitamin D was reported at >156 ng/mL, then quantified at 240 ng/mL. Calcitriol was elevated at 71 pg/mL (nl: 18-64 pg/mL). Echocardiography was thought to be from excess vitamin D intake. Cr & Ca improved with hydration, calcitonin & pamidronate. He was readmitted at >156 ng/mL, then quantified at 240 ng/mL. Calcitriol was elevated at 71 pg/mL (nl: 18-64 pg/mL).
PO1866
Kidney Pathology Findings in Patients with AKI Associated with Tyrosine Kinase Inhibitors
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Background: Tyrosine kinase inhibitors (TKIs) are widely used targeted cancer therapy as they play a critical role in the modulation of growth factor signaling. Nephrotoxicity associated with TKIs can lead to interruption of therapy. However, the literature on the kidney pathology associated with TKIs nephrotoxicity is limited. Here, we present our center observation of tubular and glomerular lesions attributed to possible TKIs.

Methods: We retrospectively reviewed all cancer patients from 2018 to 2020 who were treated with TKIs and underwent a kidney biopsy at the University of Texas MDACC.

Results: We identified 13 cancer patients treated with Sunitinib, Cabozantinib, Lenvatinib, Regorafenib, Erlotinib, Osimertinib and Irinotecan between 2018-2020 and developed acute kidney injury (AKI) attributed to possible TKI nephrotoxicity. The median age was 70 (range, 43 to 80) and the median time to develop AKI was 4 months (range, 1 to 58 months) of starting TKI. AKI was severe (stage ≥3) in 6 patients, among which 4 required hemodialysis. Most of the patients had bland urine (7 out of 13) and proteinuria was observed only in 6 patients. Thrombotic microangiopathy (TMA) was the most common pathological finding followed by acute tubular injury (ATI) as they were observed in 5 and 4 patients, respectively. One patient had proliferative glomerulonephritis, one patient had chronic lymphocytic leukemia infiltration, and one patient had no active lesion. TKIs were discontinued in nine patients, and nine patients had partial kidney recovery. Five patients had disease progression and died within 4 months of AKI.

Conclusions: Our case series has demonstrated that limited type TMA and ATI are common pathology findings in patients with suspected TKI nephrotoxicity. Nonetheless, half of patients with TMA were on concurrent checkpoint inhibitor therapy with TKI and half of the patients with ATI had associated sepsis diagnosis. The mechanism is likely multifactorial and possibly related to mTOR and VEGF inhibition leading to endothelial injury, and inhibition of the downstream signaling pathway of MAPK/ERK1/2 leading to ATI. Urinary analysis was not predictive of the kidney pathology. Treating nephrotoxicity by discontinuation of the offending TKI was associated with partial kidney recovery, however patients had poor overall prognosis.

PO1867
Renal Pathology in Cancer Patients in a New Era of Treatments
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Background: Classically patients with metastatic cancer were not submitted to invasive procedures because of their short life expectancy. Kidney biopsy(KB) is an especially useful diagnostic and prognostic tool in these patients when they develop kidney injury. The aim of our study is to assess clinical and histological characteristics of patients with active solid organ malignancy that underwent KB in a multicenter cohort.

Methods: We performed a multicenter collaborative study. Clinical, demographical and pathological data from patients with an active neoplasia or active cancer treatment who underwent KB were collected. We studied the follow-up of the patients in terms of renal function and survival.

Results: 124 patients with cancer who underwent KB during the study period from 2017 to 2020 were included. Sex ratio men/women was 46/78, mean age 60.8 (SD 18.5). The indications of KB were acute renal failure (56.2%), proteinuria (20.2%) and exacerbation of CKD (15.3%). At the time of the KB, 30.6% patients presented diabetes and 63.7% high blood pressure. Malignancies: lung (30.6%), intestinal (27.4%), melanoma (7.3%) and urothelial (7.7%), with a relative metastatic rate of 45%, with 35.5% received chemotherapy, 31.4% immunotherapy (of which 26.3% received more than 1 checkpoint inhibitor), 24.2% specific therapies and 3.2% conservative treatment Baseline renal function before KB,16.1% presented Cr=1.5mg/dL. At the time of KB, mean Cr 2.55mg/dL, [1.7-3.97] [25-75%], protein/Cr ratio 959mg/gCr [585-1050] and 53.2% hematuria kidney diagnosis:35.5% acute interstitial nephritis (AIN), acute tubular necrosis(8.9%) and IgA nephropathy(8.1%),65% of patients received corticosteroids for an average of 4.8 months[SD ± 5.9] 2.0% required kidney replacement therapy and 36.3% presented Cr=1.5mg/dL at 3 months. Average follow-up 16.2±5.5 (IQR 2.5-75%) 31 patients died at 37.9% died at the end of KB, and the moment of KB was identified as an independent risk factor for mortality (p=0.012)

Conclusions: Currently, AIN is the first cause of kidney injury in biopsied patients with active cancer. This is followed by bythombocytopenia, membranoproliferative nephropathy and IgA among others. KB in this group of patients provides valuable diagnostic and prognostic information. More studies are needed to expand the consensus in the diagnosis and treatment of oncological patients with renal injury.
as etiology for above laboratory abnormalities and history of treatments with ICI (nivolumab), while awaiting these lab results, patient was started on fluid restriction and salt tablets for management of hyponatremia based on available labs at that point which pointed to hypotonic hyponatremia with high urine osmolality pointing to ADH release and goal for correction for sodium level maintained 6-8 Meq for 24hours. Both serum sodium function corrected and ACTH levels were found to be low with values of 1.4ug/dl and 3.5pg/ml respectively. Patient was subsequently started on IV fluids and IV Hydrocortisone 100 0.9%L. Serum sodium level improved at an appropriate rate during the course of hospitalization and serum sodium at the time of discharge was in safe range (135mmol/L). Other peripheral hormones including prolactin, GH, TSH, LH and FSH which were normal. MRI Brain was done to rule out Hypothysis which revealed normal sella.

Discussion: Long-term follow-up of endocrine irAEs suggests that on occasions thyroid function may recover, but that dysfunction of the corticosteroid and gonadal axis is likely to be permanent. Patients should be informed of the potential adverse events prior to initiation of immune checkpoint inhibitors. Laboratory findings similar to our patient should raise concern for adrenal insufficiency to allow timely diagnosis and management and thus prevent morbidity and mortality.

PO1870 Immune Checkpoint Inhibitors Associated Distal RTA with and without AKI
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Introduction: As immune checkpoint inhibitors (ICPI) gain popularity as a widely used anti-cancer therapy, unique immune-related adverse events (irAE) are being associated with their use. Hereby, we present two cases that link ICPI therapy to distal RTA, one with and one without AKI.

Case Description: A 73-year-old male with urothelial cancer on pembrolizumab was evaluated for AKI and acidosis. After 5 doses of ICPI therapy, he was noted to have a serum creatinine of 1.8mg/dl (normal baseline) and a serum CO2 of 20mmol/L. Over the next few days, the serum CO2 further decreased to 11mmol/L and serum potassium declined to 3.0mmol/L. Further workup revealed a urine pH of 6.5 with a positive urine anion gap. He was diagnosed with likely ICPI-induced AKI with distal RTA and initiated on sodium bicarbonate, potassium citrate, and prednisone 60mg/day. His ICPI was held. After 2 weeks of treatment, his serum creatinine returned to 1.2mg/dl and serum CO2 to 22mmol/L. A 46-year-old female was diagnosed with metastatic lung cancer and squamous cell cancer colitis. She had a history of renal transplant for which she was initially treated with Carboplatin/Paclitaxel/Pembrolizumab followed by maintenance Pembrolizumab. Almost 3 months after being initiated on ICPI, she was noted to have normal gap metabolic acidosis that gradually worsened to serum CO2 of 15mmol/L along with serum potassium of 2.4meq/L and serum creatinine of 0.6 mg/dl. Further workup showed a urine anion gap of 126, urine osmolar gap of 80, urine pH of 6.0. 24-hour urine citrate was undetectable. Diagnosis of distal RTA secondary to pembrolizumab was made and therapy was held. Steroids were not initiated, as the kidney biopsy, performed within 2 months of holding the therapy, did not reveal any tubulitis or cellular infiltrates. She is being treated with potassium citrate with normalization of acidosis and hypokalemia.

Discussion: We describe two cases of distal RTA presenting as immune related adverse events associated with use of ICPI. AKI presence is not necessary. Prompt recognition and management of hypokalemia as soon as it is noted has been reported. A potential difference in the expression of PD-L1 among the tubular epithelial cells is responsible for isolated distal RTA.

PO1871 Immune Checkpoint Inhibitor-Associated Electrolyte Disorders: Query of the FDA Adverse Event Reporting System
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Background: Electrolyte disorders with immune checkpoint inhibitors (ICI) therapy are not well characterized. Single center studies have noted hyponatremia as the most common electrolyte disorder associated with ICI. nivolumab. We performed a revised more recent query of the FAERS database with a more detailed look at electrolyte disorders only (search terms: hyponatremia, hypernatremia, hypokalemia, hypercalcemia, hypophosphatemia, hypomagnesemia, acidosis, hyperphosphatemia and renal tubular acidosis) from 2011-2021.

Results: A total of 2556 cases of electrolyte disorders were reported to the FAERS system. The most commonly reported abnormality is hyponatremia (53.7%), followed by hypokalemia (18.71%), hypercalcemia (9.65%), hyperkalemia (5.6%) and hypocalcemia at 4.06%. The remaining abnormalities were <4%. In all three groups of the agents (CTLA4 inhibitors, PD and PDL1 inhibitors), the trend remained similar. Most events were reported at a median age of 64 in all 3 groups analyzed. Among reported events, proportions of events in male were statistically more significant (p<0.01) than females in all 3 drug groups. Nivolumab (n=1130) and ipilimumab (n=676) were the most frequently reported events. In total, 554 cases of hyponatremia, 63 cases of hypernatremia, 275 cases of hypokalemia and 18 cases of hypercalcemia were reported in the literature demonstrates similar incidence of immune-related adverse events in patients with ESKD receiving dialysis as compared to the general population (49%). Grade 3 and 4 adverse events had been seen in fifteen patients (16%). Cancer remission (complete and partial) was seen in close to 30% of patients. Stable disease was seen in 28% and progression of disease in approximately 36% of patients. Overall, 60% of the patients died. Urothelial and RCC represented approximately half of all treated cancers, and accounted for approximately 50% of all deaths reported (Figure). Eighteen of the reported dialysis patients had prior kidney transplant. Of these, 11 (61%) initiated dialysis around 3-4 months after ICI-related rejection of their kidney allograft.

Conclusions: ICI is well tolerated in ESKD patients. Additional data in the dialysis population with use of ICI, and involvement in prospective studies, is needed to better assess outcomes, particularly within specific cancer types.
distress and hemoptysis concerning for diffuse alveolar hemorrhage led to ICU transfer. Kernicterus was ruled out as the patient showed no evidence of kernicterus, intraparenchymal hemorrhage, glomerulosclerosis, interstitial fibrosis or immune complex-deposits. Proximal tubules were focally dilated, suggestive of tubular injury. HLH was subsequently diagnosed and treatment with steroids and intravenous immune globulin was followed by electrolyte normalization and improved clinical status.

Discussion: Immune checkpoint inhibitors are increasingly used for cancer treatment. These medications carry risk of immune-related adverse effects. While secondary HLH has been reported with use of immune checkpoint inhibitors, cases are few and renal involvement even rarer. To date there has been no documented case of HLH with profound electrolyte derangements but normal GFR after receiving bintrafusp alfa. Awareness of these adverse events is necessary as these medications see more widespread use. The views expressed are those of the authors and do not necessarily reflect the official policy of the Department of Defense or the U.S. government.

Utility of Liquid Chromatography in Monitoring Methotrexate Levels After Glucarpidase for Methotrexate Toxicity

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Introduction: Methotrexate (MTX) is an anti-metabolite with a 1,000-fold affinity for dihydrofolate reductase, competitively inhibiting the reduction of dihydrofolate to tetrahydrofolate that is needed for DNA/RNA and protein synthesis. High-dose MTX is defined as a dose higher than 500 mg/m² and results in acute kidney injury in 2-12% of patients. Values above 10 µM at 24 h post-infusion confer a high risk for toxicity.

Case Description: A 61 y/o male with newly diagnosed primary CNS diffuse B cell lymphoma was admitted for De Angelis regimen which included MTX 3,500 mg/m². His creatinine increased from 0.9 to 3.1 mg/dL despite concurrent hydration, intravenous corticosteroids, and leucovorin. MTX level was 90 at 24 h, confirming MTX toxicity. He then received a single dose of glucarpidase 50 U/kg IV. Plasma MTX levels remained high at 44, 41, and 14 on post-glucarpidase days 1, 2, and 3. In contrast, high-performance liquid chromatography (HPLC) measurement of MTX was below 0.05 on post-glucarpidase days 2, showing efficacy of glucarpidase in lowering MTX levels.

Discussion: After high-dose MTX, serum levels must be monitored to determine when to administer leucovorin and glucarpidase, a recombinant carboxypeptidase-G2 that cleaves MTX to inactive metabolites. Intrarenal MTX crystallization can 1) obstruct the tubules, 2) damage the tubular epithelium, and 3) vasoconstrict the afferent arterioles. Because volume depletion and acidic urine are major risk factors for glucarpidase, hyperhydration and urine alkalinization are mandatory during high-dose MTX treatment. Early intervention with the combination of leucovorin and glucarpidase is highly effective in patients who develop kidney dysfunction. A single dose of glucarpidase 50 U/kg IV reduces plasma MTX concentration by >97% within 15 mins. Liquid chromatographic measurement of MTX is recommended within 48 hours of glucarpidase administration, as the MTX metabolites 7-hydroxymethotrexate and 4-deoxy-4-amino N10 methylpteroic acid (DAMPA) cross react with standard immunoassays and falsely elevate the level. In our patient, the serum MTX levels were still elevated by immunoassay, while they were undetectable by liquid chromatography. We recommend using HPLC when available to confirm the lowering of MTX by glucarpidase.
However, BNP is produced primarily by myocardial cells of the left ventricle in response to stretching. The two primary natriuretic peptides of the CNS are thought to be C-type natriuretic peptide and D-type natriuretic peptide, which have been shown to induce natriuresis leading to hyponatremia and suppressed ADH levels, as was possibly seen in our patient. We report this case to allow clinicians to be aware of this possible occurrence.

PO1877
Cisplatin-Induced AKI Cancer Mouse Model Refinement
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Background: Cisplatin (CIS), a common chemotherapeutic, causes acute kidney injury (AKI) in up to one-third of patients. Traditional mouse models use healthy mice and a single, lethal dose of CIS (20-30 mg/kg). This model does not accurately reflect the clinical use of CIS where cancer patients receive 25-100 mg/m² every 3-4 weeks. There is a need for a multi-dose mouse cancer model of CIS-AKI that more closely reflects CIS clinical use.

Methods: C57BL/6 male mice (8 weeks old; n=45) were injected in the right flank with murine lung cancer cells (CMT167; 0-1,500,000 cells). Subcutaneous solid tumors were allowed to grow for ~2 weeks until digital caliper measurement confirmed they were ≥50 mm³. Mice were then dosed with CIS (0, 12.5, 15 mg/kg) or vehicle (saline) 1x/week for up to 4 weeks. Mice were evaluated for outcomes of general health (body weight), survival, cancer progression (tumor volume), and kidney injury (Scr, BUN, KIM-1). Assessments were performed a1x/week until sacrifice after 1-4 weeks of CIS treatment. Analyses for differences from baseline to sacrifice based on both cancer cells injected and CIS dose were assessed by 2-way ANOVA with a Tukey-Kramer post-hoc test; p<0.05 was considered statistically significant.

Results: Groups injected with >1 million CMT167 cells experienced the greatest decline in survival due to rapidly growing tumors and ulceration (0% at 8 d). Cancer-free mice treated with CIS also experienced poor survival due to dehydration and weight loss (60% at 15 d). Mice injected with 50,000 CMT167 cells had the best survival (100% at 13 d). Body weight was significantly decreased as CIS dose increased (p=1.9x10⁻⁸) and increased as number of CMT167 cells increased (p=5.5x10⁻⁹). Tumor volume was significantly increased as number of CMT167 cells increased (p=5.1x10⁻⁸) and somewhat decreased as CIS dose increased (p=0.002). CIS dose did not significantly impact BUN or Scr levels but an increase in KIM-1 was somewhat associated with an increased CIS dose (p=0.105; 12.5 vs 15 mg/kg CIS p=0.191). There were no significant differences in body weight, tumor volume, or survival between the 12.5 and 15 mg/kg CIS treated mice.

Conclusions: The results indicate that the ideal CMT167 mouse cancer model of CIS-AKI should use 50,000 CMT167 cells and 15 mg/kg CIS. This model can be used to better understand CIS-AKI and to test potential protective compounds.

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PO1878
Renal Outcomes in High-Dose Cisplatin in Locally Advanced Squamous Cell Carcinoma of the Head and Neck: A New and Interesting Perspective
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Background: Three-weekly high-dose cisplatin (100 mg/m²) concomitant to radiation is considered a standard of care with a curative intent in most of locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN). Nevertheless, cisplatin is known as a particularly nephrotoxic drug especially at the cumulative dose of 200 mg/m² or more. The aim of this study was to investigate the incidence of AKI in patients with LA-SCCHN during and after treatment with high-dose cisplatin-based CRT to identify risk factors for cisplatin-induced AKI.

Methods: A consecutive cohort of 82 patients treated with cisplatin cumulative dose ≥200mg/m² concomitant to radiotherapy, was enrolled in a tertiary single hospital from 2019 and 2020. Serum creatinine, hemoglobin, lymphocytes and eGFR formulas (CKD-EPI, MDRD, Cockcroft-Gault) were detected at baseline and after each cycle of chemotherapy. AKI and CKD onset were determined according to K-DIGO criteria. Clinical tumor stage as well as comorbidities were also included. Bayesian linear regression model was used to evaluate the impact of the clinical and pathological features on eGFR decay through cycles.

Results: At baseline, 57% of pts were CKD stage 3, 37% CKD II stage, 6.1% CKD III stage A-B. Medium decay of eGFR from the baseline to the end of 3 cycle is reported in table 1 showing CKD different stages. The marked decay appears in day 10 during cycle 2 (Figure 1). Performing a Bayesian linear regression over cycles, hypertension showed a remarkable impact on the eGFR decay through the therapy over time (Figure 2). However, the AKI incidence was very low in all CKD classes; 2.4% in 1 cycle, 4.8% in 2 cycle and 2.4% in 3 cycle.

Conclusions: Surprisingly, from these data high dose of cisplatin seems feasible in different CKD stages with very low rate of renal toxicity events and AKI-CKD onset.

PO1879
Double Hit: A Case of Chromogranin A-Mediated Proximal Tubulopathy That Progressed to Full-Blown Fanconi Syndrome After Treatment with Everolimus
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Introduction: Hypophosphatemia is an independent risk factor for poor patient outcomes. We present a rare case of hypophosphatemia from a complication of a neuroendocrine tumor (NET) and the treatment for it.

Case Description: A 54-year-old female with metastatic NET presented with dyspnea. Patient had Pneumonia which was treated but a comprehensive electrolyte panel revealed profound hypophosphatemia (phosphorous levels < 1 mg/dl). Initial suspicion was that poor nutritional status may be the underlying etiology, however despite aggressive intravenous phosphorus supplementation, the hypophosphatemia persisted and progressed. Workup revealed obvious evidence of Fanconi syndrome. Patient had profound glucosuria with normal serum glucose. 24 hours urine phosphorus excretion was markedly elevated at 900 mg. Vitamin D level was borderline low but activated (1,25-vitamin D) levels were markedly low at 1.8 pg/ml. PTH levels were only mildly elevated at 120 pg/ml. A deeper investigation into her course found that patient was diagnosed with a NET 8 months prior to this presentation and had evidence of mild glucosuria with mild-moderate hypophosphatemia at that time. Chromogranin A levels from her NET were substantially elevated at that time. Serial urine analyses during the course of her disease were repeated, and it was evident that the glucosuria became markedly worse after the patient was started on everolimus therapy. We concluded that hypophosphatemia in this patient is from chromogranin A mediated proximal tubulopathy that developed to full blown Fanconi Syndrome after everolimus. We changed phosphorous supplementation to oral only and recommended holding everolimus provided it was appropriate from an oncological standpoint. Follow up of the patient in 4 weeks off everolimus showed continued improvement in phosphorous levels.

Discussion: Both chromogranin-A and mitor inhibitors have shown to cause acute tubular injury in proximal tubules. Our case is unique in the sense that it presented as severe hypophosphatemia from Fanconi syndrome secondary to two uncommon culprit agents that acted in a sequential manner to worsen the proximal tubulopathy. Based on this case we recommend that in NET patients with high chromogranin A levels, we check for signs of proximal tubulopathy before starting mitor inhibitor therapy.
Conclusions: Our study surprisingly highlights that both cisplatin/carboplatin-based CT and immunotherapy display a similar incidence of AKI and eGFR decay over time in NSCLC metastatic patients.

PO1881
AKI with BRAF and MEK Inhibitors May Not Be a Class Effect
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Introduction: BRAF tyrosine kinase inhibitors are used in the treatment of BRAF mutant metastatic melanoma. Simultaneous MEK inhibition has been shown to provide better response rates and fewer side effects. Renal toxicity has been reported with these agents which can include AIN, ATN and Fanconi syndrome. We report a case of AKI due to biopsy proven AIN from BRAF and MEK inhibitor vemurafenib and cobimetinib.

Case Description: This is a 64-year-old woman with diabetes mellitus type 2, stage IV melanoma with BRAF V600E mutation and baseline serum creatinine (Scr) of 0.8 (0.6-1.1) mg/dL. She has been treated with multiple chemotherapy regimens and immunotherapy (last dose of immunotherapy 28 months prior to presentation). Patient received dabrafenib and trametinib until 8 months prior to presentation but stopped due to development of fever and AKI (Scr 1.7mg/dL). She was started on vemurafenib 480 mg BID every other day and cobimetinib 40mg every other day 6½ months before presentation. Two months later the vemurafenib dose was increased to 960mg BID but patient was noted to have AKI with Scr of 4.5 mg/dL and vemurafenib and cobimetinib were stopped. Her blood pressure was elevated to 154/70 mmHg. Urinalysis showed protein of 100 mg/dL, 0-3 RBC/HPF and 0-6 WBC/HPF. Scr improved to 2.2 mg/dL but remained elevated and renal consult was obtained with subsequent kidney biopsy. It showed active, subacute, and chronic interstitial nephritis with extensive tubular atrophy. Patient was treated with prednisone 50 mg daily and was tapered down to 10 mg daily over two months. Repeat CT scan showed new peritoneal nodules and she was started on a new BRAF/MEK combination of encorafenib and binimetinib. She is followed on a new regimen and her kidney function is improving.

Discussion: This case strengthens the importance of being vigilant for renal toxicity from BRAF and MEK inhibitors. Renal toxicity has been reported in 1% of patients of the phase 2 trial but not in the phase 3 trial. Nectin-4 protein and leads to subsequent cell apoptosis through impaired cell division. Dermatologic disrupting agent monomethyl auristatin E (MMAE). The drug binds to Nectin-4, expressed on tumor cells, with high affinity, which induces the internalization of MMAE and leads to subsequent cell apoptosis through impaired cell division. Dermatologic toxicity occurs from drug binding to Nectin-4 expressed on normal skin cells. AKI was reported in 1% of patients of the phase 2 trial but not in the phase 3 trial. Nectin-4 protein is expressed and can be stained in renal tubular epithelial cells. While DKA may have contributed to our patient’s tubular injury, direct tubular toxicity may be possible and requires further research. Physicians prescribing Enfortumab vedotin should be aware of this potential side effect.

PO1884
An Elevated Serum Creatinine in a Patient Receiving Palbociclib
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Introduction: Serum Creatinine (Scr) is the most widely used parameter in clinical practice to estimate glomerular filtration rate (GFR). Various drugs have been reported to cause a reversible and transient elevation in Scr without a true reduction in overall kidney function.

Case Description: A 66-year-old woman with a past medical history of metastatic right breast poorly differentiated invasive ductal carcinoma, hormone receptor-positive, and HER2 negative. Who received treatment with fulvestrant and palbociclib, the dose of Palbociclib was 100mg orally a day. Presented for evaluation of elevated serum creatinine with decreased eGFR. On initial evaluation Scr was 1.6mg/dL, blood urea nitrogen of 21mg/dL, eGFR of 33mL/min/1.73m², her baseline eGFR was ranging from 42 to 52 mL/min/1.73m² in the past one year. An estimated glomerular filtration rate by cystatin C was performed and showed a value of 47mL/min with a cystatin-C level of 1.36mg/dL, which was at her baseline kidney function for the past year.

Discussion: Creatinine is freely filtered by the glomerulus and actively secreted by the proximal tubule from the peritubular capillaries, which accounts for 10-40% of creatinine clearance. The organic cation transporter 2 (OCT2), multidrug and toxin extrusion protein (MATE) 1 and MATE2-K, are the solute carrier transporters in the kidney that mediate clearance. Of these, OCT2 has been shown to have a reversible increase in creatinine of about 15-40% over baseline of patients with cancer and healthy subjects. This effect has been seen in about 25% of patients treated with abemaciclib however none of the clinical trials on palbociclib have
reported an increase in serum creatinine. In our case, the difference between eGFR by cystatin C and by serum creatinine demonstrated not a true decrease in kidney function. We have attributed these events to inhibition of the tubular secretion of creatinine by palbociclib and decided to continue treatment with palbociclib. Physicians should be aware that patients undergoing therapy with palbociclib require monitoring of kidney function and an increase in serum creatinine from baseline, might represent an inhibitory effect of the secretion of creatinine and not an actual decrease in kidney function.

**PO1885**

A Case of IgA Nephropathy in the Setting of Sezary Syndrome and Mogamulizumab

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Introduction: IgA Nephropathy (IgAN) is an autoimmune disease with complex pathogenesis. Sezary syndrome (SS) is a leukemic subtype of cutaneous T cell lymphoma (CTCL). A rare association has previously been reported between IgAN and CTCL. Mogamulizumab (MG) is a monoclonal antibody drug targeting C-C chemokine receptor type 4 (CCR4) and is used in the treatment of CTCL and SS. MG has been associated with drug eruptions and systemic immune-mediated adverse events.

Case Description: A 63 year-old woman with SS was treated with MG. Her skin symptoms improved and circulating Sezary cells cleared. Due to a cutaneous drug eruption, the frequency of MG administration was reduced to monthly after cycle 7. Labs prior to cycle 19 demonstrated serum creatinine (Cr) 1.77 mg/dL from a prior baseline ~0.9-1.0 mg/dL. She received intravenous fluids but Cr worsened to 3.97 mg/dL. Urinalysis (UA) revealed more than 20 red blood cells (RBCs) per high powered field (HPF). 24 hour urine protein to creatinine ratio (UPCR) was 2.03 g/g. Serologies and complement levels were normal except double stranded DNA which was 12 IU/mL (normal <4 IU/mL). Kidney biopsy demonstrated mesangial immune complex deposition with IgA, IgG, and C3 predomiance consistent with IgAN (Oxford M1/0/R/T/I/T/3C). Prednisone was initiated at 1 mg/kg/day and tapered over 6 months. MG was stopped. After 6 months Cr had improved to 1.10 mg/dL. UA showed 3-5 RBCs per HPF with UPCR of 0.122 g/g. Her SS remained well controlled without systemic toxicity.

Discussion: This case reinforces the association between IgAN and CTCL which has been described in prior case series. In patients with CTCL, altered T cell populations and a dysregulated immune response may contribute to the pathogenesis of IgAN. Complicating this case is the use of MG which can deplete normal CCR4-expressing regulatory T cells and thus dysregulate immune response leading to increased renal injury. In the presence of pre-existing renal pathology, MGRS and induced kidney injury should be suspected due to its potential risk for exacerbating pre-existing glomerulonephritis.

**PO1886**

Filgrastim-Induced Crescentic Glomerulonephritis

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Introduction: Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is caused by deposition of monoclonal immunoglobulins in the glomeruli. It is one of renal disorders included in the spectrum of monoclonal gammopathy of renal significance (MGRS). IgG3 kappa light chain is the most common type. Autologous stem cell transplantation (SCT) provides a durable remission and better renal outcomes. Granulocyte colony stimulating factor (GCSF) is a recombinant glycoprotein used for mobilization of bone marrow in SCT. GCSF has been implicated as a cause of crescentic transformation of an acute glomerulonephritis in one prior case with a monoclonal deposits in a kidney transplant patient. In this case, we report the clinical and pathologic findings of GCSF induced exacerbation and crescentic transformation of pre-existing PGNMID with successful treatment and SCT.

Case Description: A 48-year-old male with recent diagnosis of MGRS presenting as MPGN and monoclonal IgG Kappa with C3 deposits on biopsy and treated with Velcade, cyclophosphamide and dexamethasone with a plan for SCT. Patient was admitted after acute increase in creatinine from 2.87 mg/dl to 6.6mg/dl with hematuria and proteinuria after receiving GCSF during stem cell mobilization. Timing of acute renal injury correlated with increase in WBC after GCSF injections with a peak of 69 K/ul. Repeat kidney biopsy was significant for crescentic membranoproliferative (62% crescents) glomerulonephritis with monoclonal IgG/kappa deposits. Patient received 5 sessions of plasmapheresis, one dose of renally adjusted IV Cytosan, and pulse steroids followed with a taper. After a month he undergo an Autologous SCT (creatinine at baseline 1mg/dl). His kidney function continued to improve and after 16 months post SCT his creatinine is at 1.4mg/dl.

Discussion: GCSF enhances neutrophils activation in large counts and induces its endothelial activation. In the presence of pre-existing renal pathology, MGRS and MPGN with IgG kappa and C3 deposits in this case, the localized immunoglobulin and complement deposits in the glomeruli can attract activated neutrophils leading to its infiltration and degranulation in the glomerular microenvironment, and resulting in rupture of glomeruli basement membrane and formation of crescent. Therefore, GCSF induced kidney injury should be suspected due to its potential risk for exacerbating pre-existing glomerulonephritis.

**PO1887**

Creatinine-Cystatin C Ratio and Mortality in Cancer Patients: A Retrospective Cohort Study

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Background: Muscle wasting is prevalent in cancer patients, and early recognition of this phenomenon is important for risk stratification. Recent studies have suggested that the creatinine-cystatin C ratio may correlate with muscle mass in several patient populations. The association between creatinine-cystatin C ratio and survival was assessed in cancer patients.

Methods: A total of 3,060 patients who were evaluated for serum creatinine and cystatin C levels at the time of cancer diagnosis were included. The primary outcome was 6-month mortality. The 1-year mortality, and length of intensive care unit (ICU) and hospital stay were also evaluated.

Results: The mean age was 61.6±13.5 years, and 1,409 patients (46.0%) were female. The median creatinine and cystatin C levels were 0.9 (interquartile range [IQR], 0.6-1.3) mg/dL and 1.0 (IQR, 0.8-1.5) mg/L, respectively, with a creatinine-cystatin C ratio range of 0.12-12.54. In the multivariate Cox analysis, an increase in the creatinine-cystatin C ratio was associated with a significant decrease in the 6-month mortality (per 1 creatinine-cystatin C ratio, hazard ratio [HR] 0.35; 95% confidence interval [CI], 0.28-0.44). When stratified into quartiles, the risk of 6-month mortality was significantly lower in the highest quartile (HR 0.30; 95% CI, 0.24-0.37) than in the lowest quartile. Analysis of 1-year mortality outcomes revealed similar findings. The highest quartile was also associated with shorter length of ICU and hospital stay (both P<0.001). These associations were independent of confounding factors.

Conclusions: The creatinine-cystatin C ratio at the time of cancer diagnosis significantly associates with survival and hospitalization in cancer patients.

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**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

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Poster 580
Methods: We enrolled 181 cancer patients treated at an academic tertiary cancer hospital in Brazil (Instituto do Cáncer do Estado de São Paulo), who had undergone abdominal imaging and measurement of GFR by plasma clearance of 51Cr-EDTA within 60 days. eGFR was determined based on the CKD-EPI equation using Scr (eGFRcr) and Scr combined with Scys (eGFRcr-cys). eGFR and mGFR were non indexed for body surface area. Total kidney volume (TKV) was measured using a semi-automatic segmentation program, excluding non-functional tissues. The correlations between mGFR and TKV as well as mGFR and eGFR were calculated using the Pearson correlation coefficient. Linear regression models for mGFR having TKV and eGFR equations as predictors were built.

Results: Patients were 55 (14.0) y, 50.3% male. Most common cancer sites were breast (22.7%), male genital (21.8%) and gastrointestinal (20.9%). ECOG levels 0/1 corresponded to 95% of patients. Mean (SD) Body mass index was 27.18 (5.18). Mean (SD) mGFR, eGFRcr and eGFRcr-cys were 84.0 (27.23), 90.4 (24.9), and 83.8 (25.9), ml/min, respectively. Mean (SD) TKV for both kidneys was 302.2 (77.9) cm3. PCC for mGFR-TKV, mGFR-eGFRcr and mGFR-eGFRcr-cys were 0.76, 0.78 and 0.85, respectively. TKV improved the coefficient of determination of the linear regression models when added to both eGFRcr and eGFRcr-cys, in overall and assessed subgroups (Table 1).

Conclusions: In conclusion, our results suggest that measurement of TKV is a reliable predictor of mGFR in cancer patients with the potential to be incorporated to the current eGFR equations used in clinical practice.

Table 1: Linear regression models for measured glomerular filtration rate (mGFR) and estimated glomerular filtration rate (eGFR).

POI1890
Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits: Searching for the Underlying Clone

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Background: The pathophysiological mechanisms of proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) are still largely unknown. Only 30% of PGNMID cases have a detectable circulating monoclonal immunoglobulin (Ig) and a bone marrow corresponding clone.

Methods: We reviewed a French cohort of PGNMID with particular focus on hematological characteristics. A high-throughput sequencing assay from bone marrow and/or blood mRNA encoding immunoglobulins (RACE-RepSeq) was used to detect the underlying clone.

Results: Seventy-one patients (M/F ratio=1.6, median age 59 years) were included. At diagnosis, 73% had renal insufficiency (median serum creatinine=1.7 mg/dL). All patients had proteinuria, with nephrotic syndrome in 59% and microscopic hematuria in 85% of cases. No patient had extra-renal manifestations. Light microscopy, kidney biopsy, revealed mesangial proliferation and mesangial glomerulonephritis in 69% cases. By immunofluorescence (IF), deposits were revealed in 18/26 cases (mostly IgG3, IgM in 7 cases, IgA in 4 cases or light chain (LC) only in 5 cases. Serum and/or urine immunofixation was positive in 26 cases (37%). An underlying clone was found in 21 cases (30%) using bone marrow or blood flow cytometry analysis. The clonal detection rate was particularly low in IgG3-PGNMID (9%). The nature of the clone differs with PGNMID subtype: lymphoplasmacytic in IgM-PGNMID, and plasmacytic in IgA-LC-PGNMID. RACE-RepSeq analysis failed to detect a bone marrow or blood clone in 18/26 cases (IgG3-PGNMID, n=17; IgGAK-PGNMID, n=1). IF analysis of kidney samples using anti-Vκ antibodies showed positive staining for Vκ in 26 cases and Vλ in 3/3 tested IgG3k-PGNMID patients without a detectable clone, whereas deposits stained only for Vκ in one IgG1k-PGNMID patient who had a bone marrow Vκ clone by RACE-RepSeq analysis.

Conclusions: These results suggest that PGNMID is a heterogeneous medical condition and that some cases might involve oligoclonal production of nephrotoxic Ig restricted to the IgG3k isotype. Such cases should no longer be classified as MGUS.

POI1891
Rituximab-Associated Flare of Cryoglobulinemic Vasculitis


Background: Patients with cryoglobulinemic vasculitis (CV) can develop disease flare after rituximab administration. The pathogenesis is hypothesized to be from immune complex deposition in the microvasculature, wherein the immune complex consists of the involved cryoglobulin and an antigenic portion of rituximab. Our objective was to describe the prevalence, clinical characteristics, predisposing factors, and outcomes of rituximab-associated flare of CV.
Methods: We conducted a retrospective study in a tertiary referral center. We defined renal deterioration within two days following rituximab administration, including onset of new organ involvement or worsening of the underlying CV not clearly explained by disease progression alone - with or without laboratory evidence.

Results: Among 64 patients with known CV who received rituximab therapy in our center, 14 (22%) developed disease flare. Median age was 67.5 years. Seven patients (50%) had type II CV while the other half had either type I (n=6) or type III (n=1). Twelve patients (86%) had IgM-mediated CV flare. Twelve patients (86%) had an underlying B-cell lymphoproliferative disorder as the cause of their CV flare occurred after a median time of 5.5 days (range: 2-8 days). The organ systems most involved were the skin (n=10), kidneys (n=5), and peripheral nerves (n=3). Nearly all patients received treatment directed against their underlying diseases, including chemotherapy, corticosteroids, and/or immunosuppressives, with or without correlation to monoclonal IgG deposits (MGMID) is a recently described entity characterized by a membranous pattern of injury with monoclonal IgG-kappa restriction, unmasked by pronase digestion on deposits (MGMID). The aim of this study was to characterize the clinicopathologic features of MGMID and compare the differences between drug-induced TMA and other causes of TMA from our academic center with biopsy proven TMA, describe their clinical characteristics of response to treatment. Clinicians should be cognizant of its existence and have a high index of suspicion for this phenomenon.

PO1892 Membranous-Like Glomerulopathy with Masked Monoclonal IgG Deposits
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Introduction: Membranous-like glomerulopathy with masked monoclonal IgG (MGMID) is a recently described entity characterized by a membranous pattern of injury with monoclonal IgG-kappa restriction, unmasked by pronase digestion on formalin-fixed paraffin-embedded (FFPE) tissue by immunofluorescence microscopy (IF). Retrospective pathology and chart review was performed within a large health system in the USA between 2019-2021 identifying 5 patients.

Case Description: All 5 patients were Caucasian females with median age 17 years (range 12-40). On presentation, 4 patients had elevated urine protein to creatinine ratio (UPC), 3 had microscopic hematuria, and 1 patient had an eGFR <90ml/min/1.73m². Low C3 and C4 levels were noted on presentation along with a normal COMP and CH50 suggesting a hypocomplementemic, anti-thrombotic complement mediated mechanism of injury. Two patients had complement C3 levels of <50 mg/dl at diagnosis. Electron microscopy revealed subepithelial/intramembranous deposits without substructural organization. On FFPE after pronase digestion, all cases revealed glomerular capillary wall staining for gamma-1 (4 cases) or gamma-3 (1 case) and kappa light chains; lambda light chains were negative. Extensive hemotologic workup was negative for monoclonal bands or lytic lytic processes. All patients were treated with angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) therapy, and 2 patients were also treated with Rituximab. Eight patients had an improvement in UPC. None of the patients remained dialysis dependent on discharge from the hospital as opposed to 33% at presentation, and 15/33 had MAHA. In those in which a cause was able to be determined, 12/33 had drug induced TMA with the most common medication being VEGF inhibitors and Tyrosine kinase inhibitors with anti-VEGF properties (8/12). Three patients had TMA secondary to calcineurin inhibitors and one patient had cocaine induced TMA. 3/33 had complement mediated TMA, diagnosed by confirming activation of the alternative complement cascade. In patients with drug induced TMA, 6/12 patients had delayed proteinuria and kidney function after withdrawal of the drug. 3 remained dialysis dependent and 2 were transitioned to home hospice. In the drug induced TMA category, 33% patients were dialysis dependent on discharge from the hospital as opposed to 43% in the non-drug induced TMA category.

Conclusions: Every patient with biopsy proven TMA should undergo a thorough history including medication use and work up, so optimal management can be initiated. In our series, 50% of the patients with drug induced TMA improved after withdrawal of the culprit medication.

PO1894 TAFRO: A New Cause for Thrombotic Microangiopathy Mimicking Atypical Hemolytic Uremic Syndrome Successfully Treated with Anakinra and Eculizumab

Introduction: atTAFRO is syndrome of Castleman’s disease with thrombocytopenia, anaasarca, myelofibrosis, AKI & organomegaly. We present a 17 yr old girl with abdominal lymph nodes who rapidly developed anaasarca, splenomegaly, AKI requiring dialysis, & respiratory failure requiring mechanical ventilation. After a lymph node bx 2 months later showed multicentric Castleman’s, plasma cell variant, we realized she early on had TAFRO.

Case Description: She rapidly developed anaasarca, an 18 cm spleen, & abdominal nodes to 1.9 cm. Bacterial cultures, spinal tap, viral resp panel, mono, HIV, HIV-1 levels were normal (NLM). Hgb dropped to 6.7 g/dl without hemolysis, platelets 57,000 & WBC,15,500. CRP was 32.5 & sed rate 130. Oliguria ensued & creatinine rose to 3.6 mg/dl. Urea was 18,930 pg/ml, CXCL9 107 pg/ml but Il-6 was only 11.3 pg/ml. Bone marrow showed increased megakaryocytes & no hemoglobinosis. aHUS testing was negative for all genetic causes & no abs were found to any complements(C) but both, C3, 65 mg/dl & C4, 4 mg/dl were low & the membrane attack complex C5-C9, markedly elevated at > 50 mg/dl. Renal bx showed endothelial swelling & thrombotic microangiopathy (TM) confirmed on EM with negative IF. 3 pulses of solomedrol daily, dialysis, 2 plasmaphereses before the aHUS panel returned were started along with 2 doses of Anakinra, an anti-IL-1 drug, 4mg/kg sub q separated by 3 days & 1 dose of Eculizumab, 1200 mg iv. She rapidly improved, was extubated & was discharged off dialysis with a NL creatinine & no edema.

Discussion: We conclude: 1) TAFRO can mimic aHUS & present with markedly elevated IL-2R levels rather than IL-6 levels which can fix complement by the classic pathway leading to high membrane attack complexes adding to capillary leak, anaasarca and TM. 2) An Anti IL-1 drug, Anakinra, & a drug inhibiting C5 cleavage to C5a & C5b, Eculizumab can be combined to successfully treat TAFRO 3) TAFRO must now be added to all reviews and textbooks as a new cause for TM & aHUS with classic complement pathway activation.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Large Abdominal Mass: An Unusual Presentation of Multiple Myeloma
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Introduction: Extramedullary Soft Tissue Mass (ESTM) is an infrequent presentation of Multiple Myeloma. We present a unique case of Multiple Myeloma with very large bulky tumor masses.

Case Description: A 69 year old AA female presented with severe abdominal distention. CT Scan showed a 17 x 10 x 10 cm mass originating in the retroperitoneal region, a 12.5 cm mass in the pelvis and a 4.3 x 2.7 cm mass in the liver as shown in the image. Further testing showed anemia and renal failure. Biopsy of the mass revealed multiple myeloma, driving a monoclonal IgG lambda clone. FISH panel was positive for 17p/TP53 deletion which is very unfavorable. Patient was treated initially with dexamethasone/cyclophosphamide/Velcade and later with Daratumumab/Carfilzomib/dexamethasone without any response and remained on dialysis ultimately succumbing within 6 weeks of diagnosis.

Discussion: Initial Extramedullary Soft Tissue Mass (ESTM) manifestations in Multiple Myeloma occur in about 3% of the cases. In a large majority (93.5%) these lesions are solitary. Our patient had large, multiple masses with high tumor burden and unfavorable cytogenetic signature. She did not respond to therapy despite utilization of aggressive regimens. This is a very unique presentation of myeloma and with the unfavorable characteristics, had a dismal prognosis despite aggressive therapy.

Fibrils in mesangial matrix

PO1896

Fibrillary Glomerulonephritis and Graft vs. Host Disease
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Introduction: Fibrillary Glomerulonephritis (FGN) is rare and seen in 1% of kidney biopsies. Etiology is unknown. It is associated with malignancy, monoclonal gammopathy, autoimmune disorders and infections. There has not been FGN case reported in a pt with Graft Versus Host Disease (GVHD). We present a case AKI seen to FGN with h/o Acute Lymphocytic Leukemia, status post Allogeneic Stem Cell Transplant complicated by Gastrointestinal GVHD.

Case Description: 67 yo African American female with DM, HTN, ALL s/p ASCT in remission, recently diagnosed with GI GVHD, presented with nausea, vomiting & diarrhea. Labs: BP 140/70, Temp 37.4°C, HR 109. Exam showed 3+ LEs edema. Labs: Cr 3.5 mg/dL, baseline of 1.1mg/dL. Urinalysis showed hematuria and 14.6g/g protein. Histology showed C3 crescentic GN. DNAJB9 stain returned positive and EM findings confirmed FGN. Patient received Solumedrol, followed by Rituximab and then Cyclophosphamide. She was dialysis dependent within 6 mos of diagnosis.

Discussion: FGN may have an undescribed association with GVHD. It is understudied because of rarity. It can present with AKI and kidney Biopsies. Etiology is unknown. It is associated with malignancy, monoclonal gammopathy, autoimmune disorders and infections. There has not been FGN case reported in a pt with Graft Versus Host Disease (GVHD). We present a case AKI seen to FGN with h/o Acute Lymphocytic Leukemia, status post Allogeneic Stem Cell Transplant complicated by Gastrointestinal GVHD.

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Underline represents presenting author.
He remained in remission for four years. In 2020 he had relapse of his nephrotic syndrome and eGFR dropped to 17 ml/min. Further imaging suggested progression of the CTLL. He had further renal biopsy which again confirmed recurrent Fibrillar GN. He was started on the Tyrosine kinase inhibitor (TKI) Ibrutinib in December 2020 and within 3 months his renal function had improved to an eGFR of 33 ml/min and reduction in proteinuria.

TKIs have mostly been linked with kidney injury secondary to the potential deleterious effects on the renal endothelium. This is the first reported case of the use of a TKI as a treatment for Fibrillar GN secondary to C. L. In addition, there is scarcity of experience with relapse of Fibrillar GN as it is usually a progressive disease and with little prospect of recovery. This case highlights the following: If there is an identifiable cause driving Fibrillar GN, treatment can be associated with remission of proteinuria and improvement in renal function. Monitoring of the underlying disease is important as recurrence can result in subsequent relapse of nephrotic syndrome. TKIs used with caution can be beneficial in the setting of MGRS.

**PO1898**

Ruxolitinib for Graft vs. Host Disease-Associated Nephrotic Syndrome: A Case Report


**Introduction:** Graft-versus-host disease (GVHD) is a serious complication of allogeneic stem cell transplant in which donor T-cells attack the host antigens. We report a case in which ruxolitinib successfully treated GVHD-related nephrotic syndrome.

**Case Description:** A 48-years-old male known to have myelodysplastic syndrome (MDS) was referred for evaluation of proteinuria. He was diagnosed with MDS four years previously. A 1-year history of this disease was consistent with azacitidine, he received allogeneic stem cell transplant (SCT) about a year after the MDS diagnosis and he achieved complete remission. However, the post-transplant course was complicated by chronic GVHD which manifested mainly as non-specific interstitial pneumonia (NSIP) about three and a half-year post-transplant. NSIP was treated with high-dose oral steroid therapy, which was slowly tapered down to a maintenance dose of 10 mg daily, and Mycophenolate Mofetil. During his course of GVHD, he had persistent mild proteinuria (UPCR less than 1 g/g of creatinine) without active urine sediment. This proteinuria was noted initially prior to NSIP diagnosis, improved while on high-dose prednisone but progressively worsened after the prednisone was tapered to 10 mg once daily. The proteinuria peaked at 2.4 g/g of creatinine with hypoalbuminemia of 2.6 g/dL at which point it was investigated with a renal biopsy. Renal biopsy showed Membranous Nephropathy with negative staining for anti-PLA2R antibody. The patient was started on ruxolitinib at a dose of 10 mg twice a day. Subsequent follow-up showed dramatic reduction in proteinuria. UPCR (g/g of creatinine) of 0.96, 0.4 and 0.09 was noted at 12- and 5-months post-therapy initiation respectively.

**Discussion:** Nephrotic syndrome is a rare manifestation of GVHD with membranous nephropathy histology seen in almost two thirds of patients. Traditionally treated with high-dose steroid with variable efficacy, we decided against it due to the patient-reported adverse effects from prior high-dose steroid therapy. Recent studies such as REACH2 and REACH3 trials have demonstrated that ruxolitinib, a selective Janus Kinase (JAK) 1 and 2 inhibitor, has superior efficacy than other second-line therapy options available. Hence, ruxolitinib can be considered in GVHD-associated nephrotic syndrome especially if a steroid-sparing approach is needed.

**PO1899**

Clonal Hematopoiesis of Indeterminate Potential Is Associated with Worse Kidney Function and Anemia in a Cohort of Patients with Advanced CKD

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**Background:** Clonal hematopoiesis of indeterminate potential (CHIP) is an inflammatory premalignant disorder resulting from acquired genetic mutations in hematopoietic stem cells. CHIP is common in aging populations and associated with cardiovascular morbidity and overall mortality, but its role in chronic kidney disease (CKD) has not been investigated.

**Methods:** We performed targeted sequencing to detect CHIP mutations in a cohort of 87 adults with advanced CKD (eGFR < 60 ml/min/1.73 m2). Kidney function, hematologic, and mineral bone disease parameters were assessed cross-sectionally at baseline, and a total of 2,091 creatinine measurements and 3,382 hemoglobin measurements were retrospectively collected over the following 12-year period.

**Results:** At baseline, 26 of 87 (23%) cohort participants had CHIP detected. Those with CHIP had lower baseline eGFR (22.2 ± 2.5 vs. 28.2 ± 1.4 ml/min/1.73 m2, P = 0.04) in age- and sex-adjusted regression models. Individuals with CHIP had a 2.5-fold increased risk of a 50% decline in eGFR or ESKD in a Cox proportional hazard model adjusted for age and sex (95% confidence interval, 1.3–4.7). Further, those with CHIP had lower hemoglobin at baseline (11.6 ± 0.3 vs. 12.8 ± 0.2 g/dL, P = 0.0003) and throughout the follow-up period despite a greater use of erythropoiesis-stimulating agents. Mean cell volume was associated with variant allele fraction, suggesting CHIP may contribute to defective erythropoiesis in CKD.

**Conclusions:** CHIP was associated with lower eGFR, progression of CKD, and anemia in individual and advanced CKD. Further assessment of the direction of causality between CHIP and CKD and validation in additional cohorts is required.

**Funding:** Private Foundation Support

**PO1900**

Case of C3 Glomerulopathy in a Patient with Mesothelioma

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**Introduction:** C3 glomerulopathy has been described in autoimmune diseases and in monoclonal gammopathy caused by plasma cells and B-cell lineage cells malignancies. There have been no reports of C3 glomerulopathy that is associated with mesothelioma. We report here a case of C3 glomerulonephritis diagnosed in patient with pulmonary mesothelioma.

**Case Description:** 84-year-old male patient presented with shortness of breath with fluid overload and vasculitic rash in the lower extremities, elevated BUN and creatinine and potassium of 5.7. Patient has been diagnosed with resectable pulmonary mesothelioma two months prior to his presentation and had received only one treatment of immune check inhibitor (Nivolumab plus Ipilimumab) one day prior to admission. Work up was done and showed AKI, proteinuria and hematuria, but negative work up for autoimmune disease or paraproteinemia or an infectious etiology. Decision was made to proceed with kidney biopsy which showed C3-dominant immune-complex mediated glomerulonephritis affecting about 35% of glomeruli with segmental crescent formation in about 5% of the glomeruli, diffuse acute tubular injury and minimal interstitial fibrosis and tubular atrophy.

**Discussion:** C3 glomerulopathy has been associated with autoimmune diseases and hematological malignancies and is related to unrelated activation of the alternative complement pathway, however solid tumors like mesothelioma may also trigger an immune mechanism that would lead to C3 glomerulopathy. We will discuss the possibility that the C3 glomerulopathy was due to or in association with the recent diagnosis of mesothelioma, also we will discuss the possible mechanisms of this association.

**PO1901**

NELL-1 Membranous Nephropathy Associated with Diffuse Reactive Lymphadenopathy

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**Introduction:** We present a case of a neutrophilic epidermal growth factor like-1 (NELL-1) MN associated with diffuse lymphadepathopathy without evidence of malignancy or autoimmune disease.

**Case Description:** A 53-year-old woman with a BRCA 1 mutation presented with nephrotic syndrome. Diffuse lymphadepathopathy was found on examination. Laboratory evaluation revealed serum albumin of 1.9 mg/dl, creatinine of 0.4 mg/dl, and UPCR 13.5 g/g. Urine microscopy showed protein (4+), and bland urine sediment. Serum PLA2R antibody was negative. Four excisional lymph node biopsies were performed, all of which revealed reactive hyperplasia without evidence of hematological malignancy. Flow cytometry and a bone marrow biopsy were negative. Serology for ANA, CRP, ESR, C3, C4, EBV, HV, and Hepatitis B, and C were all negative. Renal pathology revealed diffuse, fine pinholes along the glomerular basement membranes using a Jones silver stain. By immunofluorescence (IF), glomeruli showed diffuse, global finely granular capillary loop staining for IgG (3+), C3 (1-2+), and stained equally for κ and λ light chains. An IF stain for NELL-1 showed diffuse granular staining capillary loops (3+) while immunohistochemical stains for PLA2R and EXT2 were essentially negative. The ultrastructural evaluation revealed numerous, confluent subepithelial electron-dense deposits along with severe foot process effacement.

**Discussion:** NELL-1 associated MN was recently discovered as a distinct type of MN. In one series, 33 % of NELL-1 MN associated with malignancies, which is more often than the other known types of MN. The constellation of findings in this case with NELL-1 MN associated with reactive diffuse lymphadepathopathy without evidence of malignancy or autoimmune disease is a rare presentation. Therefore, this case adds to the existing literature on NELL-1 associated MN, which helps to raise the awareness of this novel clinical presentation.
Methods: In cisplatin group, male C57BL/6 mice were intraperitoneal injected with saline and killed at the same timepoint as cisplatin group. cisplatin (10mg/kg) on day 0, 7 and 21, and killed on day 28. In control group, mice were intraperitoneal injected with saline and killed at the same timepoint as cisplatin group.

Results: Through real-time PCR, western blot and masson staining, successful establishment of a mouse model with cisplatin induced renal interstitial fibrosis was confirmed. Through RNA high-throughput sequencing, 387 long noncoding RNAs (lncRNAs) and 2427 mRNAs were differently expressed between cisplatin group and control group. The expression of lncRNA MSTRG.8677 and lncRNA MSTRG.405 were verified by real-time PCR with the same tendency as RNA sequencing. Complement C3 was found to be at the top among the different expressed mRNAs by RNA sequencing. Several terms related to immunity were found to be within the top 20 terms through GO enrichment analysis of different expressed mRNAs. Systemic lupus erythematosus pathway (ko05322, P<3.4e-17), including the complement cascade pathway, was found to be the top pathway through KEGG enrichment analysis of different expressed mRNAs. The mRNA expression of C3, C1q, C2 and C4 were found to upregulated remarkably in cisplatin group by RNA sequencing and verified by real-time PCR.

Conclusions: Renal interstitial fibrosis could be induced by intraperitoneal injection of cisplatin periodically in mice, with complement cascade pathway activation in the diseased kidney.

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PO1903
Complement Activation in a Mouse Model of Cisplatin-Induced Renal Interstitial Fibrosis
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Background: Cisplatin is widely used for tumor chemotherapy. Renal interstitial fibrosis and chronic renal failure could be induced by periodic use of cisplatin. The mechanism of cisplatin induced renal interstitial fibrosis needs to be clarified.

Methods: In cisplatin group, male C57BL/6 mice were intraperitoneal injected with cisplatin (10mg/kg) on day 0, 7 and 21, and killed on day 28. In control group, mice were intraperitoneal injected with saline and killed at the same timepoint as cisplatin group. The kidney tissue was collected for RNA Illumina high-throughput sequencing, real-time PCR, western blot and masson staining.

Results: Through real-time PCR, western blot and masson staining, successful establishment of a mouse model with cisplatin induced renal interstitial fibrosis was confirmed. Through RNA high-throughput sequencing, 387 long noncoding RNAs (lncRNAs) and 2427 mRNAs were differently expressed between cisplatin group and control group. The expression of lncRNA MSTRG.8677 and lncRNA MSTRG.405 were verified by real-time PCR with the same tendency as RNA sequencing. Complement C3 was found to be at the top among the different expressed mRNAs by RNA sequencing. Several terms related to immunity were found to be within the top 20 terms through GO enrichment analysis of different expressed mRNAs. Systemic lupus erythematosus pathway (ko05322, P<3.4e-17), including the complement cascade pathway, was found to be the top pathway through KEGG enrichment analysis of different expressed mRNAs. The mRNA expression of C3, C1q, C2 and C4 were found to upregulated remarkably in cisplatin group by RNA sequencing and verified by real-time PCR.

Conclusions: Renal interstitial fibrosis could be induced by intraperitoneal injection of cisplatin periodically in mice, with complement cascade pathway activation in the diseased kidney.

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PO1904
Changes in Humoral Biomarkers (Klotho) in Patients with Haematological Tumors Undergoing Chemotherapy and Allogeneic Bone Marrow Transplantation Developing AKI
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Background: Acute kidney injury (AKI) is a complication in patients with hematological cancers after chemotherapy (CT) receiving allogeneic bone marrow transplant. It increases the morbidity and mortality rate associated with the procedure. Some urinary/plasma biomarkers (Klotho) have been evaluated as predictors of AKI development after cardiac surgery showing high prognostic value.

Methods: Our work is investigating the role and association of these determinants as early markers of susceptibility to AKI during CT, and predictors of CKD. So far, we have enrolled 13 leukemic patients who are candidates for induction CT and subsequent bone marrow transplantation. All the patients carried out sampling for renal function at each
cycle and at the same time plasma and urine were collected. Klotho plasma levels were measured in 4 phases diagnosis (t1); onset of AKI/2 months from diagnosis in patients without damage (t2); 15 days after t2 (t3); bone marrow tx (t4)

Results: We measured Klotho levels in 13 patients. The subjects are respectively 9 M and 4 F, mean age 49 years, all with normal renal function (mean creatinine 0.81 mg/dL) at diagnosis. The mean number of chemotherapy courses was 3.2. 7 patients developed stage 1 AKI according to AKIN criteria. No differences in anthropometric parameters were observed between the two groups. In subjects with development of renal damage, the average time of development was 2 months from diagnosis. While plasma KI decreases in a similar way in the first CT in the two groups, in no-AKI group the filtrate return normal before the next cycle. The restoration of normal kidney function is not observed in the Aki group (MANOVA p<0.006)

Conclusions: This trend allows us to hypothesize that KI is an indication of incomplete recovery of renal (tubular?) function before the next CT cycle, predisposing to the development of kidney disease

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PO1905

Systemic Amyloidosis Presenting as Progressive Dysphagia, Hypercalcemia, and Proteinuria
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Introduction: Systemic amyloidosis consists of several disorders whereby amyloid fibrils deposit in the extracellular tissue of multiple organs and as such, is associated with a wide spectrum of disease leading to significant morbidity and mortality. The severity and clinical manifestations of systemic amyloidosis is highly dependent on the site of amyloid fibril deposition.

Case Description: We present a 75-year-old male with no medical history who presented with dysphagia and epigastric abdominal pain. Lab work revealed moderate hypercalcemia and acute kidney injury (AKI) with urinalysis significant for >500mg/dL of protein. He received intravenous fluid re-education with improvement in renal function and temporary resolution of hypercalcemia. His AKI and hypercalcemia were attributed to volume depletion and possible milk-alkali syndrome due to consumption of calcium carbonate. After discharge however, he continued to have persistent sub-nephrotic range proteinuria, mild hypercalcemia and progressive renal insufficiency. UPEP and serum free light chain analysis revealed elevated kappa light chains. A kidney biopsy showed glomeruli with mesangial expansion as well as Congo red positive staining of glomeruli, interstitium, and vessels. Electron microscopy showed mesangial deposition of fibrillary material consistent with AL kappa light chain renal amyloidosis. Prior to follow up with Hematology, he was re-hospitalized for AKI, acute liver injury concerning for hepatic amyloidosis and progressive dysphagia likely due to gastrointestinal involvement. Therapy was initiated with bortezomb and dexamethasone; however, no significant kidney recovery was observed, and he remained dependent on dialysis. Due to rapid clinical decline, additional chemotherapy was not offered, and he was transitioned to comfort care.

Discussion: This patient presented with dysphagia, persistent hypercalcemia, renal insufficiency and proteinuria highlighting the clinical variability of systemic amyloidosis. As such, systemic amyloidosis, a rare infiltrative disorder, requires a high level of clinical suspicion in order to reach an early diagnosis and prevent long-term complications and mortality associated with advanced, multi-organ involvement. In addition, it is crucial to exclude coexisting multiple myeloma in patients presenting with hypercalcemia, renal insufficiency and AL amyloidosis.

PO1906

Will the Real Creatinine Please Stand Up? Elevated Creatinine in a Patient with Smoldering Myeloma
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Introduction: Monoclonal gammopathies cause altered kidney function by a variety of mechanisms. The assessment of patients with monoclonal proteins is further complicated by non-physiologic alterations in laboratory assays, including the assessment of serum creatinine, as reported in this case of a patient with smoldering myeloma.

Case Description: A 47 yo woman with a history of mixed connective tissue disease, hypertension, and IgG lambda light chain smoldering myeloma was referred for evaluation of creatinine of 1.6 mg/dL. Her medications were acebutolol, furosemide, hydrochlorothiazide and aspirin. Examination revealed BP 129/86, HR 60 without notable physical findings. Her laboratory evaluation was significant for a creatinine of 0.88 mg/dL, BUN of 10 mg/dL, albumin of 4.6 g/dL and total protein of 9.0 g/dL, with an M-spike of 1 g/dL. Her urine protein-creatinine ratio was 0.47 g/g creatinine. Over the next year, creatinine at her primary oncologist ranged from 1.2-1.3 mg/dL (except for a single episode of acute kidney injury), while in the nephrology clinic the creatinine was 0.9-0.9 mg/dL. Further investigation determined that the external laboratory used a picric acid-based creatinine assay, while creatinine from the nephrology clinic was measured using an enzymatic method.

Discussion: Monoclonal proteins have previously been reported to interfere with creatinine assays, primarily in patients with Waldenstrom’s macroglobulinemia. We report here a patient with a monoclonal IgG lambda paraprotein interfering with a Jaffe-based creatinine assay leading to pseudohypercreatininemia. Both nephrologists and oncologists should be aware of this phenomenon in the care of patients with all types of paraproteinemias, so that alternative means of kidney function assessment (such as measurement of cystatin c) can be employed when creatinine assays are unreliable.

PO1907

A Unique Case of Light Chain Proximal Tubulopathy
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Introduction: Light chain proximal tubulopathy (LCTP), a rare form of monoclonal gammopathy of renal significance (MGRS), is characterized by the accumulation of monotypic light chains within proximal tubular cells. LCTP may present in multiple ways, including acute kidney injury, chronic kidney disease (CKD), Fanconi’s syndrome, and proteinuria. We present a case of LCTP, presenting with CKD and non-nephrotic range proteinuria (NNRP).

Case Description: A 62 year old Caucasian male with a past medical history of IgM kappa light chain monoclonal gammopathy of undetermined significance (MGUS) presented for evaluation of CKD. Serum creatinine at the time of initial presentation was 1.4 mg/dL, which correlated with an estimated GFR of 54. No other electrolyte derangements were present. Urinalysis was negative for glycosuria, pyuria, or hematuria with unremarkable urine microscopy. He had NNRP on spot quantification of approximately 400 mg/g creatinine and 32 mg/g of this proteinuria was albuminuria. There was no history of hypertension or diabetes, and he denied NSAID use. He was taking no medications felt to cause chronic interstitial nephritis. Renal ultrasound was unremarkable, and 24 hour ambulatory blood pressure monitoring documented normal BP levels, on no medications. At follow up, the patient’s creatinine fluctuated between 1.4-1.6 mg/dL, which was indolent in nature, but was confirmed on renal biopsy using paraffin digestion to prove monoclonality of the crystalline deposits. This led to the diagnosis of a MGRS, and necessitated initiation of chemotherapeutic agents. LCTP is a rare manifestation of MGRS, and might not have been recognized in this case if suspicion had not been high, and biopsy had not been pursued.

Discussion: We present a case of LCTP manifesting as CKD G3a A1-2. The case was indolent in nature, but was confirmed on renal biopsy using paraffin digestion to prove monoclonality of the crystalline deposits. This led to the diagnosis of a MGRS, and necessitated initiation of chemotherapeutic agents. LCTP is a rare manifestation of MGRS, and might not have been recognized in this case if suspicion had not been high, and biopsy had not been pursued.
PO1908
Deceiving Schistocytes
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Introduction: Myelodysplastic syndrome (MDS) is a clone bone marrow disorder characterized by dysplasmatipoiesis, which may manifest as cytopenias and non-immune hemolytic anemia. Schistocytes are commonly associated with causes of microangiopathic hemolytic anemia (MAHA), however, they can be also observed in the peripheral blood smear in a rare and unusual manifestation of MDS.

Case Description: We report the case of a 63-year-old male who presented with complaints of asthenia, fatigue and malaise for the past 3 months. His previous medical history included a past of heavy smoking, arterial hypertension and grade 3 chronic kidney disease (CKD) developed after nephrectomy due to urothelial carcinoma in 2012. He also had in situ papillary urothelial carcinoma of the bladder in 2016, with a course of intra-vesical mitomycin. Vital signs were normal and physical examination was unremarkable. Blood work revealed macrocytic anemia (hemoglobin 7.2 g/dL; MCV 101 fL) and thrombocytopenia (77,000/µL) and peripheral blood smear demonstrated 16% schistocytes, with normal coagulation tests, lactate dehydrogenase and lactate dehydrogenase. Coombs test was negative. Renal function was stable and there was no evidence of hematopoietic infiltration. Inflammatory markers were negative. A diagnosis of microangiopathic hemolytic anemia was assumed and the patient was started on daily plasmapheresis and steroids, while further investigation was under way. Folate and cobalamin levels were normal, anti-nuclear antibodies and HIV, hepatitis B and C serologies were negative and full-body CT scan did not show signs of occult malignancy. Levels of CRP and C4 were also within the normal range. ADAMS-13 activity was 21%. No clinical or analytical improvement was noted after 6 sessions of plasmapheresis (platelet count nadir of 38,000/µL and persistence of schistocytosis). Bone marrow biopsy was performed and a diagnosis of refractory anemia with excess blasts was made.

Discussion: Hemolytic anemia is a common occurrence in patients with hematologic malignancies, particularly acute and chronic myeloid leukemia, but are rarely observed in MDS, with only a few cases reported in the literature. This case highlights the importance of considering a diagnosis of MDS in patients presenting with refractory cytopenias and MAHA.

PO1909
Granulomatous Interstitial Nephritis Secondary to Chronic Lymphocytic Leukemia
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Introduction: Granulomatous interstitial nephritis (GIN) is a rare disorder defined by histological interstitial nephritis and interstitial granulomas. Common association includes medications, sarcoidosis, and infections. We present a less common case of GIN secondary to chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).

Case Description: A 57 year old male with benign prostatic hypertrophy presented in early 2020 with leukopenia, lymphopenopahathy, and sicca symptoms. A lymph node biopsy in March 2020 revealed non caseating granulomatous lymphadenitis diagnosed as sarcoidosis without clear pulmonary involvement and treated with steroids. His creatinine (Cr) was 0.83 mg/dL, calcium 9.5 mg/dL, white blood cell count of 2600, hemoglobin 12.6 g/dL, platelet count of 322,000, lactate dehydrogenase 1094 U/L, uric acid 8.3 mg/dL, negative SS-A/SS-B, negative Epstein Barr Virus, angiotensin converting enzyme 70 U/L, and a normal urinalysis. In August 2020, his Cr rose to 4.24 mg/dL, with urine studies notable for 1+ protein and rare eosinophils. He had negative hepatitis B, hepatitis C, ANA, MPO, and PR3. His free kappa/lambda ratio was 1.89 (normal) and negative SS-A/SS-B, negative Epstein Barr Virus, angiotensin converting enzyme 70 U/L, normal PTH (19 pg/mL), normal PTHrP (2.2 pmol/L) and low normal calcitriol (28 pg/mL). Kidney ultrasound was normal. Liver ultrasound revealed an ill-defined mass not seen in CT scan. FGF-23 levels were sent due to suspicion of Osteoporosis and returned very high at 12,715 IU/mL. Patient was readmitted to the hospital for accelerated work up to identify the source of FGF-23. Repeat labs on admission showed Cr of 2.2 mg/dL, normal phosphorus 3.2 mg/dL and bilirubin 12 mg/dL. Random liver biopsy showed tumor cells positive for CD56 and Ki-67, with a proliferation rate of 80% indicating high grade metastatic neuroendocrine tumor. Localization of primary tumor was unsuccessful. Oncology was consulted and chemotherapy was entertained, but the patient rapidly deteriorated and opted for comfort measures.

Discussion: Redused phosphate excretion in patients with AKI leads to hyperphosphatemia, stimulating FGF-23 production to facilitate phosphaturia. However, when AKI is associated with inappropriately low or normal phosphate levels, renal phosphate wasting from other causes should be suspected. Fractional excretion of phosphate might also be falsely low as the decreased eGFR can potentially hinder phosphate excretion. Early detection and accelerated work up could potentially lead to early diagnosis and appropriate treatment.

PO1910
A Case of Oncogenic Osteomalacia with Urinary Phosphate Wasting Masked by AKI
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Introduction: Hypophosphatemia in patients with oncogenic osteomalacia (OO) is due to excess production of fibroblast growth factor 23 (FGF-23) causing urinary phosphate wasting. However, in patients with coexisting acute kidney injury (AKI), hypophosphatemia may normalize as the AKI worsens potentially masking renal phosphate wasting. In-appropriately low or normal phosphorous levels in patients with AKI should prompt further work up to identify potential renal phosphate wasting.

Case Description: 36-year-old morbidly obese woman presented with right-sided abdominal pain and fatigue for 2 weeks. Initial laboratory evaluation revealed AKI (Cr 2.1 mg/dL, baseline 1.2) that failed IV fluid therapy prompting nephrology consultation. Other labs included urine protein creatine ratio 0.2 g/g, alkaline phosphate (895 U/L), mild hyperbilirubinemia (1.8 mg/dL), mild hypercalcemia (corrected Ca 11 mg/dL), hypophosphatemia (1.8 mg/dL), low vitamin D (28 ng/mL), normal PTH (19 pg/mL), normal PTHrP (2.2 pmol/L) and low normal calcitriol (28 pg/mL). Kidney ultrasound was normal. Liver ultrasound revealed an ill-defined mass not seen in CT scan. FGF-23 levels were sent due to suspicion of Osteoporosis and returned very high at 12,715 IU/mL. Patient was readmitted to the hospital for accelerated work up to identify the source of FGF-23. Repeat labs on admission showed Cr of 2.2 mg/dL, normal phosphorus 3.2 mg/dL and bilirubin 12 mg/dL. Random liver biopsy showed tumor cells positive for CD56 and Ki-67, with a proliferation rate of 80% indicating high grade metastatic neuroendocrine tumor. Localization of primary tumor was unsuccessful. Oncology was consulted and chemotherapy was entertained, but the patient rapidly deteriorated and opted for comfort measures.

Discussion: Reduced phosphate excretion in patients with AKI leads to hyperphosphatemia, stimulating FGF-23 production to facilitate phosphaturia. However, when AKI is associated with inappropriately low or normal phosphate levels, renal phosphate wasting from other causes should be suspected. Fractional excretion of phosphate might also be falsely low as the decreased eGFR can potentially hinder phosphate excretion. Early detection and accelerated work up could potentially lead to early diagnosis and appropriate treatment.

PO1911
Lysozyme Nephropathy: A Rare Yet Treatable Cause of AKI in Chronic Myelomonocytic Leukemia
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Introduction: Lysozyme is a small lytic enzyme with bactericidal properties synthesized by monocytes that is freely filtered by the glomerulus. It can be produced in large quantities by neoplastic cells of monocytic lineage resulting in nephrotic range proteinuria (lysozymuria). Lysozyme can accumulate in proximal tubular cells thereby causing toxic injury resulting in tubular cell injury.

Case Description: A 69 year old woman was referred to nephrology clinic for evaluation of elevated serum Cr. Her past medical history included Type-2 Diabetes Mellitus, Hypertension, Hyperlipidemia, JAK2/V617F-positive Polycythemia Vera, Chronic Myelomonocytic Leukemia, bilateral renal angiomyolipomas and gout. Physical exam was unremarkable. Lab data were notable for creatinine (Cr) 1.7 mg/dL (baseline 1.2), Calcium 11.1 mg/dL, Uric acid 7.7 mg/dL, WBC 65.1 x 1000/uL (ANC 40.4; Monocytes 14.3), Hemoglobin 11.6 g/dL and Platelets 141 x 1000/µL. Electrolytes, liver function tests, and viral hepatitis serologies were within normal limits. Urinalysis was unremarkable. Urine albumin/Cr ratio was 79.4 mg/g of creatinine. A kidney biopsy was performed. Light microscopy revealed focal acute tubular injury and PAS-positive cytoplasmic granules. Electron microscopy revealed electron dense aggregates in the cytoplasm of the proximal tubular cells. Serum lysozyme was > 60 mcg/mL (reference range 5-11 mcg/mL). A diagnosis of lysozyme-induced nephropathy (LyN) was made. Repeat bone marrow biopsy revealed myeloid neoplasia with 13% blasts. She started treatment with Decitabine/Cedazuridine and her WBC improved to < 10 x 1000/µL and her Cr improved to 1.2 mg/dL.

Discussion: This case demonstrates an uncommon and often under-recognized cause of acute tubular injury in patients with chronic myelomonocytic leukemia. Lysozyme-induced nephropathy can be reversed with targeted therapy.
Lactic acidosis is an endogenous substrate for gluconeogenesis produced by muscle and other tissues. Lactate is the anion of lactic acid and is a source of base needed to maintain acid-base balance. Lactic acid levels can increase due to impaired oxygen delivery to cells and other tissues. Lactate is the anion of lactic acid and is a source of base that can be used to maintain the blood's pH balance. It is produced when the supply of oxygen is insufficient to allow complete oxidation of glucose, a process known as anaerobic metabolism.

In the context of this patient's case, the persistent lactic acidosis and atypical interstitial infiltrate led to the diagnosis of relapsed disease. The patient's clinical condition deteriorated, and continuous renal replacement therapy was started in ICU. Chemotherapy was initiated, however he remained critically ill with worsening lactic acidosis, multi-organ failure and ultimately expired from cardiopulmonary arrest.

Discussion: Malignancy associated HLH is a challenging diagnosis which is often misdiagnosed. Diffuse large B cell lymphoma infiltrating the kidney confers a poor prognosis and this case illustrates the utility of a kidney biopsy in early diagnosis of diffuse lymphoproliferative disorder which can improve patient outcomes.

A Unique Case of Paraneoplastic Lupus Nephritis Biopsy Finding in a Patient with Head and Neck Cancer

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Introduction: Rheumatic disease can be one of manifestations of paraneoplastic syndrome. We present a case of supraglottic squamous cell carcinoma (SCC) associated nephritic syndrome and kidney biopsy suggestive of lupus-like changes.

Case Description: 56-year-old male with past medical history of hypertension, opioid abuse (on methadone) and an active smoker was admitted to the hospital for evaluation of painful neck swelling which he first noticed four days prior to admission. Examination was remarkable for lower extremity edema and left neck mass. Nephrology was consulted for evaluation of nephritic syndrome. Significant laboratory workup revealed elevated serum proteinuria (29.1 g/dl), serum creatinine of 1.7 mg/dl and a normal serum creatinine 0.9 mg/dl. Serological workup for proteinuria including phospholipase A2 receptor antibody (PLA2R Ab) was negative. Biopsy of the neck swelling was suggestive of supraglottic squamous cell carcinoma. Subsequently, the patient was referred to radiation oncology and chemotherapy with carboplatin and radiation therapy. A kidney biopsy was done for further evaluation. While there were no glomerular changes on light microscopy, immunofluorescence (IF) showed full house capillary staining (IgG, IgM, IgA, C3, C1q, kappa and lambda light chains). Also, enhanced glomerular staining for PLA2R was seen. Electron microscopy revealed subepithelial deposits which were suggestive of IgM, kappa and lambda light chains. The patient did not respond to treatment and expired from cardiopulmonary arrest.

Discussion: Paraneoplastic systemic lupus erythematosus has been reported in patients with Hodgkin and non-Hodgkin lymphoid tumors. Proteinuria is often associated with auto-antibodies. Autoimmune disease usually precedes the diagnosis of malignancy and patients develop symptoms later. Our...
case is unique, although biopsy was indicative of lupus nephritis, patient had no clinical or laboratory finding for lupus. Nephrologist and rheumatologist should be aware of this rare clinical association for appropriate diagnosis and management.

PO1916
Light Chain Deposition Disease (LCDD) in the Setting of Smoldering Myeloma (SM)

Introduction: Only 50-60% of patients with LCDD meet the criteria for multiple myeloma (MM). SM, a proliferative plasma cell disorder is a precursor for active symptomatic MM. As LCDD is rare, there is limited data for the treatment of LCDD in the setting of SM.

Case Description: A 49-year-old female was found to have proteinuria and microscopic hematuria during a routine workup. Further evaluation showed proteinuria of 4.0 g/day, serum creatinine of 1.3 mg/dL, kappa light chain (KLC) 94.7 mg/dL, lambda light chain (LLC) 1.57 mg/dL, kappa-Lambda ratio (K/L) 60.24, Hemoglobin 12.8 g/dL, Calcium 9.26 mg/dL. Kidney biopsy showed nodular mesangial expansion with mild hypercellularity. Moderate tubular atrophy and interstitial fibrosis. Immunofluorescence showed strong kappa staining of mesangium, glomerular, and tubular basement membrane (TBM) with negative lambda staining. Electron microscopy showed the presence of subendothelial, mesangial, and TBM electron dense deposits. Findings were considered to be consistent with kappa associated LCDD. Bone marrow biopsy showed monoclonal plasma cell population in the bone marrow (5% by flow cytometry and 10-15% by CD138 stain) consistent with smoldering myeloma. FISH was abnormal for monosomy of 13 and 11;14 translocation. The skeletal survey was negative for any lytic lesions. She was treated with Bortezomib/Dexamethasone/Cyclophosphamide based regimen weekly for 8 weeks which resulted in a decrease in KLC to 1.45 mg/dL, LLC to 1.0 g/dL, and K/L ratio to 1.45 with negative serum immunofixation. 24-hour urine protein improved to 2.6 g/d. Serum creatinine remained stable at 1.3 mg/dL. Bone marrow biopsy after chemotherapy showed residual plasma cell myeloma involving 5% of the marrow cells. She underwent high dose melphalan followed by Autologous Stem Cell Transplantation (HDM/ASCT). Follow-up labs six years later confirmed successful treatment with serum creatinine improving to 1.02 mg/dL, 24hr-urine protein 48mg/d without microscopic hematuria.

Discussion: We report a case of successfully treated LCDD with high dose chemotherapy followed by HDM/ASCT in the setting of smoldering myeloma with six years of follow-up. Patients with LCDD in smoldering myeloma may benefit from high dose chemotherapy along with HDM/ASCT and it should be considered a treatment option.

PO1917
Delayed Thrombotic Microangiopathy Post Bone Marrow Transplant, an Atypical Presentation: A Case Report
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Introduction: Thrombotic Microangiopathy (TMA) is a potentially lethal complication of Bone Marrow Transplantation (BMT). We report a case of delayed TMA post-BMT which was successfully treated with Rituximab.

Case Description: A 53-year-old male known to have hematopoietic gamma-delta T-cell lymphoma (HSTCL) was referred for evaluation of worsening creatinine. He was diagnosed with HSTCL 6 years ago that was refractory to multiple therapies, and ultimately, two years later, he received Double Unit Cord Blood (dUCB) transplantation with good response and minimal residual disease. Despite receiving tacrolimus and mycophenolate mofetil (MMF) for prophylaxis of Graft versus Host Disease (GVHD), he developed mild popular rash consistent with Grade 1 GHVD skin and recurrent pneumonitis concerning for lung GVHD which responded to steroids. The tacrolimus and MMF were discontinued and steroids were gradually tapered off. Eight months post-transplant, serum creatinine (SCr) started to gradually increase from a baseline of 1.0 mg/dL. We were consulted eighteen months post-dUCB when SCR reached 1.8 mg/dL. Additional evaluation showed mild proteinuria (UPCR 0.77 g/g of creatinine), no active urine sediment, low haemoglobin (~ 30 mg/dL) and worsening thrombocytopenia (105 THO/dL). A renal biopsy showed glomeruli with variable capillary wall thickening and double contours, moderate fibrosis of 40-50%, negative immunofluorescence for complement and immunoglobulin, and the electron microscopy showed subendothelial expansion and endothelial swelling. These findings were compatible with chronic TMA lesion concerning for renal GVHD. The patient was treated with weekly Rituximab 375 mg/m² for a total of 4 doses with stabilization of SCr and normalization for hemolysis labs, including normalization of platelet count.

Discussion: TMA is a well described complication post-BMT with multifactorial etiology (medication, GVHD, radiation, etc.) with early onset within the first 30-45 days after transplantation, and the mortality rate is approximately 30-80%. Our patient had the unusual delayed presentation post-BMT (after 18 months). Although historically not the first line, several case reports have been published showing use of Rituximab, an anti-CD20 monoclonal antibody, with positive response.
Review of Onconephrology Cases: An Insight from the Middle East

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Background: Onconephrology is a new subspecialty of nephrology and its data was sparse from the middle east. We have collected data of cancer patients admitted to a tertiary care center and referred to the department of Nephrology to recognize the most common preventable causes of AKI and their outcome in this patient population.

Methods: We conducted a retrospective observational study of 39 admitted cancer patients referred to the department of Nephrology between November 2020 and March 2021.

Results: In our study 69% were males, 31% were females. Tumors were prostate cancer(n=6), bladder cancer (n=5), RCC (n=5), HCC(n=4) and Colon cancer (n=3); breast cancer (n=3), unknown primary (n=2), (n=1) were SCC, tongue, ovary, thyroid, endometrial carcinarad laryngeal cancer; additionally B cell lymphoma (n=1) and multiple myeloma (n=4). Background history of CKD was present in, 38% (n=15) of the cohort.

CKD stage 3 was the most prevalent (n=10). 1 patient had ESRD and maintained on dialysis and 2 patients had undergone a kidney transplant. Recurrent AKIs were most common (n=6), followed by nephrectomy (n=4) and hypertension (n=4), other included diabetes mellitus, urinary tract obstruction, atrophic kidneys, and multiple myeloma. Causes of AKI were Sepsis 30%, hypovolemia 12%, urinary tract infection 10.2%, drug-induced AKI 10% & Hypercalcemia 7.6%.Less common causes were hemorrhagic shock and IV undated contrast exposure. Only 35% of the study population was actively receiving oncotherapy at the time of admission. Amongst the cohort, 48% were oliguric and the rest were non-oliguric. A total of 16 patients, received renal replacement therapy during admission; CRRT was done in 10/16 patients, 5/16 patients received conventional hemodialysis and 1 patient received both modalities. Amongst the patients requiring CRRT; the survival rate was 21%, and for patients who received hemodialysis, the survival rate was 50.41% of the patients died during the admission; 62% of the deaths were deemed secondary to underlying cancer and the remaining 38% were attributed to other causes; the most common being sepsis.

Conclusions: Our study reiterates the importance of prevention of AKI by early recognition and prompt management of risk factors. This study prompts the need for quality improvement initiatives aiming at improving the outcomes of such patients at all tertiary care centers.

Pseudohyperkalemia Leading to Pseudohyponatremia in Severe Leukocytosis

Hameeda Leukocytosis

Introduction: Electrolyte abnormalities are common in oncologic malignancies. However spurious derangements are rarer. Here we present a case of coexisting reverse pseudohyperkalemia and pseudohyponatremia in chronic lymphocytic leukemia.

Case Description: An 84 year old man was diagnosed with chronic lymphocytic leukemia at admission with present weight loss and fevers. Labs showed a WBC of 760 K/mcl, Plasma sodium was 133 Meq/L, plasma potassium 8.8 Meq/L, BUN 15mg/dl, Creatinine 2.8 mg/dl and a GFR of 20 ml/min. Urine analysis showed 100 mg/dl of protein, 300 mg/dl of glucose and small blood. Urine sodium of 82 meq/L and osmolality of 444 mosmol/kg with serum osmolality of 300 mosmol/kg. EKG did not show any hyperkalemic changes. He received insulin, dextrose and ketoxalate. Repeat plasma potassium was 10.7 Meq/L.

Given high suspicion for reverse pseudohyperkalemia due to leukocytosis, serum labs were sent. Serum potassium was 4.2 Meq/L and serum sodium 134 Meq/L with a concurrent plasma Potassium of >9.0 Meq/L and plasma sodium of 127 Meq/L. The WBC count remained elevated at 693.2 K/mcl. The serum is measured at our institution with direct ion-specific electrode method making derangements from hyperlipidemia and hyperproteinemia unlikely. Treatment was started with methylprednisolone and Rituximab for CLL. The WBC count trended down from 693 to 339.5 K/mcl. Serum potassium remained stable (3.7-4.9) as well as serum sodium (138-141) with concurrent plasma values decreasing in disparity from potassium >9Meq/L to 4.9 Meq/L and sodium 127 Meq/L to 139 Meq/L as the WBC count decreased.

Discussion: This case portrays a challenging case of reverse pseudohyperkalemia and pseudohyponatremia in severe leukocytosis. While the phenomenon of reverse pseudohyperkalemia in leukemia/lymphomas is established, reverse pseudohyperkalemia where plasma potassium is falsely elevated compared to normal serum levels is lesser known. Furthermore, no mechanism has been established for pseudohyponatremia in plasma samples compared to serum samples in leukocytosis however it was postulated that sodium levels decreased reciprocally to potassium due to potassium release from the leukocytes. Hence in cases of reverse pseudohyperkalemia serum samples are preferred over plasma samples. Parameters need to be established to avoid treatment of spurious electrolyte disorders to avoid treatments resulting in hypokalemia and hyponatremia.

Light Chain Proximal Tubulopathy Without Fanconi Syndrome as the Sole Presenting Feature of Multiple Myeloma

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Introduction: Light chain proximal tubulopathy (LCPT) is a rare pattern of immunoglobulin-related renal injury that occurs in the setting of dysproteinemias. Classic disease associations for LCPT are multiple myeloma, monoclonal gammapathy of renal significance, and other hemopathies and neoplasms. The key LCPT pathologic feature is the accumulation of monoclonal light chains within the cytoplasm of proximal tubule (PT) cells with resultant clinical PT defects, proteinuria, and renal dysfunction.

Case Description: A 64-year-old man with prostatic adenocarcinoma presented for evaluation of incidental discovered proteinuria (3.852 g/24 h creatinine) and stage two chronic kidney disease. Initial evaluation was significant for a kappa/lambda ratio of 474.79, serum M-spike of 0.9 g/dl, and urine M-spike of 1.082 g/dl. Urine immunofixation electrophoresis revealed 94.1% Bence-Jones protein (1.629 g/24h) comprised of monoclonal IgG, kappa type. Other laboratoratory features of myeloma (hypercalcemia, anemia) were absent. Renal biopsy revealed monoclonal kappa light chain crystal inclusions in the cytoplasm of PT epithelial cells. Glomeruli show no significant histologic or ultrastructural abnormalities. Despite the severe histopathologic dysfunction, no clinical features of Fanconi Syndrome were present, including a negative work up for renal tubular acidosis as well as no renal wasting of phosphorous, amino acids, glucose, uric acid, or potassium. PET scan revealed diffuse marrow infiltrating disease with multiple lytic osseous lesions, and the patient was referred to oncology to begin chemotherapy.

Discussion: LCPT continues to be a rare pattern of kidney injury with significant variability in presentation based largely on the composition of the light chains. The toxicity of kappa light chains results from their ability to form crystals, which resist lysosomal proteolysis. Although our patient had extensive crystalline inclusions and significant evidence of tubular injury, no clinical evidence of proximal tubulopathy was evident with proteinuria as the sole presenting feature of diffuse myeloma. The views expressed in this abstract are those of the authors and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense (DoD), or the U.S. Government.

Monoclonal Gammapathy of Renal Significance: Not Reserved for the Elderly

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Introduction: Monoclonal gammapathy of renal significance (MGRS) is defined by renal involvement of monoclonal immunoglobulins in the absence of other organ involvement. MGRS includes a wide variety of renal lesions. It is particularly important to distinguish MGRS from monoclonal gammapathy of undefined significance (MGUS), as early treatment improves renal survival.

Case Description: 36F with a history of pre-eclampsia, stage II chronic kidney disease, and hypertension well-controlled on aspirin for 120 mg, presented 2 years postpartum with worsening hypertension and proteinuria. Initial urinalysis was positive for 3+ proteinuria and 2+ blood, with dysmorphic RBCs on sediment. Urine protein to creatinine ratio (UPC) was 1574 mg/g Cr. ANA and ANCA were negative as were anti-dsDNA and complement. Her creatinine rose from 1.2mg/dL to 1.8mg/dL over the next two years, and proteinuria rose to 20 g/d. Renal biopsy confirmed IgG kappa monoclonal immunoglobulin deposition disease, with large subepithelial deposits and moderate tubular injury, with 20% global and segmental glomerulosclerosis, 10% mesangial hypercellularity, and mild tubulointerstitial sclerosis. Serum and urine immunofixation and serum free light chain ratio were normal. Bone marrow biopsy was also negative, confirming the diagnosis of MGRS. She was treated with dexamethasone and bortezomib for a year, followed by lenalidomide, with stabilization of her renal function and proteinuria for over 3 years. Her creatinine is 2.4mg/dl and UPC is 354g/g Cr. She has been off therapy for 4 months with no change.

Discussion: There has been historical resistance to treat MGRS, as it does not meet criteria for a proliferative disorder and chemotherapy toxicity is of concern. However, it is associated with progression to CKD/ESRD without treatment. Treatment depends on renal pathology and clone type, and may include proteasome inhibitors, alkylating agents, or immunomodulators. Certain forms of MGRS, such as AL amyloidosis, may benefit from autologous hematopoietic stem cell transplantation due to its high rate of recurrence. Further research is needed on MGRS. This case highlights the need for renal biopsy in patients with worsening proteinuria and renal function out of proportion to hypertension, and the role of chemotherapy in MGRS to change the trajectory of disease.

Variable Expression of Eighteen Common Housekeeping Genes in Human Non-Cancerous Kidney Biopsies

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Background: Housekeeping, or reference genes (RGs) are, by definition, loci with stable expression profiles that are widely used as internal controls to normalize mRNA levels. However, due to specific events, such as pathological changes, or technical prerequisites, gene expression may be altered, failing to fulfill critical normalization pre-requisites.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
Methods: To identify RG genes suitable as internal controls in human non-cancerous kidney tissue, we selected 18 RG candidates based on previous data and screened in 30 expression datasets (>800 patients), including our own, publicly available or provided by independent groups. Datasets included specimens from patients with hypertensive and diabetic nephropathy, Fabry disease, focal segmental glomerulosclerosis, IgA nephropathy, membranous nephropathy, and minimal change disease. We examined both microdissected and whole section-based datasets. Expression variability of 4 candidate genes (YWHAZ, SLC4A1AP, and ACTB) was further examined by qPCR in biopsies from patients with hypertensive nephropathy (n=11) and healthy controls (n=5).

Results: Only YWHAZ gene expression remained stable in all datasets whereas SLC4A1AP was stable in all but one Fabry dataset. All other RGs were differentially expressed in at least 2 datasets, and in 4.5 datasets on average. No differences in YWHAZ, SLC4A1AP, RPS13 and ACTB gene expression between hypertensive and control biopsies were detected by qPCR.

Conclusions: Although RGs suitable to all techniques and tissues are unlikely to exist, our data suggest that in non-cancerous kidney biopsies expression of YWHAZ and SLC4A1AP genes is stable and suitable for normalization purposes.

PO1925

Performance of Creatinine-Based Equations to Estimate Glomerular Filtration Rate in the Context of Drug Dosage Adaptation

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Background: The 1976 Cockcroft-Gault (CG) creatinine-based equation is still used to estimate GFR (eGFR) for dose adaptation of drugs excreted by glomerular filtration although it estimates creatinine clearance. It was developed based on non-standardized creatinine assays and is not recommended by any nephrology guidelines. Incorrect eGFR may lead to hazardous over- or under-dosing. We aimed to compare the performance of CG with modern equations based on standardized creatinine assays.

Methods: In a cross-sectional analysis CG was validated against measured GFR (mGFR; using various tracer methods) in 15,479 participants and compared with the Modification-of-Diet-in-Renal-Diseases (MDRD), Chronic-Kidney-Disease-Epidemiology (CKD-EPI), L-Med-Mixed-Revised (LMR), and European-Kidney-Function-Consortium (EKFC) equations. Validation focused on bias, imprecision and accuracy (percentage of estimates within ±30% of mGFR, P30) overall and stratified for mGFR, age and body mass index intervals at mGFR <60 mL/min, as well as classification in mGFR stages.

Results: The CG equation performed worse than the other equations, overall and in mGFR, age and BMI subgroups in terms of bias (systematic overestimation), imprecision and accuracy (P30 overall for CG/MDRD/CKD-EPI/LMR/EKFC 73.6%/81.0%/82.4%/87.5%/86.9%) except for patients age5 years where bias and P30 were similar to MDRD and CKD-EPI, but worse than LMR and EKFC. At BMI [18.5, 25]kg/m^2, all equations performed similarly and at BMI=18.5 kg/m^2 CG and LMR had the best results though all equations had poor P30-accuracy (CG/MLR 58.7%/57.2%). At BMI>25 kg/m^2, bias of CG increased with increasing BMI (+19.3 mL/min at BMI>40 kg/m^2). The four more recent equations also classified mGFR stages better than CG.

Conclusions: The CG equation exhibited worse performance to estimate GFR overall and in analyses stratified for GFR, age, and BMI. CG was inferior to correctly classify the patients in the mGFR staging compared to more recent creatinine-based equations.
Comparison of Aptamer-Based and Antibody-Based Assays for Protein Quantification in CKD

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Background: Novel aptamer-based technologies can identify over 7,000 analytes per sample, offering a high-throughput alternative to traditional immunassays in biomarker discovery. However, the specificity for distinct proteins has not been thoroughly studied in the context of chronic kidney disease (CKD).

Methods: We aimed to validate the use of SOMAscan, an aptamer-based technology, for the quantification of 8 immune activation biomarkers and cystatin C in 243 participants from the African American Study of Kidney Disease and Hypertension (AASK) using immunoassays as the gold standard.

Results: Six biomarkers (IL-8, TNFRSF1B, cystatin C, TNFRSF1A, IL-6 and suPAR) had moderate-to-high correlations (Pearson r=0.22 to 0.94, Spearman r=-0.03 to 0.98), between SOMAscan and immunoassay measurements and three (IFN-γ, IL-10 and suPAR) had moderate-to-high correlations (Pearson r=0.22 to 0.94, Spearman r=-0.03 to 0.96). Of those with moderate-to-high correlations, TNFRSF1B, cystatin C, TNFRSF1A, and suPAR were negatively and significantly correlated with iothalamate-measured GFR and associated with higher risk of ESKD. All three had strong positive correlations with iothalamate-measured GFR (Pearson r=0.98, r=0.91, r=0.84, Spearman r=0.30 to 0.64).

Conclusions: SOMAscan is an efficient and reliably reliable technique for the quantification of biomarkers in the setting of CKD and for the detection of potential associations with clinical outcomes. Targeted immunoassays of candidate proteins may provide additional prognostic information.

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Prescribed Sodium Bicarbonate and Incident CKD in US Veterans

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Background: Sodium bicarbonate is prescribed for a variety of medical conditions including treatment of hypocarbonatemia that may happen in the setting of metabolic acidosis or due to other pathologies. Hypocarbonatemia is usually observed with chronic kidney disease (CKD) when eGFR < 60 mL/min/1.73 m2 and is uncommon without established CKD (eGFR > 60 mL/min). It is not known whether incident sodium bicarbonate prescription in patients with normal kidney function is associated with adverse outcomes including de novo chronic kidney disease, which we sought to examine in a large national cohort of Veterans.

Methods: In 2,524,842 US Veterans with normal baseline eGFR (≥60 mL/min/1.73 m2) and available data on albuminuria in 2004-2006, we examined the association of de novo prescription of bicarbonate medications during the baseline period with incident CKD over 14 years. Associations were examined in hazard models adjusted for demographics, major comorbidities, baseline eGFR, and albuminuria category.

Results: We identified 759 Veterans who were incident bicarbonate users. Overall, patients were a mean 61±14 years old, 7% female, 16% Black, and 5% Hispanic. Bicarbonate users were more likely to be male, Black, smokers, with higher frequencies of comorbidities such as chronic obstructive pulmonary disease, cancer, diabetes, and cardiovascular comorbidities. They also were more likely to have albuminuria. Bicarbonate medication users had a 4.8-fold higher risk of incident CKD (HR: 4.81, 95%CI: 4.38, 5.27).

Conclusions: Veterans with eGFR ≥60 mL/min/1.73 m2 who were prescribed sodium bicarbonate exhibited nearly five times greater likelihood of incident CKD. Whether bicarbonate therapy is a surrogate of disease condition with higher risk of CKD or whether it causes CKD directly remains to be examined in additional studies.

Funding: Clinical Revenue Support
respiration or glycolysis in megalin KO MEF expressing mutant LRP2, while mutant hSTC1 (L8/L9/L11 -> A8/A9/A11) fails to reach the mitochondria or induce respiration and glycolysis in WT MEF.

**Conclusions:** Our data suggest direct regulation of mitochondrial metabolism by extracellular cues and reveal an important role for signal peptides and their leucines in protein-protein interactions and signaling.

**Funding:** Veterans Affairs Support

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**Table 4** Logistic regression for TG groups and histopathologic parameters

**PO1931**

**Percutaneous Kidney Biopsy in Outpatient Setting: Can I Go Home Now?**

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**Background:** Kidney biopsies are a key diagnostic tool in renal dysfunction; however, complications ranging from bleeding to hematoma requiring embolization can occur. There is conflicting evidence on how long to keep patients post-biopsy. Some studies show 100% of serious complications occur within 8 hours, while others show that one-third can occur after 8 hours. Shorter observation periods prevent unnecessary testing and help reduce healthcare costs. Our study aims to assess if patients can be safely discharged after 6 hours post-biopsy.

**Methods:** Single-center retrospective Quality Improvement (QI) study of patients undergoing outpatient percutaneous native kidney biopsy over last 5 years (567) divided into 2 groups: Group A: Same-day discharge after< Group B: >23-hour observation after US-guided biopsy by Urology Outcomes comprised included timing of hemoglobin (Hb) drop post-procedure, readmission rates, need for transfusions, imaging or interventions.

**Results:** Of 177 patients, 75 (42.3%) were in Group A and 102 (57.6%) in Group B. Drop in Hb and post-biopsy complications were not significantly different between the groups. Three patients had bleeding complications, two of which required transfusion (Table). All three patients with bleeding complications had >10% Hb drop within first 6 hours post-biopsy. No readmissions related to biopsy occurred.

**Conclusions:** There were no major complications in either group. This QI study suggests that the majority of asymptomatic patients can be safely discharged at 6 hrs post-biopsy if Hb is stable. This could help reduce healthcare costs and burden to patients. This is a limited single center study: further larger studies are needed to confirm this.

**Table 3** Linear regression for TG and the histopathologic parameters

**PO1932**

**Does Obtaining an Extra Biobank Sample Increase the Risk of Post-Kidney Biopsy Complications? A Single-Center Experience**

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**Background:** Kidney biopsy(KB) is the “gold standard” for nephropathies diagnosis and it has a low rate of complications. Obtaining material for KB biobank requires the extraction of extra renal cylinder. The objectives of study are to analyze the characteristics of a cohort of patients with KB, the safety and show whether obtaining extra renal cylinder is associated with an increased risk of complications.
Methods: Observational and prospective study of KBs performed in our center during 2019 and 2020. We started a collection of KB samples to biobank at 2019. In patients who accepted, instead of two cylinders, three cylinders were obtained during the procedure. Clinical and laboratory data of patients were reviewed. Risk factors for complications, including the number of cylinders obtained, was also assessed.

Results: 221 patients in whom we performed a KB at our hospital were included in the biobank. 8 patients (3.6%) underwent trans-jugular renal biopsy, which we have excluded. Of the remaining 213, 126 (59.2%) were men, the mean age 56.8 ± 16.9 years, 122 (57.3%) patients had hypertension, 46 (23%) were diabetics, 14 (6.5%) were under anticoagulants, and 35 (16.4%) were under antiprotein treatment. The mean creatinine was 2.22 ± 1.9 mg/dl, protein/creatinine urine ratio 1119.6 (448.3-2957.9) mg/gr, the hemoglobin pre-KB was 12.6 ± 2.3 g/dl, 25438.0 (8873) platelets, INR 0.98 ± 0.09, prothrombin time 11.8 ± 1.16 seconds. 69.5% (n=148) of patients 3 renal cylinders were obtained, 27.2% (n=58) 2 cylinders and in 3.3% (n=7) one cylinder. Minor complications were observed in 13.6% (n=29) and major complications in 3.3% (n=7). We observed that patients with complications in KB were younger (p=0.034), had less weight (p=0.022), more transfusions (p=0.003), more platelets (p=0.038), a lower PT (p=0.005) and 1 cylinder was obtained in the KB with more frequency (p=0.012). In a multivariate regression logistic analysis PT (OR:1.497,p=0.042), transfusion(OR:5.38,p=0.032) and 1 cylinder obtained(OR:7.258,p=0.032) were identified as a risk factors of KB complications.

Conclusions: KB is a procedure with a low complication rate. Obtaining three KB cylinders for biobank has not shown an increase in the rate of complications, which is in concordance with previous published studies remains low.

PO1933
Assessment of Glomerular Number in Fresh Renal Tissue and Renal Pathological Specimens
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Background: On-site evaluation of fresh renal tissue at the time of renal biopsy is useful. However, some cases present poor correlation in glomerular number between fresh renal tissue and pathological specimens.

Methods: To examine the usefulness of on-site evaluation, the correlation between glomerular number in fresh renal tissue and renal pathological specimens, and associated factors disturbing the evaluation were investigated via a retrospective cross-sectional observational study.

Results: In the included 129 cases, there was a significant positive correlation between glomerular number in fresh renal tissue and renal pathological specimens. The median ratio of glomerular number (renal pathological specimen/fresh renal tissue) was 0.74 (0.48–0.97). According to this ratio, all cases were divided into three groups: a reasonable estimation group (65 cases), underestimation group (32 cases), and overestimation group (32 cases). Comparing the reasonable estimation group with the underestimation group, significant differences were detected in the extent of interstitial fibrosis and tubular atrophy (IFTA) and in the extent of interstitial inflammation. Logistic regression analyses also demonstrated that IFTA and interstitial inflammation were significantly associated with underestimation.

Conclusions: In conclusion, glomerular number counted by on-site evaluation of fresh renal tissue estimated the actual number of glomeruli in the renal pathological specimen, suggesting clinical benefit. Since tubulointerstitial lesions, such as IFTA and/or interstitial inflammation, may make it difficult to recognize glomeruli in fresh renal tissue, the possibility of underestimation of results for cases with possible severe tubulointerstitial lesions should be considered.

PO1934
Variability in Estimates of Nephron Number from Biopsy
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Background: Nephron number may predict kidney health and functional capacity. It is uncertain whether biopsies can be used to predict glomerular number (NgHm) in individuals, or how many subjects are required to detect differences between populations. We aimed to determine the precision of NgHm measured from biopsy.

Methods: We examined 6 human kidneys, rejected for transplant. We performed 8-10 needle biopsies. We used this and cortical volume to estimate NgHm. We simulated 210-227 "virtual biopsies" (VB) from 3D cartonized ferritin- enhanced MRI (CFE-MRI), in 4-5 clusters of 12-18 VBs in bottom, upper, and middle poles (Fig. 1Aii).

Results: NgHm estimated from single needle biopsy had up to 70% error depending upon where it originated (Fig. 1Bii). NgHm estimated from needle and VB varied consistently by ~ 50% (Fig. 1Biv), and there was no preferred biopsy location for accurate estimation of NgHm. The maximum variability in NgHm within clusters of closely packed virtual biopsies was 11.56% (Fig. 1Bvi). Based on statistical analysis, > 200 physical biopsies are required to be 95% certain that the estimated NgHm is within +/- 20% of true NgHm.

Conclusions: A single biopsy is not sufficient to predict NgHm in the individual kidney, but this work provides the required number of subjects required to detect differences in NgHm between populations.

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PO1935
Epidemiology of Medical Kidney Disease in the Southwestern United States, 1989-2018
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Background: Kidney biopsy is the main source of epidemiological information for kidney disease. However, large-scale epidemiological studies for glomerular disease (GD) in the US are very limited, and there are no such studies for non-glomerular disease (non-GD). Here, we describe 30-year temporal and demographic trends in GDs and non-GDs in the southwestern US between 1989 and 2018.

Methods: In this retrospective study, all kidney biopsy data at Pathology, Cedars-Sinai Medical Center (CSMC), Los Angeles, CA, between 1989 and 2018 were reviewed. We analyzed the most common 26 GDs and the most common 9 non-GDs. The frequencies of GD and non-GD subtypes and the temporal trends in each disease subtype within demographic subgroup were our primary and secondary outcomes. In addition, the frequency distribution of each disease category was evaluated across age categories stratified by sex and race.

Results: Among 48,068 patients (mean age =50 ± 19.3 y.o.; 52.0% men; 55.5% whiten; 18.4% Latino; 11.1% black; 9.8% Asian; 5.2% others), GD and non-GD composed 83.4% and 16.6% of all biopsies, respectively. In GDs, the frequency of diabetic glomerulosclerosis increased over the three decades (8.4%, 12.2%, and 22.0% of diagnoses; P for trend <0.003). The frequency of FSGS, lupus nephritis, immune complex-glomerulonephritis (GN), membranous nephropathy, and minimal change disease declined substantially over time. On the other hand, IgAN and ANCA/pauci-immune GN remained stable. In non-GDs, nephrosclerosis was the most frequent in the late 10 years. These temporal trends were largely preserved within all demographic subgroups, although cross-sectional frequency distributions differed according to age, sex, and race.

Conclusions: We reported the largest epidemiological study of medical kidney disease in the US. The relative renal biopsy frequencies of many GDs and non-GDs showed significant changes over the three decades in the southwestern US. Temporal

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trends were consistently observed within all major demographic groups. We provided evidence that changes in demographics (age, sex, and race) contributed minimally to these findings, suggesting that environmental and lifestyle factors contribute to them.

PO1936
Pathology Core Scoring Parameters and Reproducibility in the CureGN Study
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Background: CureGN is an NIH-funded multi-center, prospective, observational cohort study of patients with minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), or IgA nephropathy from 66 international sites with 2500 enrolled participants. The large scale of CureGN requires a practical systematic approach to pathologic scoring that can be applied consistently across a large number of cases and multiple scoring pathologists. The method reflects current pathology practice, generating data for assignment to current/candidate disease classifications and use in future studies utilizing conventional parameters. The objective of this analysis was to determine and evaluate the pathology scoring reproducibility.

Methods: The CureGN Core Scoring Workgroup established definitions of multiple glomerulopathy, tubular, interstitial, and vascular lesions using pathologist consensus (GS) and microscopic images; these were evaluated, semi-quantitatively, as observed by light, immunofluorescence, and electron microscopy (EM). All cases with complete pathology data as of April 2019 were randomly assigned for scoring of whole slide and EM images to one of eleven pathologists; a random subset of >10% were scored by each pathologist. Reproducibility was assessed using Gwet’s AC1 statistic at 3,6, and 9 months.

Results: Of 797 biopsy specimens (141 MCD, 186 FSGS, 205 MN, 265 IgA) scored by at least one pathologist, 94 were scored twice (12%). Of 60 pathology features, 46 (77%) demonstrated excellent reproducibility (Gwet’s AC1>0.8), and 12 (20%) had good reproducibility (Gwet’s AC1>0.6). Mean glomerulopathy score as absent, focal or diffuse, had moderate reproducibility (AC1=0.58), but scored as absent vs present had AC1=0.71. The percent glomeruli scored as having no lesions had fair reproducibility (AC1=0.34).

Conclusions: The majority of pathologic features showed excellent reproducibility, suggesting that the hypothesis that these features can be scored consistently by multiple pathologists. Future studies will include correlation of these histopathologic classifications and use in future studies utilizing conventional parameters. The objective of this analysis was to determine and evaluate the pathology scoring reproducibility.

PO1937
Dysmorphic Lysosomes, Pathognomonic Dysmorphia
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Background: Dysmorphic Lysosomes occur in multiple disorders, however, in young persons with agricultural exposure, non-nephrotic proteinuria, presence of tubular inflammation, presence of smooth rounded clusters of DL are pathognomonic. Morphology of the DL is dictated by the contents of the lysosomes as in the case of LCPT; further, evaluation is recommended.

PO1938
Reduction of Globotriaosylceramide Inclusions in Renal Peritubular Capillaries in Patients with Fabry Disease Following Treatment with PEGulinisadase Alfa
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Background: There are limited reports on kidney biopsy findings in patients with Fabry disease (FD). Fabry disease (FD) is a rare genetic disorder characterized by reduced activity of the lysosomal enzyme α-galactosidase A (α-Gal A), leading to accumulation of sphingolipids such as globotriaosylceramide (Gb₃) and globotriaosylsphingosine (Gb₄). A vasare,1 Behzad Behzad,2 S. M. Robinson,3 P. Alman,1 R. Cherkoff,2 D. Hughes.12

Methods: In a phase 1/2 dose-ranging study (NCT01678898), 18 adults with FD received 0.2 mg/kg, 1.0 mg/kg, or 2.0 mg/kg of pegunisal domain by intravenous infusion every 2 weeks for up to 12 months. Kidney biopsies were taken at baseline and after 6 months of treatment. Levels of Gb₃ inclusions in renal PTCs were determined using the Barisoni Lipid Inclusions Scoring System (BLISS) protocol (Barisoni L et al. J Am Soc Nephrol 32: 2021)

Conclusions: Reduction in Gb₃ reduction, and 3 patients (21.4%) had ≥20% reduction, 11 patients (78.6%) had ≥20% reduction in Gb₃ inclusions in GB₃ inclusions in renal PTCs were determined using the Barisimi Lipid Inclusions Scoring System (BLISS) protocol (Barisoni L et al. Arch Pathol Lab Med. 2012;136:816–824).

Results: Of 14 evaluable patients with available kidney biopsies at baseline and 6 months, 12 patients (85.7%) had 20% reduction, 11 patients (78.6%) had ≥50% reduction, and 3 patients (21.4%) had ≥90% reduction in GB₃ inclusions. In the analysis (n=13; excluding 1 male patient due to minimal renal involvement), the mean BLISS score was reduced from 4.23 at baseline to 2.02 at 6 months (p=0.007). The magnitude of reduction of Gb₃ inclusions was greater in males (n=7; reduction: 85.0%) vs females (n=6; reduction: 47.7%). Overall, mean BLISS score was reduced from 4.23 at baseline to 0.83 at 6 months (67.8% vs 8.9%). Reduction in GB₃ inclusions at 6 months was correlated with a reduction in plasma LysGB₃ at 12 months (R=0.905).

Conclusions: Results from this phase 1/2 study demonstrated that pegunisal domain reduced the affected tissue and effectively reduced the number of GB₃ inclusions in renal PTCs at 6 months in adults with FD.

PO1939
Patients with Active Manta Cell Lymphoma May Present With Monoclonal, Polyclonal, or C3-Dominant Glomerulonephritis, Which Respond to Lymphoma-Directed Therapy
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Background: There are limited reports on kidney biopsy findings in patients with mantle cell lymphoma (MCL). We initiated a multi-institutional, retrospective review of kidney biopsy findings from patients with active and treated MCL.

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Underline represents presenting author.
PO1940

Anti-Brush Border Antibody Disease with Nephrotic Syndrome: A Clinicopathologic Analysis of Five Cases

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Background: Anti-brush border antibody (ABBA) disease is a recently described etiology of acute kidney injury and progressive renal tubular injury that mainly affects the older patients. ABBA is characterized by the presence of circulating autoantibodies to proximal tubular brush border protein LRP2 (megalin) and IgG immune complex deposits along the basement membrane of proximal tubules. In the present study, we report 5 cases of ABBA that all presented as nephrotic proteinuria.

Methods: We retrospectively screened for ABBA disease through our renal biopsy cohort from January 2018 to May 2021. The anti-brush border antibody disease was diagnosed based on the presence of ABBA in the serum, showing positive ABBA on a kidney section by indirect immunofluorescence with patient’s serum, and kidney histology. Histology of the biopsies and clinical data were analyzed.

Results: Twenty-nine patients (31 biopsies) with MCL and kidney biopsies were identified, with a median age of 66 (range 4-87), 76% of whom were men. Nineteen patients had active MCL at the time of biopsy, 13 of which (68%) presented with acute kidney injury, proteinuria and/or hematuria, and biopsy findings attributable to lymphoma (Table); 6 (32%) had findings not readily attributable to MCL. Of the former, 10 (77%) had immune complex (IC) diseases including proliferative glomerulonephritis with monoclonic Ig deposits (PGNMID, 2), C3 dominant GN (3), PLAR-negative membranous (MN, 3), and/or tubular basement membrane deposits (2). Lymphomatous infiltration was present in 6, 3 with coincident IC lesions. Four with available follow-up were treated for MCL, all with remission of GN (1 PGNMID, 2 C3 dominant GN, 1 MN). Ten patients were biopsied while MCL was in remission; these findings were attributed to various underlying diseases.

Conclusions: In patients with active MCL who undergo kidney biopsy, 68% had kidney biopsy findings attributable to lymphoma. Diverse immune complex diseases were seen in ~50%, including monoclonal, polyclonal, and C3 dominant GN patterns, and nearly 1/3rd had lymphomatous infiltration. Limited follow-up suggests these IC lesions respond to MCL-directed therapy.

PO1941

Time-Course Kidney Injury in Mice Remnant Kidney Model Fed by High-Protein Diet

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Background: Numerous animal models of CKD have been developed, but mice are relatively resistant to kidney injury. The remnant kidney model mimics progressive renal failure, and widely used in CKD research. The present study was performed to evaluate the effects of combined high-protein diet (HPD) loading and 5/6 nephrectomy (Nx) in a susceptible strain of mice (129/Sv).

Methods: Male 8–11-week-old 129/Sv mice underwent 5/6 Nx or sham surgery, then 2 weeks later were switched to an HPD, and cardiovascular parameters, kidney function, and renal histology were assessed after 4, 8, or 12 weeks.

Results: The 5/6 Nx group showed blood pressure elevation, cardiac hypertrophy, renal function decline, severe albuminuria, and glomerular hypertrophy. However, the glomerulosclerosis by 5/6 Nx was very mild and there was only modest tubulointerstitial inflammation and fibrosis in the 5/6 Nx group, even after 12 weeks of HPD loading. Furthermore, the sham group showed no histological changes.

Conclusions: Thus, an HPD alone is insufficient to cause renal pathology, and a combination of 5/6 Nx and HPD loading induces mild renal pathology.
Neutralizing Antibodies in Preventing Polyomavirus Nephropathy: Lessons from the Mouse

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Background: Definitive polyomavirus nephropathy (PyVN) affects kidney transplants and impacts allograft function and survival. Data suggest that neutralizing PyV strain specific antibodies can attenuate and possibly even prevent disease. Here we report observations from the mouse on the protective role of anti-PyV antibodies.

Methods: Six breeding mice had been exposed to murine PyV (MUPyV). They had developed a robust IgG response while lacking definitive PyV and only showing minor qPCR evidence of intra organ MUPyV. Newborns of exposed breeders were split: group 1 (n=23) was injected at birth with MUPyV; group 2 (n=19) was not injected. Group 3 (n=24) was born to unexposed breeders and injected with MUPyV at birth. Tissue, plasma, and urine were analyzed at various time-points (0,1,2,3,6, and 10 weeks) by light microscopy, immunohistochemistry, qPCR, and MUPyV antibody titer testing. The nonparametric Wilcoxon Rank Sums test was used for p-value comparisons.

Results: Newborns from exposed breeders had IgG titers between 160-640, no IgM, and only subclinical minor molecular evidence of intra organ MUPyV by qPCR. During 10 weeks of follow up, groups 1 and 2 both cleared MUPyV. By week 10, MUPyV was largely undetectable in the setting of significantly reduced IgG titers (0-40; no IgM). Prior to clearance, both groups displayed a mild transient increase in IgG titers (up to 2560; no IgM) at weeks 2 and 3. MUPyV clearance occurred earlier in group 2 with significantly lower qPCR reads in kidney and spleen noted on week 2 (P<0.03). There was no MUPyV induced organ injury. In contrast, group 3 showed persistently high intra organ qPCR reads starting post MUPyV injection on day 0 and lasting through week 10 (p=0.05 compared to groups 1/2). Histologically apparent viral tissue injury was first noticeable at week 1 and persisted thereafter. IgG and IgM levels remained undetectable until week 2, when they began to slowly rise. By week 10, IgG titers had risen significantly (up to 20480) while IgM titers had decreased to 0.

Conclusions: Preexisting neutralizing antibodies protect from PyVN and facilitate clearance of subclinical MUPyV. In contrast, established MUPyV induced disease/injury is unaffected by neutralizing antibodies. This data can help with developing preventative treatment strategies in man.
A. Atypical cast with sharp edges surrounded by epithelial cells of distal tubules (PAS). Congo red-positive intratubular casts (inset).
B. Intratubular casts are positive for Kappa light chain (Direct Immunofluorescent).
C. Renal cortex shows intracytoplasmic magenta-colored structures (arrow) in proximal tubules (PAS).
D. Ultrastructural images of proximal tubular cells show rod and rhomboid intracytoplasmic crystals (black arrow) and hexagonal and oval-shape crystal (white arrow/inset) (transmission EM).

**PO1946**

**Insidious Granulomatous Interstitial Nephritis (GIN) in a Patient with a History of Diffuse Large B Cell Lymphoma (DLBCL)**

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**Introduction:** GIN has diverse etiology as infections, vasculitis, sarcoidosis, and lymphoma. These diseases can occur in the same patient, making diagnosis and treatment decisions challenging. Here, we report a case of GIN with a fever that developed after a long period since the complete remission (CR) of DLBCL.

**Case Description:** A 46-year-old man was admitted to our hospital with malaise, dyspnea, and severe renal failure (RF). Twenty years before the admission, he was diagnosed with DLBCL. After 4 years of treatments, he achieved CR. Thirteen years after CR, he presented to our hospital with a persistent fever. At this time, impaired renal function (serum [s] Cr 1.8 mg/dL) was noted. FDG-PET CT showed uptake in the enlarged lymph nodes (LN) around the pancreas and in both kidneys. Biopsy of the LN revealed multiple epithelioid granulomas and no evidence of recurrence of DLBCL, and his fever was resolved spontaneously. Two years later, he was admitted due to advanced RF (sCr 11.8 mg/dL), and hemodialysis (HD) was initiated. Both kidneys were atrophic on CT scan, whereas they still showed intense uptake on Ga scintigraphy. The renal biopsy showed diffuse GIN, but recurrence of DLBCL, sarcoidosis, and vasculitis was denied. Examinations for Tuberculosis (TB) were only positive for the interferon-gamma release assays (IGRAs) and negative for renal stains, systemic cultures, and image studies for lung TB. Anti-TB therapy was administered for his persistent fever that recurred after hospitalization. After the initiation of the anti-TB treatment, his fever gradually resolved, and he has been well, although he cannot withdraw HD.

**Discussion:** The course of our case suggests that the GIN was induced by TB infection, although our patient did not show typical features of systemic TB except for positive IGRAs. There has been an increase in the number of cases of TB infection diagnosed following GIN, which is presented not with the typical features of classical renal TB but with a more insidious form (Oriolera et al., Clin Kidney J 2017). These cases are often diagnosed later and may associate with a poor prognosis. Our case suggests that anti-TB therapy should be considered for patients with IGRAs-positive GIN after excluding other etiologies of GIN, even without the other diagnostic evidence of systemic TB.

**PO1947**

**Severe Vasculitis Masquerading as Guillain-Barre Syndrome**

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**Introduction:** Polyarteritis nodosa (PAN) is a rare ANCA-negative, necrotizing arteritis affecting small-medium arteries. Due to rarity of the disease, studies are limited. We present a case of PAN with missed diagnosis at presentation and complicated treatment course.

**Case Description:** 75-year-old man with hypertension diagnosed 10 months ago presented to outside hospital with bilateral lower extremity ascending numbness and weakness, and arthralgia. Lumbar puncture was inconclusive. He was treated for Guillain-Barre syndrome with IVIG with some improvement. Two months later, he presented to our hospital with localized petechial rash, oliguria, lower extremity edema, right foot drop, marked weakness, and acute kidney injury (creatinine (Cr) 4.09 mg/dL). He had hematuria, subnephrotic range proteinuria, high inflammatory markers, and low complements. Renal biopsy revealed necrotizing medium vessel arteritis, consistent with PAN. He was started on steroids and oral cyclophosphamide (CYC) with rapid, dramatic improvement in neurologic symptoms. Unfortunately, a month later, he developed acute hypoxia with worsening multifocal opacities despite adequate diuresis and infectious work-up, including negative bronchoalveolar lavage. Pneumonitis from CYC toxicity was diagnosed. Hypoxia resolved with steroids and replacing CYC with mycophenolate mofetil (MMF). Cr improved to 2.2 mg/dL with continued improvement in neuromuscular symptoms.

**Discussion:** This is a rare presentation of vasculitis causing severe AKI, debilitating peripheral neuropathy and weakness. Neurologic and renal manifestations improved rapidly with treatment. Development of CYC-induced pneumonitis leading to transition to MMF for induction is a rare complication, resulting in rare, but effective treatment. Lastly, development of new onset hypertension in the 8th decade of life warrants work-up for secondary etiologies.
PO1949

A Case of Asymptomatic Juxtaglomerular Cell Tumor (JGCT)
Arvind K. Garg,1 Lagu A. Androga,2 1Mayo Clinic Health System, La Crosse, WI; 2Mayo Clinic Minnesota, Rochester, MN.

Introduction: JGCT/reninoma is an extremely rare benign neoplasm of kidneys typically manifesting as hypertension and hypokalemia secondary to renin secreting tumor cells. We present a case of JGCT presenting as an asymptomatic renal mass.

Case Description: A 61-year-old male of with diabetes mellitus, hypertension (>15 years duration, well-controlled with Losartan 100mg daily) presented with right upper quadrant abdominal pain. Computed tomography scan of abdomen/pelvis with intravenous contrast revealed cholelithiasis without cholecystitis and an incidental 3cm mass at the mid-pole of the left kidney without renal vascular involvement. Kidney ultrasound 5 years prior did not show any renal mass. Spot urinalysis showed no hematuria and proteinuria was 96 mg/dl (normal < 150 mg/dl). Baseline serum creatinine was 1.3-1.4 mg/dl (normal 0.7-1.3 mg/dl). 24-hour urine creatinine clearance was normal. Given the high suspicion for a malignancy, the patient underwent recommended left radical nephrectomy. Kidney mass biopsy diagnosed JGCT. Light microscopy showed well circumscribed tumor with glomeroid appearance with sheets of uniform round- to-polynuclear cell with clear to eosinophilic cytoplasm. In addition, there were focal endocrine-like, markedly atypical hyperchromatic nuclei occasionally scattered throughout the tumor. Immunohistochemical stains demonstrated diffuse positivity in tumor cells for CD34 (Figure 1), CD117 and vimentin (Figure 2). Patient sustained a slight rise in creatinine post nephrectomy as expected and he continued to require only one anti-hypertensive medication. Patient remained in remission with stable kidney function without recurrence of tumor at 2 years follow-up.

Discussion: JGCT can present as hypertension and hypokalemia. Our patient had optimal blood pressure control on monotherapy. Losartan may have masked the associated hypokalemia. Nephrectomy (partial or radical) is curative and is the recommended treatment.

Figure 1: CD34 stain, 10x
Figure 2: Vimentin stain, 20x

CD 34 stain and vimentin stain kidney mass pathology images

PO1950

Disseminated Histoplasmosis Mimicking Crohn Disease in Kidney Transplant Recipient
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Introduction: Fungal infections can occur after a kidney transplant due to the use of immunosuppressants. Histoplasmosis is an endemic infection in Mexico and it’s pulmonary phase is very common. The risk of complications is high, so an early diagnosis should ideally be made with a biopsy of the affected tissue. We report the case of a kidney transplant recipient with chronic diarrhea associated with disseminated histoplasmosis simulating Crohn’s disease.

Case Description: A 50-year-old woman with history of CKD of unknown etiology underwent living donor kidney transplant. She received induction with basiliximab and maintenance therapy based on azathioprine, prednisone and cyclosporine. Six years after transplantation, the calcineurin inhibitor was discontinued due to toxicity documented by biopsy and continued with Sirolimus and mycophenolate mofetil. One year after transplantation, she was evaluated for fever and pulmonary nodules, without detecting infectious etiology. One year later, she presented diarrhea and based on the presence of colonic ulcers, Chrust’s disease was suspected and treatment with mesalazine was started. Due to the persistence of diarrhea, a second colonoscopy was performed establishing the diagnosis of histoplasmosis by means of biopsies of the colonic mucosa and with urinary antigen. Amphotericin B treatment was initiated and 2 weeks later urinary antigen was negative and renal function returned to baseline. Itraconazole-based maintenance therapy was chosen.

Discussion: Acute pulmonary histoplasmosis is caused by inhaling spores and it tends to be a self-limited disease. Disseminated histoplasmosis is common in immunocompromised patients. Gastrointestinal involvement is clinically manifested in 20% of cases, although urinary antigen has a 95% specificity, histopathological identification with PAS(+) and Giemsa(-) stains, remains the ideal test, as they showed submucosal and lamina propria macrophage invasion at the intestinal tissue. Chronic diarrhea can be a manifestation of systemic fungal infection in kidney transplant recipients.

PO1951

Improving the Identification of AKI in the Neonatal ICU: Three Centers’ Experiences
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Background: Acute kidney injury (AKI) is common in neonates. Despite its high prevalence, neonatal AKI is diagnosed in <30% of affected neonates. Neonates with AKI are at increased risk for repeated episodes of AKI and CKD. Without an AKI diagnosis, neonates may not be identified for long-term follow up, reducing early identification of CKD and limiting opportunities to slow disease progression.

Methods: In this retrospective cohort study of 3 academic Neonatal Intensive Care Units (NICUs), we evaluated the impact of local standardized approaches implemented to improve neonatal AKI identification. Each center implemented different standardization practices, ranging from automated nephrology consult to neonatology identification based on creatinine. Patients were divided into two groups: 6 months prior to (Cohort 1) and 6 months following (Cohort 2) standardization. We compared AKI incidence and identification, nephrology consultation and nephrology follow-up.

Results: In total, 1887 infants were included. Neonatal AKI identification improved in all three NICUs following protocol implementation (26% to 85%, p<0.0001). Each center also saw increases in nephrology consultation (15% to 83%, p<0.0001) and nephrology follow-up (7% to 73%, p=0.0001). Notably, AKI incidence decreased significantly (21% to 12%, p<0.0001).

Conclusions: Multiple strategies can be successfully operationalized to improve neonatal AKI identification. While different in approach, each strategy resulted in increased AKI identification and nephrology involvement. We also report a decrease in AKI rates. This study emphasizes the importance of local standardized approaches to improve AKI identification in the NICU. Further collaborative work by nephrologists and neonatologists is needed to improve identification and follow-up of AKI.
PO1952

Diuretic Use, Comorbidity, and Length of Stay in Pediatric AKI

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Background: Acute kidney injury (AKI) and fluid overload (FO) both have well-known negative effects on morbidity and mortality in many populations. The combination of AKI and FO is associated with synergistically worse outcomes in critically ill children. Diuretic use in management of AKI and FO has been studied in adults with widely varied outcomes ranging from improved mortality to no significant change to increased comorbidity such as prolonged mechanical ventilation. Therefore utility of diuretics remains unclear, and their use in pediatric patients with AKI has not been characterized.

Methods: The Pediatric Hospital Information System (PHIS) database was queried for patients with diagnosis of AKI from January 2015 to December 2019 with admission LOS ≥ 15 days. Those <1 or >18 years of age were excluded. ICD codes were used to discern complex chronic conditions (CCCs) as well as acute comorbidities. Daly medication exposure was used to determine diuretic use. LOS in both the ICU and the inpatient floor was assessed. CCCs of interest were chronic kidney disease (CKD), kidney transplant, and heart failure. Measured comorbidities included: shock, mechanical ventilation, hyponatremia, fluid overload, ascites, edema, and oligoanuria. Numeric data were summarized as medians and IQRs and categorical data as frequency and percent. Associations between diuretic use and comorbidity was assessed by Wilcoxon’s rank-sum test and Fisher’s exact test. Length of stay was then assessed by longitudinal regression.

Results: There were 5490 encounters for analysis with diuretic use in 951. Demographics were similar between groups. Those with CKD or heart failure were more likely to receive diuretics, while those with transplant status were less likely to receive diuretics. LOS was 1.67 days longer in those who received diuretics despite adjustment for age, gender, and illness severity including CCCs. All acute comorbidities were increased in those who received diuretics.

Conclusions: Children with underlying CCCs were more likely to receive diuretics and to have longer LOS. Comorbidities and LOS were also increased in children with AKI who received diuretics regardless of disease severity. This is clinically important as diuretic use may be correlative for worse outcomes and increased costs. Due to database limitations, temporal association is unknown and further study is needed.

PO1953

The Association of Diuretic Therapy with Fluid Balance and AKI in Hospitalized Preterm Neonates

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Background: Fluid homeostasis is essential in critically ill preterm neonates because fluid overload is associated with poor outcomes including need for mechanical ventilation, bronchopulmonary dysplasia (BPD) and necrotizing enterocolitis (NEC). Acute kidney injury (AKI) is a common comorbidity in preterm neonates. Diuretics are often used to enhance urinary output (UOP) in AKI-associated oliguria and to achieve negative fluid balance (FB).

Methods: Retrospective study of preterm neonates < 37 weeks gestational age (GA) who received diuretics during the first 14 postnatal days in a single level IV NICU (2014/05-2015/04). We analyzed FB, UOP, and Scr levels on and off diuretics over first 14 days. We studied prevalence of AKI.

Results: 191 preterm neonates met inclusion criteria. By day 8, 50% of patients were treated with diuretics. After adjusting for birthweight and time after birth, there was a statistically significant decrease in weights while on diuretics with a mean difference of 10g. Peak median FB was 58 mL on postnatal day 8. Mean FB difference on and off diuretic therapy was -35 mL. There was smaller difference in FB between those on or off diuretics in younger GA patients compared to older GA patients (Figure 1). UOP increased by 0.6 mL/kg/h and Scr by 0.2 mg/dL while on diuretics compared to no diuretic therapy (Table 1). AKI occurred in 9% and 19% of patients based on an increase in Scr of ≥ 0.3 mg/dL or UOP < 1 mL/kg/h for 24 hours respectively. In patients who met AKI criteria, oliguria was noted while off diuretics and increased Scr while on diuretics.

Conclusions: In hospitalized preterm neonates, treatment with diuretics was associated with improved UOP and negative fluid balance. Scr increased while on diuretic therapy. Further studies should analyze the effects of diuretics as mediated by FB and AKI on development of BPD and NEC.

PO1954

Neonatal AKI Is Associated with Impaired Renal Function at 24 Months of Age

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Background: Neonatal acute kidney injury (nAKI) is common, occurring in up to 30% of neonatal intensive care admissions. However, there are currently no guidelines for nephrologic evaluation after the neonatal period. Our objective was to determine the incidence of renal dysfunction at 24-months of age and to identify associated risk factors following nAKI.

Methods: Retrospective single-center cohort study of infants with nAKI (defined as rise in creatinine (Cr) ≥ 0.3, abnormal initial Cr for gestational age, or abnormal rate of Cr decline) seen in pediatric nephrology clinic at 24-months. Abnormal estimated glomerular filtration rate (eGFR) (< 90 mL/min/1.73m²), hypertension (BP ≥ 95%tile), proteinuria (TPC ≥ 0.5), and renal length (a ≥ 95th or b ≤ 5th tile) were correlated with high risk NICU events and exposures. Data was obtained by chart review. eGFR was calculated using cystatin C and creatinine separately, using the CKID cystatin C and the revised Schwartz equations, respectively. Data was analyzed using t-tests, Wilcoxon Rank Sum Test, or Chi-square as appropriate.

Results: 36/42 infants with history of nAKI referred to nephrology had a 24-month visit. 20 of 36 subjects (55.5%) had at least one renal abnormality, with 14 (39%) having eGFR < 90 mL/min/1.73m² by cystatin C, 7/36 (19.4%) had proteinuria, 3/36 (8.3%) had hypertension, and 4/36 (11.1%) had abnormal renal length. 1/15 subjects with reduced Cr had prolonged diuretic use in the neonatal period. 24 months had a neonatal history of more vaspressors exposure days (mean, 4.5 vs 0.25, p = 0.002), more total diuretic days (mean 122 vs 51 p=0.03), were more likely to be taking a diuretic at discharge (x²=11 vs n²=5, p=0.026), or to be of extremely low birth weight (ELBW < 1000 g) (x²=14 vs n²=4, p=0.007) compared to those without renal dysfunction.

Conclusions: The majority of children with nAKI had evidence of renal dysfunction at 24-month of age. Serum Cystatin C was more sensitive at identifying kidney dysfunction compared to creatinine. Therefore utility of diuretics should follow up with a particular focus on children who were ELBW, required vasopressors, or had prolonged diuretic use in the neonatal period.

PO1955

Kidney Outcomes Among Extremely Preterm Born Adolescents with Neonatal AKI

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Background: Infants born preterm are at increased risk for neonatal acute kidney injury (nAKI). AKI increases the risk for CKD long term however, lower term kidney outcomes among preterm born survivors of nAKI are not well known. The aim of the study is to evaluate associations between nAKI and microalbuminuria, elevated blood pressure (BP), and reduced kidney mass in adolescents born extremely preterm.

Methods: We obtained 2 manual BPs, a random urinalysis, and kidney ultrasound on adolescents of the University of North Carolina ELGAN (Extremely Low Gestational Age Newborn) cohort between 2017-2019. We retrospectively obtained serum creatinine (Scr) studies from the initial neonatal intensive care unit hospitalization between 2002-2004. We defined nAKI by neonatal KDIGO guidelines.

Results: Of the 31 participants born ≥ 28 weeks gestation, mean age was 15.2 years and 58% were overweight/obese. 32% of adolescents had elevated BP, 13% had reduced kidney mass, and 13% microalbuminuria. 52% of the adolescents had a history of nAKI. 81% experienced Stage 1 AKI, 19% had Stage 2 AKI, and no participants experienced Stage 3 AKI. Those with nAKI had lower birth weight, lower APGAR scores, more mechanical ventilator days, lower urine output, greater vaspressor exposure, greater indomethacin exposure, less methylxanthine exposure, greater # of serum Scr measurements, and more days in the hospital. During adolescence, those with nAKI had lower frequency of elevated BP and microalbuminuria but greater frequency of reduced kidney mass (Table 1).

Conclusions: Adolescents with a history of nAKI were more frequently exposed to nephrotoxic factors and had more indicators of severe illness in early life. However, nAKI was not significantly associated with elevated BP, microalbuminuria, or kidney mass in this sample of adolescents born extremely preterm. Further follow up is needed to better characterize manifestation of CKD in adolescents after nAKI.
Severe Urinary Tract Dilatation Prediction Model of CKD at the Age of One Year Following Prenatal Pediatr Nephrol: AKI, Dialysis, Transplant, CKD, and Nephrotic Syndrome

**Renal hypoplasia defined by body surface area related total kidney volume below the 10th percentile of normative TKV/BSA [1, 2]**

**Urine output in the first 12 hours of life;**

**Table 1**

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>eGFR (ml/min/1.73 m^2)</th>
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<tr>
<td>0-12</td>
<td>50.3 ± 13.7</td>
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**Table 1 shows the baseline characteristics of patients with CKD post-LT compared to those who did not. In bivariate analysis, age, African American race, tumor diagnosis, baseline eGFR, pre-transplant HD and AKI were associated with progression.**

PO1956

**Prediction Model of CKD at the Age of One Year Following Prenatal Severe Urinary Tract Dilatation**

**Yael Borovitz,1 Yossi Geron,2 Miriam Davidovits,1,3 Yinon Gilboa,2,3 Sharon Perlman,1,2,3 ‘Schneider Children’s Medical Center of Israel, Petah Tikva, Israel; 2Rabin Medical Center, Petah Tikva, Israel; 3Tel Aviv University Sackler Faculty of Medicine, Tel Aviv, Israel.**

**Background:** Early childhood chronic kidney disease (CKD) has a wide spectrum of health and developmental implications. Renal replacement therapy may be needed during childhood. Prenatal counselling regarding future renal outcome in cases presenting prenatally with severe urinary tract dilatation (UTD) is challenging. We aimed to create a prenatal ultrasound model for the prediction of early childhood CKD following fetal severe UTD.

**Methods:** A retrospective cohort study was conducted in a national referral centre. Fetuses diagnosed with severe UTD and maintained follow up comprised the study group. The main outcome was CKD at the age of one year. Logistic regression analysis was used to identify prognostic prenatal ultrasound variables for the renal outcome. Analysis of Maximum Likelihood Estimates was performed to create a multivariable predictive model.

**Results:** 87 fetuses comprised the study group. 15 cases (17.2%) developed CKD by the age of one year. In all, renal dysfuction and renal dysplasia were diagnosed at birth. Post-natal diagnoses were lower urinary tract obstruction in 5 cases, vesical-ureteral reflux in 10 cases, Bilateral hydronephrosis, abnormal bladder, hydroureter, calyceal dilatation, and abnormal parenchyma, were all significantly related to CKD at the age of one year. A combination of prenatal ultrasound variables yielded a model with a discriminatory ability of c=0.976.

**Conclusions:** A prediction model incorporating prenatal ultrasound features can discriminate between a normal and an impaired renal outcome at the age of one year. These sonographic features are related to the extent of renal dysplasia and to the remaining functioning nephron mass. Data presented may be used to develop more effective risk assessments and customized parent counseling.

PO1957

**Association of Antenatal Corticosteroids with Later Kidney Function in Adolescents Born Preterm with Very Low Birth Weight**

**Whitney N. Floyd, Andrew M. South. Wake Forest University School of Medicine, Winston-Salem, NC.**

**Background:** Antenatal corticosteroids (ANCS) are given to pregnant women who are at risk of preterm delivery to accelerate fetal lung development. While studies in sheep suggest that ANCS program deleterious effects on renal development leading to higher blood pressure (BP) and worse kidney function, the persistent effects of ANCS exposure on the long-term health of at-risk individuals remains undescribed. We investigated the association of ANCS with BP and kidney function in adolescents born preterm and hypothesized that ANCS are associated with worse BP and kidney function.

**Methods:** This was a long-term prospective birth cohort of 175 1-4-year-old adolescents born preterm with very low birth weight (VLBW, <1500 g). We measured manual BP, serum creatinine, and first-morning urine albumin-to-creatinine ratio (ACR), defined high BP as ≥120/80 mmHg and albuminuria as ACR >50 mg/g, and calculated the estimated glomerular filtration rate (eGFR). We used generalized linear models to estimate the association of ANCS with the outcomes.

**Results:** The cohort consisted of 58% non-Black participants, 55% female participants, and 53% were exposed to ANCS. Among all participants, mean systolic BP was 106.4 mmHg, 13% had high BP, median eGFR was 124.9 ml/min/1.73 m^2 (n=123), and 7% had albuminuria (n=134). In unadjusted analyses, ANCS was not associated with high BP (RR 1.08 mmHg, 95% CI 0.49–2.37), eGFR (β 3.74 ml/min/1.73 m^2, 95% CI -6.74 to 14.22), or albuminuria (RR 1.31, 95% CI 0.34–5.01).

**Conclusions:** Our research findings indicate that ANCS exposure was not associated with compromised kidney function or worse BP in adolescents born preterm with VLBW. Future analyses will include adjusting for potentially confounding factors in multivariable models and continuing to assess participants’ long-term BP and kidney function.

PO1958

**Predictors of Renal Function in Pediatric Liver Transplant Recipients**

**Rim Elchaki, Holly Wilhalme, Robert S. Venick, Marciana Laster. University of California Los Angeles, Los Angeles, CA.**

**Background:** Impaired kidney function is a well-recognized complication following liver transplant (LT). In adult LT recipients, the cumulative incidence of renal insufficiency is as high as 10% in 10 years. The burden of kidney dysfunction is thought to be higher in pediatric LT recipients due to longer exposure to nephrotoxic agents & longer lifespan. The aim of this study is to identify predictors of renal function decline in pediatric LT recipients.

**Methods:** This is a retrospective study of pediatric LT recipients between June 2008 to November 2014. Clinical and biochemical characteristics and eGFR were obtained at baseline, 6, 12, 24, and 60 months. CKD was defined as an eGFR <90 ml/min/1.73 m^2 for a least 3 months post-LT. A Multivariable Cox Proportional Hazards model was created to determine predictors of progression to CKD post-LT.

**Results:** Table 1 shows the baseline characteristics of patients with CKD post-LT compared to those who did not. In bivariate analysis, age, African American race, tumor diagnosis, baseline eGFR, pre-transplant HD and AKI were associated with progression.
PO1959

Clinical Evaluation of Membrane Therapeutic Plasma Exchange Using Prismaxflex Machines and Fresh Frozen Plasma in Pediatric Patients Siddharth A. Shah. University of Louisville, Louisville, KY.

Background: Previous studies have shown that membrane-based therapeutic plasma exchange (m-TPE) can be an effective method. The availability of a TPE 2000 filter membrane set with Prismaxflex machines provides added advantage to perform TPE along with continuous renal replacement therapy (CRRT). The extracorporeal volume of this filter at 125 ml is lower than centrifugation-based apheresis systems. There is very little data on the efficacy and complications of this procedure in small children. Fresh frozen plasma (FFP) has a high citrate content (20 mmol/L). There may be the risk of significant hypocalcemia using FFP as replacements.

Methods: We performed a retrospective analysis of children who underwent m-TPE using the TPE 2000 filter membrane set with Prismaxflex machines at our center during last year. We included children who required heparin, or bivalirudin as anticoagulation, and FFP as replacements. Given the minimum blood flow requirements of 100 ml/min, we only performed this procedure with children < 10 kg who were on ECMO. To prevent hypocalcemia, we administered calcium chloride drip with starting dose of 20 mg/kg/hr before initiation of TPE. We adjusted the calcium chloride drip based on the ionized calcium monitoring scale. Additional calcium boluses were given for hypocalcemia persisting after drip adjustment to a maximal rate of 50 mg/kg/hr.

Results: We included eight children in the analysis who required both CRRT and TPE. The age range was 23 days-15 years (median: 2 years). On average, we performed 3.1 treatments per patient with a mean treatment time of 175 minutes. In 2/8 patients, bivalirudin was used. Common complications included hypocalcemia requiring additional calcium bolus (2/8), high transmembrane pressure (TMP) (1/8), and hemodynamic instability (1/8). There was no significant correlation between age and dose of calcium drip required (p-value: 0.433); and ECMO and requirement of additional calcium boluses (p-value: 0.107). There was a significant improvement in inflammatory markers (D-dimer, CRP, IL6) and bilirubin level post-pheresis treatment.

Conclusions: The TPE procedure using Prismaxflex may be a practical option for children undergoing CRRT, but further studies are required to assess its use in children with weights less than 20 kg. Most children tolerated the procedure well in our study. Hypocalcemia is a critical complication with this procedure.

PO1960

Comparison of Nafamostat Mesylate and Regional Citrate Anticoagulation in Pediatric CRRT Anticoagulation
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Background: Regional Citrate Anticoagulation (RCA) is the preferred CRRT anticoagulation strategy for children in the US. Nafamostat Mesilate (NM), a synthetic serine protease, has been used widely for CRRT anticoagulation (ACG) in Japan and Korea. While NM is considered safe and effective, there is a paucity of evidence in pediatric CRRT. We compare the safety and efficacy of NM to RCA for pediatric CRRT.

Methods: Using one pediatric hospital in Japan and one in the US, medical records of patients (pts) <21 years of age on CRRT between 2016-2019 were reviewed, excluding pts receiving CRRT with ECMO. Pt demographics, CRRT characteristics, and outcomes were compared between RCA and NM groups. Filter life (FL), defined as the number of hours a single CRRT filter was in use, was the primary outcome. Safety is assessed by bleeding complications.

Results: 76 pts (248 filters) received RCA and 89 pts (226 filters) received NM. Baseline characteristics are shown Table 1. RCA pts were older and received higher Qb. Median FL (hours) did not differ by ACG type (RCA: 35 [16,67] vs. NM: 38 [22,68]). The lack of difference in FL between groups persisted when controlling for pt age and CRRT Qb.

Conclusions: RCA and NM are safe and appear to be equally effective ACG for children receiving CRRT. A prospective randomized trial is required to validate these findings.

PO1961

NT-ProBNP a Potential Biomarker for Assessing Volume Status of Patients Receiving CRRT
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Introduction: Fluid overload is a significant risk factor for morbidity and mortality in patients receiving CRRT. Records of fluid balance, clinical signs of fluid overload (weight, peripheral edema), hemodynamic parameters (tachycardia, blood pressure), filling pressure (CVP), bioelectrical impedance, and radiological studies (CXR, IVC diameter) are the clinical tools that are commonly utilized to help assess volume status, each of which has their own limitations. The aminoterminal fragment of B-type natriuretic peptide (NTproBNP), a biologically inert molecule with half-life of 60-120 min produced from left ventricular myocardium, is well established as a good diagnostic and prognostic indicator of heart failure. Our previous observation of a correlation of NTproBNP with volume status in adult cardiac disease who received CRRT led us to use NTproBNP as a surrogate marker of volume status in a newborn currently receiving prolonged CRRT.

Case Description: NTproBNP levels were measured at least twice a week in a 4-month-old female (status post bilateral nephrectomy for ARPKD) infant undergoing CRRT (clearance 30 – 35 mL/kg/hr). NTproBNP levels were correlated with weight (used as surrogate for volume status), and clinical evidence of cardiorespiratory compromise.

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Underline represents presenting author.

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Over a period of 47 continuous days on CRRT, 40 NTproBNP values were obtained. The weights ranged from 3.60 kg to 4.88 kg, while the NTproBNP values ranged from 396 to 92,300 pg/mL. There was a significant correlation between patient weight and NTproBNP levels ($r = 0.57; p < 0.001$) which helped guide the patient’s fluid management. The relationship between patient weight, NTproBNP level and clinical status is shown in the figure.

**Discussion:** NTproBNP may be able to be used as a reliable complementary marker for volume status in a select (without underlying cardiac disease) group of pediatric patients receiving prolonged CRRT. Further study is required to validate the findings in a cohort of patients.

**PO1962**

**Prophylactic PD Catheter Placement for Children Undergoing Cardiac Surgery with Cardiopulmonary Bypass: Systematic Review with Meta-Analysis**

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**Background:** Infants undergoing cardiopulmonary bypass (CPB) are at high risk of fluid overload, requiring peritoneal dialysis (PD). This systematic review evaluates whether prophylactic PD catheter (PDC) insertion at the time of cardiac surgery improves post-operative outcomes.

**Methods:** Comprehensive literature search was completed Oct-2020. We identified 1067 studies, 208 underwent full-text review for eligibility, and 15 were included: 4 randomized controlled trials; 9 cohort studies; and 2 case-control studies. Intervention was prophylactic PDC insertion with passive peritoneal drainage in 6; PD in 7; and passive peritoneal drainage or PD in 2. The comparator group typically received furosemide. Baseline characteristics were heterogeneous for the included studies with respect to age, weight, and illness severity. Surgical procedures performed were also variable within and between studies. Time to negative fluid balance (FB); presence and degree of fluid overload; duration of inotropic support and mechanical ventilation; hospital length of stay; and mortality.

**Results:** Out of 1067 studies, 208 underwent full-text review for eligibility, and 15 were included: 4 randomized controlled trials; 9 cohort studies; and 2 case-control studies. Intervention was prophylactic PDC insertion with passive peritoneal drainage in 6; PD in 7; and passive peritoneal drainage or PD in 2. The comparator group typically received furosemide. Baseline characteristics were heterogeneous for the included studies with respect to age, weight, and illness severity. Surgical procedures performed were also variable within and between studies. Time to negative FB and prevention of fluid overload showed mixed results with some studies favoring prophylactic PDC and others showing no difference. Pooled unadjusted OR for in-hospital mortality was 0.75 (95% CI: 0.05-11.11) (Figure 1). No studies reported serious PDC-related complications. Risk of bias was high in most studies, due to higher illness severity in the intervention groups, small sample size, and observational nature of studies.

**Conclusions:** Prophylactic PDC insertion is relatively safe in children undergoing cardiac surgery with CPB. Some studies have shown prophylactic PDC improves post-operative outcomes, including time to negative FB and in-hospital mortality; others have shown no difference.
Factors Associated with High-Cost Hospitalizations for Hemodialysis Catheter-Associated Blood Stream Infections in Children
Heather L. Wasik,1 Alicia Neu,2 Bradley A. Warady,3 Brendan Crawford,3 Troy Richardson,4 Heidi G. De Souza,2 Diana Cardwell,1 Rebecca Ruebner.3
The Standardized Care to Improve Outcomes in Pediatric End Stage Kidney Disease (SCOPE) collaborative

**Background:** Hospitalizations of adults for hemodialysis catheter-associated blood stream infections (HD-BSI) lead to high costs. No studies have evaluated hospitalization costs for HD-BSI in children or identified factors associated with high-costs.

**Methods:** The Standardized Care to Improve Outcomes in Pediatric End-Stage Kidney Disease (SCOPE) database was used to identify HD-BSI cases. The database included cases from 2006-2011, with follow-up until 2016. The association between HD-BSI hospitalization and mortality was assessed using Cox regression analyses stratified by race, controlling for other factors.

**Results:** The median(IQR) LOS for HD-BSI hospitalization was 5(3-10) days. The median(IQR) cost for HD-BSI hospitalization was $18,375($11,584-$36,266). Cost for each service line was higher in high-cost groups(p<0.001)(Figure 1). High-cost HD-BSI hospitalization was associated with ICU stay, LOS, need for catheter replacement/rewiring(Table 1). ICU stay (aOR=4.84, 95% CI 1.66-14.08, p=0.004) and need for catheter procedure (aOR 6.29, 95% CI 2.76-14.35, p<0.001) remained associated with high-cost hospitalization in a multivariable model.

**Conclusions:** Hospitalizations of children for HD-BSI lead to high costs. Efforts to prevent HD-BSI may reduce the costs of caring for children on hemodialysis.

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Hemoglobin and Mortality Across Race Among Children Who Transferred to Dialysis Therapy: An Analysis of CEFDIM and USRDS Data
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**Background:** Low hemoglobin (Hgb) is a strong predictor for mortality in adult dialysis patients, and children on dialysis experience higher levels less frequently than adults. Racial disparities have also been identified in pediatric dialysis patients, with Blacks experiencing unfavorable clinical outcomes and poor access compared to Whites. However, there is less literature examining the impact of race on the association of Hgb with mortality among pediatric patients on dialysis.

**Methods:** We retrospectively studied two cohorts of children (age <21) using data from a large dialysis organization (CEFDIM) and a national data system (USRDS). CEFDIM (n=1069) were followed from 2006-2011, while USRDS (n=26,254) were followed from 1995-2016. The association between Hgb and mortality was observed using Cox regression analyses stratified by race, categorizing Hgb by g/dL as well as z scores (ref: Hgb 11-12g/dL, z scores -0.5 to 0.5). Covariates considered in the models included age, sex, BMI, albumin, comorbidities, and dialysis modality type.

**Results:** Among Black CEFDIM patients, Hgb <10g/dL was associated with increased mortality (7.9 [0.97,65.27]), as was Hgb z scores <-1.5 (8.62 [1.92,38.77]). Among Black CEFDIM patients, these associations were null, and no deaths occurred for z scores <-1.5. Among Black USRDS patients, Hgb above 12 g/dL appears to be protective (0.83 [0.65,1.06]), which was not a protective range for White patients. Meanwhile, z scores <-1.5 were significantly protective among Black patients (0.82 [0.70,0.96]), but not among Black patients (0.94 [0.79,1.13]).

**Conclusions:** In children undergoing dialysis, protective Hgb target ranges appear to differ by race, with White children experiencing lower mortality risk from extremely low values and Black children receiving protection from high values.
Background: The burden of readmission within one year after pediatric kidney transplant (PKTx) is poorly described, with only one single center study describing rates of readmission as high as 79%. We aimed to examine the epidemiology of readmission after PKTx in a national U.S. cohort.

Methods: We linked the Scientific Registry of Transplant Recipients (SRTR) and the Pediatric Health Information System (PHIS) database, a group of over 50 U.S. pediatric medical centers, to identify PKTx recipients <21 years old who received a kidney-only transplant. Readmission was associated with younger age, black race, public insurance, initial transplant hospitalization <5 days, and central venous catheter use. Future studies to identify modifiable risk factors associated with readmission are planned. Our findings can help improve care models to reduce healthcare utilization and cost.

Funding: NIDDK Support

Table 1: Factors associated with re-hospitalization in the first year

<table>
<thead>
<tr>
<th>Age at Transplant</th>
<th>Adjusted HR (95%CI)</th>
</tr>
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<tbody>
<tr>
<td>&lt;8</td>
<td>1.27 (1.12-1.43)</td>
</tr>
<tr>
<td>6-10</td>
<td>Ref</td>
</tr>
<tr>
<td>11-17</td>
<td>1.01 (0.91-1.12)</td>
</tr>
<tr>
<td>18-21</td>
<td>1.10 (0.96-1.26)</td>
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<table>
<thead>
<tr>
<th>Race</th>
<th>Adjusted HR (95%CI)</th>
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<tbody>
<tr>
<td>White, non-Hispanic</td>
<td>1.00 (0.96-1.07)</td>
</tr>
<tr>
<td>Black</td>
<td>1.33 (1.01-1.76)</td>
</tr>
<tr>
<td>Other</td>
<td>1.17 (0.99-1.37)</td>
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</table>

<table>
<thead>
<tr>
<th>Insurance Type</th>
<th>Adjusted HR (95%CI)</th>
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<tr>
<td>Private</td>
<td>1.22 (1.03-1.42)</td>
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<tr>
<td>Medicaid</td>
<td>0.74 (0.46-1.17)</td>
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<tr>
<th>Center Volume (transplants/year)</th>
<th>Adjusted HR (95%CI)</th>
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<tbody>
<tr>
<td>&lt;5</td>
<td>1.19 (1.12-1.29)</td>
</tr>
<tr>
<td>6-15</td>
<td>1.62 (1.26-2.14)</td>
</tr>
<tr>
<td>16-30</td>
<td>2.14 (1.31-3.47)</td>
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<table>
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<tr>
<th>Initial Transplant Hospitalization Days (transplants/year)</th>
<th>Adjusted HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 days</td>
<td>0.75 (0.69-0.82)</td>
</tr>
<tr>
<td>6-15 days</td>
<td>1.03 (0.94-1.14)</td>
</tr>
<tr>
<td>16-30 days</td>
<td>1.05 (0.95-1.15)</td>
</tr>
</tbody>
</table>

*p<0.05

Table 1. Factors associated with re-hospitalization in the first year

PO1969

Readmission After Pediatric Kidney Transplantation: A Multicenter Cohort Study

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Conclusions: Our retrospective cohort gathers an expressive number of children with this rare and severe condition of early onset of hemodialysis, with a uniform follow-up of all individuals. We observed satisfactory survival rates among children who started hemodialysis in their first year of life, comparable to the standards of the international pediatric dialysis centers. Hemodialysis became a safe method in young children until the performance of kidney transplantation.
Encouraging Outcomes from Using a Small-Donor Single Graft in Pediatric Kidney Transplantation
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Background: The use of small pediatric kidneys as single for transplantation is controversial, due to the potential risk for graft thrombosis and insufficient nephron mass. Methods: Aiming to test the benefits of transplanting these kidneys, 375 children who underwent kidney transplantation in a single center were evaluated: 49 (13.1%) received a single graft from a small pediatric donor (≤15Kg, SPD group), 244 (65.1%) from a bigger pediatric donor (>15Kg, BPD group) and 82 (21.9%) from adult living donors (group ALD).

Results: Groups had similar baseline main characteristics. After 5 years of follow-up, children from SPD group were comparable to children from BPD and ALD in patient survival (94, 96, and 98%, p=0.423); graft survival (89, 88, and 93%, p=0.426); the frequency of acute rejection (p=0.988); the incidence of post-transplant lymphoproliferative disease (p=0.671); the rates of vascular thrombosis (p=0.846); and the necessity for post-transplant surgical intervention prior to discharge (p=0.905). The longitudinal evolution of eGFR was not uniform among groups. The 3 groups presented a decrease in the eGFR, but the slope of the curve was steeper in ALD children. At 5 years, the eGFR of ALD group was 10 ml/min/1.73m2 inferior to the others. At that time, the eGFR from SPD group was statistically similar to the BPD (p=0.952).

Conclusions: In a specialized transplant center, the use of small single pediatric donor kidneys is as successful as bigger pediatric donors or adult living donors in transplants after 5 years of follow-up.

Clinical Characteristics of Recurrent Focal Segmental Glomerulosclerosis (rFSGS) After Kidney Transplant (KTx) Through Computable Phenotypic Algorithm Analyses of Multicenter Data
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Background: Recurrent FSGS, a glomerular disorder, has a high rate of progression to end stage kidney failure and varying rates of recovery after KTx. Treatment effects are hard to determine, requiring both large multicenter populations and granular site level data.

Methods: Using the PEDSnet research network of ~11 million records, we refined a published computational phenotype (Denburg et al 2019) for a pediatric nephrotic glomerular disorders cohort to identify patients with evidence of KTx. Standardized chart review was used to identify patients with FSGS and rFSGS (urine protein/creatinine ratio > 2.0 mg/mg post-KTx).

Results: In PEDSnet v4.0 data from 1/2009-11/2020 across 6 centers, 4380 patients met criteria for glomerular disorders and 1994 among those were identified as nephrotic. 220 had evidence for KTx. In charts reviewed to-date for these 220 patients, 89/133 had non-genetic FSGS, and 71 received a KTx after 2009. rFSGS was identified in 29/71 patients, mostly early after KTx (Fig. Panel A). Demographic characteristics of those with FSGS (n=89) and rFSGS (n=29) are shown in the Table. After rFSGS, plasmapheresis (n=26) or rituximab (n=24) were the most common treatments used, remission was complete in 14/29 (48%), and partial in another 6. Allograft loss occurred in 7 patients, not significantly worse than in those without recurrence (Fig. Panel B).

Conclusions: PEDSnet can identify and characterize patients with rare diseases such as rFSGS to create robust databases to compare clinical efficacy of treatments, and for recruitment into clinical trials.
PO1973

Narrow Range of Plant-Protein Intake in the CKiD Cohort Does Not Demonstrate Changes in Estimated GFR

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Background: Vegetable or plant-based sources of protein may confer health benefits in children with progressive kidney disease. There is currently a knowledge gap in understanding the effect of different proportions of vegetable-based proteins on CKD progression in children.

Methods: The CKiD study is a multicenter, observational cohort of children with CKD. The Child Harvard Service Food Frequency Questionnaire (HSFFQ) was used to assess dietary intake. The proportion of vegetable protein (VP%) was defined as the fraction of plant protein to total protein intake. Statistical analysis used a mixed model with random intercept and slope to determine the effect on log-transformed changes in eGFR.

Results: This dataset included 2000 records on 631 subjects with a baseline eGFR from 30 to 90 mL/min/1.73m² calculated using CKiD Creatinine–Cystatin C 2012 formula. Across all dichotomized groups of children (sex, African American race, Hispanic ethnicity, etc.), the median VP% was 32-35% regardless of group. Longitudinal mixed model analysis did not show any effect on eGFR due to changes in VP%.

Conclusions: Children with chronic kidney disease obtain about a third of their protein intake from plant or vegetable-based sources. More than 90% children in the CKiD cohort had a VP% that was less than 50% of total protein intake. Due to the narrow homogeneity of dietary patterns, there was no effect on the change in eGFR with changes in VP%.

Funding: NIDDK Support, Private Foundation Support

PO1974

Diagnosis-Specific Combination of Cystatin C- and Creatinine-Based eGFR

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Background: The arithmetic mean of a creatinine- and a cystatin C-based GFR estimation (eGFR) has higher accuracy than either of the two. Smaller studies indicate that the relative contribution of the creatinine- and the cystatin C-based equation should be adapted based on underlying diagnosis.

Methods: Retrospective analysis of 1712 plasma clearance GFR measurements from four pediatric nephrology centers. eGFR was calculated using the height-based Full Age Spectrum equation using creatinine (FAS-creat) and the FAS-cys equation for cystatin C. α describes the contribution of FAS-creat, (1-α) the contribution of FAS-cys. 2/3 of the cohort (mean age 11.8 years, mGFR 93.8 ml/min/1.73m²) was used to determine the α-values yielding the highest Pα-accuracy globally (FAS) and in diagnosis subgroups. These α-values were validated in the remaining 1/3 of the cohort assessing accuracy, bias and precision.

Results: Globally, the optimal α-value was 0.3 [95% CI 0.2 – 0.4, Figure]. Lower α-values were determined for spina bifida (0), glomerulonephritis (0.2), and liver disease (0.25), while CAKUT, kidney transplantation and tubulointerstitial disease had α-values between 0.35 and 0.55. Accuracy of FAS-creat, (1-α) the contribution of FAS-cys, 2/3 of the cohort (mean age 11.8 years, mGFR 93.8 ml/min/1.73m²) was used to determine the α-values yielding the highest Pα-accuracy globally (FAS) and in diagnosis subgroups. These α-values were validated in the remaining 1/3 of the cohort assessing accuracy, bias and precision.

Conclusions: For calculation of the weighted mean, a fixed mix of 30% FAS-creat and 70% FAS-cys is optimal and yields very high accuracy overall. A disease-specific adaption (i.e. 100% cystatin C eGFR) is clinically relevant only for patients with spina bifida.

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Underline represents presenting author.
PO1975

The Optimal Equation of Estimated Glomerular Filtration Rates for Pediatric CKD Patients in Transition from Adolescent to Adult: Results from KNOw-PedCKD

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Background: Estimated glomerular filtration rate (eGFR) is an important value in kidney function evaluation, and it is useful to identify chronic kidney disease (CKD) and its progression. Clinicians use various equations to calculate eGFR which is based on serum creatinine (Cr) or cystatin C (CysC) concentration with other variables such as age, sex, and height. However, there is a lack of consensus on which equation is proper for patients in transition from adolescent to adult. Therefore, we evaluated the reliability of various eGFR calculation methods compared to measured isotopic GFR (iGFR) in adolescents and young adults with CKD.

Methods: Seventy-three patients aged from 15 to 23 years were included in the Korean cohort study for Outcome in patients With Pediatric Chronic Kidney Disease (KNOw-PedCKD). We compared measured iGFRs with various eGFR calculation equations; the bedside serum Cr based equation (SchwartzCr), the CysC based equation (SchwartzCysC), combined Cr and CysC-based Chronic Kidney Disease in Children equation (CKD-EPI(Cr+Cys)), the Chronic kidney Disease in Children equation (CKD-EPI(Cr)), and the accuracy of SchwartzCr and SchwartzCysC. Results: Fifty-two (71.2%) patients were male and 86.3% of patients had non-anemic (Hb > 12 g/dl). The SchwartzCr equation had lowest bias (-0.6 mL/min/1.73m2), high correlation (0.96), and highest accuracy (81.6% within 30% of iGFR) out of 3364 citations, 40 articles were included and 13% were randomized controlled trials (Table). Most reported AE/SE were infusion-related reactions (22.0%), infections (13.9%), granulocytopenia (3.9%), and hypoglycagomulbinemia (2.7%). Reporting of the timing or duration of AE/SE was heterogeneous and frequently incomplete. Out of all patients experiencing AE/SE (n=455), 12.7% were severe (grade 3-5), 50.8% of patients developed anemia at some point during RTX administration. However, using the t-test, only Picture Vocabulary (p=0.02) and Crystallized Cognition (U =+22) and Total Cognition (U =+19), but better Pattern Comparison (U =+33), Working Memory (U =+22) and Fluid Cognition (U =+22). However, using the t-test, only Picture Vocabulary (p=0.02) and Crystallized Cognition Composite (p<0.02) were significantly different between the groups, with the anemic group performing more poorly than the non-anemic group.

Conclusions: Children with CKD and anemia had significantly lower scores on Picture Vocabulary and on the Crystallized Cognition Composite compared to non-anemic patients after adjusting for covariates, with moderate to large effect sizes. These results suggest that anemia may be a modifiable determinant of cognitive outcomes in children with CKD.

Funding: NIDDK Support

PO1977

Adverse Events Following Rituximab Infusion in Children with Nephrotic Syndrome: A Systematic Review

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Background: Rituximab (RTX) is often used off-label in children with various kidney diseases. However, there are limited data on the frequency and severity of adverse events (AE/SE) observed in children following RTX administration. The aim of this systematic review is to evaluate the AE/SE of RTX in children with nephrotic syndrome (NS). Methods: Six databases were searched to include literature from 1991-2019 that provided AE/SE data on children (< 18 yrs) receiving RTX. Article screening, data extraction, and quality assessment were independently completed and verified by two reviewers. Primary outcome was the cumulative incidence of AE/SE. Secondary outcomes included the severity (evaluated by the Common Terminology Criteria for Adverse Events), timing, and duration of AE/SE.

Results: Out of 3364 citations, 40 articles were included and 13% were randomized controlled trials (Table). Most reported AE/SE were infusion-related reactions (22.0%), infections (13.9%), granulocytopenia (3.9%), and hypoglycagomulbinemia (2.7%). Reporting of the timing or duration of AE/SE was heterogeneous and frequently incomplete.

Out of all patients experiencing AE/SE (n=455), 12.7% were severe (grade 3-5), 50.8% of patients developed anemia at some point during RTX administration. However, using the t-test, only Picture Vocabulary (p=0.02) and Crystallized Cognition (U =+22) and Total Cognition (U =+19), but better Pattern Comparison (U =+33), Working Memory (U =+22) and Fluid Cognition (U =+22). However, using the t-test, only Picture Vocabulary (p=0.02) and Crystallized Cognition Composite (p<0.02) were significantly different between the groups, with the anemic group performing more poorly than the non-anemic group.

Conclusions: Children with CKD and anemia had significantly lower scores on Picture Vocabulary and on the Crystallized Cognition Composite compared to non-anemic patients after adjusting for covariates, with moderate to large effect sizes. These results suggest that anemia may be a modifiable determinant of cognitive outcomes in children with CKD.

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were mild (grade 1-2), and the severity in the rest were indeterminate. Overall, 53/1143 (4.6%) children experienced severe AE/SE.

Conclusions: The majority of children receiving RTX for NS do not experience serious AE/SE and RTX is generally well-tolerated. However, standardized reporting of AE/SE including timing, duration, and severity grade is warranted in future studies.

Methods: We conducted a retrospective chart review of children with NS followed at our center. Patients were identified by IKD W1 code for proteinuria and included if they had primary steroid-sensitive NS. Numbers of relapses and hospitalizations each year were collected for baseline data, March 1, 2015-March 1, 2020, and for the social distancing period (SDP), March 1, 2020-March 1, 2021.

Results: 137 children with NS were identified. The rate of relapse per year and the rate of hospitalizations per year were lower during the SDP compared with baseline pre-pandemic levels (76 vs 81 relapses per year and 14 vs 19 hospitalizations per year, respectively). Importantly, within a year of NS diagnosis, there was a baseline pre-pandemic average of 1.6 relapses per patient. This was much lower for patients in the SDP with an average of 0.6 relapses per patient during the SDP (p<0.01). In contrast, there was no difference in new diagnoses of NS comparing SDP vs baseline period (15 vs 14 new cases per year).

Conclusions: Our results support our hypothesis of lower rates of NS relapse and hospitalizations during SDP. Most notably, there were significantly fewer relapses within the year following NS diagnosis during SDP compared with baseline. This is likely attributable to decreased transmission of common infections and greater attention to infection prevention by caregivers. Less hospitalizations during the SDP would suggest decreased severity of relapse, perhaps due to earlier detection, increased caregiver awareness, or fewer infections. Interestingly, the number of new diagnoses was similar. Future analysis will focus on identification of relapse triggers and associations with steroid responsiveness and other demographic characteristics.
PO1981
Efficacy of New Combination Therapy with Prednisolone, Mizoribine, and Lisinopril for Severe Childhood Iga Nephropathy
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Background: Our previous RCT shows that warfarin and dipyriramole added to prednisolone (PSL) and mizoribine (MZB) in the 2-year combination therapy have additional effect for proteinuria remission in severe (diffuse mesangial proliferation, WHO) childhood IgAN compared to that with only PSL and MZB (Pediatr Nephrol 2018;33:2013-12). However, we have to consider avoiding the use of warfarin and dipyriramole due to side effects. Meanwhile, angiotensin-converting enzyme inhibitors such as lisinopril have been widely used for childhood IgAN since the 2000s. Therefore, we intended to examine the effect of new combination therapy including PSL, MZB, and lisinopril.

Methods: This cohort study included 84 patients with severe IgAN enrolled among 546 pediatric IgAN between 1977 and 2017, and divided into 2 groups, 70 patients treated with the previous combination therapy and 14 patients with the new combination therapy. A 1:1 propensity score matching was performed to account for between-group differences and 12 matched pairs were obtained.

Results: Proteinuria remission was significantly more obtained in the new treatment group (100% vs 50.0%, p=0.001). The patients with the new treatment achieved significantly faster proteinuria remission (median 2.4 vs. 12.0 months, p=0.04). The median duration of PSL use was significantly shorter in the new treatment group (13 vs. 24 months, p=0.0001). The median observation period was 4.9 and 4.5 years, and the percentage of patients with normal urine at the latest observation was significantly higher in the new group (66.7% vs. 25.0%, p=0.04).

Conclusions: Our findings suggest the usefulness of the new combination therapy with PSL, MZB, and lisinopril for severe childhood IgAN in achieving early proteinuria remission and shortening PSL use. Further investigations with the larger-scale and long-term outcome will be needed.

PO1982
Renal Activity Index in Lupus (RAIL) Score Distinguishes Responder and Non-Responder in Pediatric Lupus Nephritis
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Background: Systemic Lupus Erythematosus (SLE) is a diagnostic and therapeutic challenge, particularly lupus nephritis (LN). We described a composite score, the Renal Activity Index for Lupus (RAIL), consisting of neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), monocyte chemotactic protein 1 (MCP-1), adiponectin, hemopexin and ceruloplasmin, where higher scores reflect more active inflammation on biopsy. We hypothesize that when followed longitudinally during induction therapy, a change in RAIL score distinguishes clinical responders from non-responders.

Methods: Pediatric patients (<18 years) diagnosed with LN with inclusion were included (IRB #2009-0635). Diagnosis was made according to ACR criteria for SLE with renal biopsy confirmation of LN. Urine was collected at diagnosis and end of induction. Responders were defined by urine protein to creatinine ratio <0.2 mg/mg, absence of hematuria, and normal glomerular filtration rate. Response also defined as improved activity index on follow up biopsy. 15 patients were included, 10 responders, 5 non-responders. Analysis by T-test, as well as sensitivity and specificity for no change in RAIL score.

Results: RAIL score in the responder group pre and post therapy was significantly different, p-value 0.015. T-Test between non-responder and responder difference scores showed trend towards significance, p-value 0.081 (Fig 1). Most responders had a difference of at least 0.5 during induction, whereas most non-responders had no difference or an increase in RAIL score, and a change scores >0 identified responders with 90% sensitivity.

Conclusions: A change in RAIL during induction therapy is promising for predicting responders vs non-responders, with average decrease of 1 compared to no change. To further evaluate, more samples are needed, which is on-going.

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PO1983
Collapsing FSGS in Siblings with Compound Heterozygous Variants in NUP93 Expand the Spectrum of Kidney Phenotype Associated with NUP93 Mutations
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Introduction: Focal segmental glomerulosclerosis (FSGS) is a major cause of end stage kidney disease, the collapsing form has the worst prognosis. Study of families with hereditary FSGS has provided insight into disease mechanisms. In this report, we describe a sibling pair with NUP93 mutations and collapsing FSGS. This is the first report of collapsing FSGS associated with NUP93 mutations.

Case Description: We identified a Caucasian sibling pair with early onset steroid resistant nephrotic syndrome. Kidney biopsy in both brothers performed at ages 5 and 2 years, respectively, showed collapsing FSGS. Lesions of segmental or global sclerosis with focal collapsing features involved 22/33 and 6/28 glomeruli, respectively. Clinical phenotypes are summarized in Table 1. We obtained DNA from the affected brothers and their unaffected parents and carried out whole genome sequencing on the two affected siblings. We applied our standard filtering algorithm and identified segregating rare compound heterozygous variants N1727G>T p.G591V, 2 c.2084T>C p.L695S in NUP93 in the two affected brothers. Both variants are rare with minor allele frequency <0.00015. Both variants are evolutionarily conserved and were predicted to be pathogenic by four in-silico tools. 3D modeling revealed that both variants created structural alterations throughout the protein including the amino and the carboxyl terminal residues. These structural alterations are predicted to alter the binding affinity for several NUP93 ligands, likely disrupting the function of the highly organized nuclear pore channel.

Discussion: To the best of our knowledge, this is the first report of collapsing FSGS in patients with NUP93 mutations. Functional studies to determine the mechanisms by which these variants cause podocyteopathy may provide insight into the pathogenesis of the more common idiopathic and virus-mediated forms of collapsing FSGS as well as aid in early disease detection and intervention.

Table 1 - Clinical Phenotypes

PO1984
Leukocyte-Derived Human RNase 6 and RNase 3 Provide Resistance to Urinary Tract Infection
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Background: Urinary tract infections (UTIs) account for 7 million office visits and $1.6 billion dollars in health care spending annually in the United States. Uropathogenic Escherichia coli (UPEC) is the primary etiological pathogen causing over 80% of UTI. Currently, there is a critical need for innovative and effective strategies to treat UTI and prevent UPEC-associated sequelae. Antimicrobial peptides (AMPs) are fundamental components of the innate immune system that serve instrumental roles in eliminating pathogenic microbes and thus represent a potential therapeutic tool to limit UTIs. We have identified AMPs within the Ribonuclease (RNase) A Superfamily that provide resistance against uropathogens. In this study, we determined the contribution of human RNase 6 and 3 to bacterial clearance following experimental UTI in vivo.
Methods: Humanized RNASE6 and RNASE3 transgenic mice (C57BL/6J) were generated by incorporating RNASE6 or RNASE3 transgene fragments into the mouse genome. Humanized RNASE6-expressing or RNASE3-expressing female mice were transurethrally infected with UPEC strain UT898. Transplanted livers were used as negative controls. Bone marrow-derived macrophages (BMDMs) and BM neutrophils (PMNs) that had been isolated from non-transgenic or RNASE3 transgenic mice, respectively, were infected with UPEC in vitro. RNASE6 and RNASE3 expression were determined by western blot, flow cytometry and immunofluorescence. Bacterial burden was assayed via quantification of UPEC colony forming units.

Results: RNASE6 transgenic mice showed reduced bacterial burden in the urine and bladder compared to non-transgenic mice following UPEC infection. F480 macrophages in the infected bladder were identified as the main source of RNASE6, while RNASE3 was predominantly expressed by Ly6G+ neutrophils in the bladder submucosa. We also found that BMDMs from RNASE6 transgenic mice had reduced intracellular bacteria compared to WT BMDMs after UPEC infection in vitro. Decreased extracellular bacterial burden was observed in cell cultures from RNASE3 transgenic PMNs compared to non-transgenic PMNs.

Conclusions: Our findings indicate that RNASE6 and RNASE3 produced by innate phagocytes have a critical anti-microbial role against UPEC in vivo and in vitro. These RNAs have the potential to effect specifically or prevent UTIs.

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PO1985

Human Bladder Tissues Express Gb3 and Are Targeted by Shiga Toxin Yang Liu,1,2 Hatim Thaker,1,2 Songhui Tian,1,2 Jie Zhang,1,2 John Manion,1,2 Siyu Wang,1,2 Shan Wu,1,2 Zhonggao Xu,1* Min Dong,1,2 Dong Lab *Boston Children’s Hospital Department of Urology, Boston, MA; 1Harvard Medical School Department of Surgery and Department of Microbiology, Boston, MA; 1Indiana University School of Medicine, Department of Pathology, Changchun, China; 2The First Hospital of Jilin University, Department of Nephrology, Changchun, China.

Background: Shiga-toxin (Stx) producing E. coli associated hemolytic uremic syndrome (STE-COLI-HUS) is the main cause of acute kidney injury (AKI) in children. Glycophosphingolipid globotriaosylceramide (Gb3) is the receptor for Stx and determines the tissue specificity of Stx. Previous studies have detected Gb3 in glomeruli, proximal tubules and collecting duct in human kidney, but whether Gb3 is also expressed in other urinary tissues such as bladders remains unknown.

Methods: We first established and validated two complementary detection methods for Gb3 on cultured cells, one with a monoclonal Gb3 antibody and the other detecting Stx binding to cells expressing Stx. Wide-type (WT) and A4GALT KO (Gb3−/−) mice were utilized as cell models. Using these two approaches, we examined Gb3 expression in the urinary system of human and different animal models. In addition, Stx was administered i.p. in WT and A4GALT KO C57 mice to evaluate the key role of Gb3 in Stx pathogenesis in kidney and bladder tissues. Finally, we examined the impact of Stx on bladder tissues with injection of Stx into the lumen of bladders.

Results: Gb3 is detected on the cell surface of WT and transgenic female mice, but not on A4GALT KO cells. Consistently, Stx binds to WT ST57 cells, but not A4GALT KO cells. We found that normal human bladder connective tissue and vascular endothelial cells express Gb3, which mediates binding of Stx. Gb3 expression was detected in Yorkshire pig, New Zealand white rabbit, CD1 and C57 mouse, but not in Dolly sheep. Exposure to Stx increased the amount of Gb3 expression in the bladder submucosa in C57 mice and, bladder transitional cell necrosis were detected by pathological evaluation, while the transitional cells of A4GALT KO mice showed no corresponding changes.

Conclusions: Here we report the novel finding that Gb3 is expressed within bladder transitional cell and that this expression is a key target of Stx in human and mouse bladders. Furthermore, we found that Gb3 expression varies among different animal models, which will guide the selection of proper animal models for investigating the impact of Stx on urinary tissues. Finally, our study revealed that Gb3 mediates bladder inflammatory cell infiltration and transitional cell necrosis in Stx treated C57 WT mice.

Funding: Other NIH Support - Borroughs Wellcome Fund

PO1986

Intercalated Cells Activate Innate Immune Defenses in Response to Uropathogenic Escherichia coli Sarah C. Ling,1,2 Laura Schwartz,1 John D. Spencer,1,3 1Nationwide Children’s Hospital, Columbus, OH; 1The Ohio State University College of Veterinary Medicine, Columbus, OH; 1The Ohio State University College of Medicine, Columbus, OH.

Background: Urinary tract infections (UTI), including pyelonephritis, are common in children. Intercalated cells (ICs), positioned in the renal collecting duct, prevent and combat UTI by secreting antimicrobial peptides (AMPs) into the urine. The mechanisms regulating IC AMP production during UTI are unclear. Here, we challenged ICs with uropathogenic E. coli (UPEC) or bacterial cell membrane components to define the innate immune responses that control AMP production during UTI.

Methods: ICs (Clone C) were infected with a UPEC pyelonephritis strain (CTFT03) or challenged with UPEC cell membrane components including lipopolysaccharide (LPS), muramyl dipeptide (MDP) and γ-D-Glu-mDAP (ε-DAP). Following stimulation, IC lysates were collected, and 87 immune genes were profiled using an antimicrobial resistome PCR array or targeted qRT-PCR. Western blot was performed to identify which innate immune responses are activated.

Results: In response to UPEC, ICs temporally activate immunomodulatory pathways and AMPs. Analysis of the PCR array data via STRING and Ingenuity Pathway Analysis identified 15 upregulated genes associated with Toll-like receptor (TLR), NOD-like receptor (NLR), and NF-kB signaling 4 hours post infection. Immunoblotting confirmed downstream targets in these pathways are activated in response to UPEC. qRT-PCR identified that AMPs like Lcn2 are activated while others, including RNASE6, are suppressed. Upon stimulation with LPS, qRT-PCR showed upregulation of Lcn2, Defa1, and RNASE8 – suggesting that TLR4 activation may regulate the expression of these AMPs. Additionally, qRT-PCR showed Lcn2 is induced in response to the NOD2 agonist, MDP, while AMP expression did not change with the NOD1 agonist, IE-DAP.

Conclusions: During UPEC infection, TLR, NLR, and NF-kB responses are activated in ICs. Activation of TLR and NLR signaling may induce downstream targets like AMPs. Confirmation studies are needed to determine how these pathways regulate AMP expression and their differential regulatory targets. Identification of these nodes may serve as future targets to increase AMP production as an additional means to treat UTIs in children and adults.

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PO1987

Renal-Derived Alpha-Defensins 1-3 Contribute to Enhanced Urinary Tract Protection in Humanized Mouse Transplant Model Challenged against Uropathogenic Escherichia coli Jorge J. Canas, Jenaya Hooks, Sam W. Arregui, Andrew L. Schwaderer, David S. Hains. Indiana University School of Medicine, Indianapolis, IN.

Background: Alpha-defensins 1-3 are pot antimiicrobial peptides expressed from DEFA13 gene locus by human neutrophils and kidneys. Decreased DNA copy numbers of DEFA13 have been associated with UTI susceptibility. Here, we utilize a human urine-backed-in transgenic mouse (Defa+) to study the role of DEFA13 in UTIs. We hypothesized that DEFA1 protects the murine urinary tract from uropathogenic E. coli (UPEC) challenge and renally derived DEFA13 is the protective source.

Methods: Female wild-type (WT) and Defa+ mice were infected by transurethral inoculation of UPEC; CFT037, pyelonephritis strain. Bacterial burdens in kidneys and bladder for each group of mice were analyzed at 6 hours post-infection (hpi). We performed transplant isografts of Defa+ → WT and WT → Defa+ as biological controls for UPEC challenges (Figure 1A). Results: Murine bladder and kidney CFU bacterial burdens results are presented in Figure 1: Comparing the groups at 6 hpi, CFU burden averages were significantly lower in the Defa+ → WT recipient infected bladder group, similarly to infected Defa+ mice when compared to its WT counterpart (B). Strikingly, kidneys from Defa+ → WT were protected against bacterial growth, in contrast to WT → Defa+ controls, which showed higher titers of CFU burdens per transplanted kidney following pyelonephritis challenge, and recapitulates the protective phenotype observed in the Defa+ infected mice when compared to its WT control group (C). Conclusions: Our findings support the role of renal-derived alpha-defensins 1-3 in not only protecting the transplanted kidney but the entire lower urinary tract from UPEC.

Funding: NIDDK Support

PO1988

Fate-Mapping Supports a Linear Model of Urothelial Formation and Regeneration Kelly Grounds, Birong Li, Brian Becknell, Ashley R. Jackson. Abigail Wexner Research Institute at Nationwide Children’s Hospital, Columbus, OH.

Background: Urothelium is a highly specialized, slow turnover epithelium that lines the kidney, ureter, bladder and proximal urethra. Bladder urothelium contains several cell types organized into basal (B), intermediate (I) and superficial (S) cell layers. The progenitor responsible for urothelial repair has been the focus of many investigations, with
strong support for both B and I cell contenders. We have previously demonstrated that keratin (K) urothelial cells (UCs) are context specific progenitors in the kidney. Here, we mapped the fate of K5-UCs across development and following cyclophosphamide (CYC)-induced urothelial injury in the bladder.

**Methods:** Using tamoxifen (TMX)-inducible Krt5flx/+;Rosa26mKate2 mice, we performed lineage tracing with zsgreen (K5+)-UCs across development and evaluated their capacity to form I and S cells during homeostasis or following CYC-induced urothelial injury. Immunofluorescence microscopy was used to determine whether zsGreen+/UCs were K5+ (B-cells), Uropakin (Upk; I and S-cells), or K20 (S-cells) expressing. Organoids were used to evaluate progenitor capacity in vitro.

**Results:** Baseline analysis of our Cre/LoxP strategy confirmed that zsgreen is specifically expressed in basal K5-UCs 24h after TMX administration at all induction stages. The fate of zsgreen+/UCs varied, with neonatal (postnatal day [P1], P7) stages giving rise to adult (P42) I and S cells, the juvenile (9-13 stage) giving rise to both I and S cells, and adult (P35, P42) stages not escaping the B cell cycle. CYC-induced urothelial injury did not engage adult zsgreen+/UCs for repair, whereas neonatal and juvenile zsgreen+/UCs gave rise to I and S cells following CYC treatment. Organoid forming assays confirmed that zsgreen+/UCs could form organoids that express B and I cell markers, and neonatal UCs formed larger organoids than adult UCs.

**Conclusions:** We show that precise temporal populations of K5-UCs form I cells during homeostasis which in turn are engaged as adults for S cell formation in response to injury. We believe that these findings unite B and I cell progenitor models, by temporally linking a linear progression of B→I→S cell formation. A more complete understanding of the role of discrete urothelial cell populations will enable precise control of urothelial cell differentiation and will inform targeted tissue regeneration strategies.

**Funding:** NIDDK Support

**PO1999**

**Urothelial Injury Triggers Adaptive Remodeling That Limits Congenital and Acquired Obstructive Nephropathy**

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**Background:** Congenital urinary tract obstruction (UTO) is the leading cause of chronic kidney disease and end stage renal disease in children. Both congenital and acquired UTO induce renal urothelial cells to remodel and assume a bladder-like morphology, but the mechanisms and significance of these changes remain unclear. We hypothesize that urothelial remodeling occurs as a consequence of injury to Uropakin (UPK) expressing cells and serves to attenuate obstructive nephropathy.

**Methods:** Urothelial injury markers were measured by ELISA in children undergoing pylonephrectomy for congenital ureteropelvic junction obstruction (UPJO) versus non-obstructed controls. Male and female mice underwent acquired UPJO via unilateral ureteral obstruction (UUO). The fate of Upk+ cells during UUO was traced through the use of Cre/LoxP mapping. The impact of UAK plaque loss on the kidney’s response to UTO was assessed through the use of Uapk1b+ mice. The effects of Upk+ cell depletion during UUO were gauged by administering diphtheria toxin (DT) to Upk2Cre/;Rosa26mKate2 mice.

**Results:** Urine from children with congenital UPJO contains elevated urothelial injury markers – including KRT4, UPK1, and KRT2 – compared to unobstructed controls. Mice with UOU exhibit urothelial apoptosis and increased mRNA and protein expression of urothelial injury markers. Lineage analysis of Upk+ cells demonstrates that UOU triggers a sequence of Upk protein downregulation, proliferation, and elaboration of a bladder-like urothelial plaque. When this process is disrupted via Uapk1b deletion or depletion of UOU cells, UOU results in augmented tubular injury and interstitial fibrosis.

**Conclusions:** Urothelial injury is a conserved response to UTO and initiates a series of events that culminate in protective, bladder-like remodeling. The resulting expansion of urothelial cells, and adult (P35, P42) stages not escaping the B cell cycle. CYC-induced urothelial injury did not engage adult zsgreen+/UCs for repair, whereas neonatal and juvenile zsgreen+/UCs gave rise to I and S cells following CYC treatment. Organoid forming assays confirmed that zsgreen+/UCs could form organoids that express B and I cell markers, and neonatal UCs formed larger organoids than adult UCs.

**Conclusions:** We show that precise temporal populations of K5-UCs form I cells during homeostasis which in turn are engaged as adults for S cell formation in response to injury. We believe that these findings unite B and I cell progenitor models, by temporally linking a linear progression of B→I→S cell formation. A more complete understanding of the role of discrete urothelial cell populations will enable precise control of urothelial cell differentiation and will inform targeted tissue regeneration strategies.

**Funding:** NIDDK Support

**PO1990**

**An Ethical Decision-Making Framework for Genomic Testing in Pediatric Kidney Disease**

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**Background:** Technological advances and increased access have led to genomics expanding beyond the genetics specialty. As a result, non-genetic specialists, including nephrologists, can now order genomic testing for their patients. Consistent decision-making of who the correct patient to test is the next-generation sequencing to evaluate 35 genes associated with NL and nephrogenesis.

**Methods:** A three-stage approach was used: 1) review of the literature on decision-making for genomic testing in nephrology and other disciplines; 2) observation of approaches to genomic testing in the general nephrology clinic and the renal genetics clinic at an Australian pediatric hospital; 3) review and revision of the framework with key stakeholders, including clinical geneticists, genetic counselors, pediatric nephrologists, clinical ethicists, and families from the renal genetics service. The initial framework was modified until consensus from key stakeholders was reached.

**Results:** A decision-making framework was created. This framework outlines the key decision-making categories and sub-categories for patient selection, with corresponding questions to aid usage. A number of case studies were developed to demonstrate the framework’s application. Key factors influencing utilization of the framework were identified, particularly funding pathway, clinical environment, and patient population.

**Conclusions:** The framework will guide decisions around patient-selection for genomic testing, to maximise equity and utility.

**PO1991**

**Genetic Testing and Biomarkers as Predictive Tools for Congenital Anomalies of Kidney and Uroinary Tract (CAKUT)**

Meredith Harris, Eili Erkan, Kenneth Kaufman. Cincinnati Children’s Hospital Medical Center, Cincinnati, OH.

**Background:** Cincinnati Children’s Hospital is 1 of ~5 centers offering fetal interventions (FI) (amnionfusions/amnioshunts) & infant hemodilisay (HD) for oligo/anhydraminos (OA), increasing survival from 17 to 50%. As a result of this unique surgical experience, congenital Anomalies of Kidney & Uroinary Tract (CAKUT) population, more investigation into genetics & biomarkers in severe CAKUT needs to be performed, particularly in our growing bilateral multicystic dysplastic kidney (bMCDK) population (fatal at most centers). We hypothesize identification of novel genetic mutations & biomarkers will aid in determination of the clinical course of infants & mechanisms of nephropathy. 

**Methods:** Inclusion criteria for severe CAKUT are women undergoing FI for OA or infants starting HD by 1 month of life. We obtained amniotic fluid (AF) during FI and blood from the mother, father, & infant for trio exome sequencing (WES).

We performed ELISA testing on AF of 4 renal tubular biomarkers produced by fetal kidneys and validated in AF (NGAL, Cystatin c, Uromodulin and ET-1). Controls are 2nd trimester AF from infants without CAKUT.

**Results:** We enrolled 18 families-6 with bMCDK & obtained 8 AF samples (2 bMCDK). We performed WES on 5 trios (4 bMCDK) & 3 singletons (1 bMCDK). We identified 4 strong candidate genes (Table). Biomarker testing included 8 AF samples & 10 controls. All 4 biomarkers are significantly lower in severe CAKUT than controls & are lower in bMCDK than bladder obstruction, likely as the bMCDK population has less renal endowment. Biomarkers are lower in those with intrauterine demise compared to liveborn.

**Conclusions:** In patients with severe CAKUT, we detected 4 strong candidate genes, 3 implicated in embryony development. This population is enriched for genetic variants, likely due to severity of presentation. We validated 4 biomarkers in AF with correlations to diagnosis & survival. WES & biomarker testing are promising techniques to predict the course of severe CAKUT prenatally. Our goal is to develop a polygenic risk score to predict disease severity in utero based on genetic & biomarker data in this unique population.

**Funding:** Other NIH Support - T-32 Training Grant

**PO1992**

**Genetic Variant in Bilateral MCDK Families**

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**Introduction:** Diagnosing genetic kidney disease has become more accessible with the advent of low-cost and rapid genetic testing. The Invitae nephrolithiasis (NL) panel performs next-generation sequencing to evaluate 35 genes associated with NL and nephrogenesis (NC).

**Case Description:** A 7-month-old, ex-full term, white female was referred to pediatric nephrology clinic for recurrent urinary tract infections (UTI). Review of systems was positive for nephrolytic diuresis. She had no allergies or 3 simon's family history. Physical exam was unremarkable. Kidney/bladder ultrasound showed bilateral medullary NC. Voiding cystourethrogram was normal. Laboratory evaluation showed hyponatremia

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Urine from children with congenital UPJO contains elevated urothelial injury markers – including KRT14, KU2, and KRT2 – compared to unobstructed controls. Mice with UOU exhibit urothelial apoptosis and increased mRNA and protein expression of urothelial injury markers. Lineage analysis of Upk+ cells demonstrates that UOU triggers a sequence of Upk protein downregulation, proliferation, and elaboration of a bladder-like urothelial plaque. When this process is disrupted via Uapk1b deletion or depletion of Upk+ cells, UOU results in augmented tubular injury and interstitial fibrosis.
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Background: Congenital Nephrotic Syndrome (CNS) is a debilitating disease that affects children within the first few months of life and is characterized by severe proteinuria and loss of kidney function. A majority of CNS cases are caused by mutation of the NPHS1 gene, particularly in other countries. Our first aim was to determine the specific genetic causes for CNS in North America (NA). Our second aim was to determine the contribution of FOXC1, FOXL1, and GATA3 to NPHS1 transcription and nephron production, which could serve as potential drug targets for CNS therapy.

Methods: A retrospective chart review was performed to determine the prevalence of CNS mutations in NA. A survey was administered to members of the Pediatric Nephrology Section of the American Society of Nephrology (PSNA), and a questionnaire was developed for pediatric nephrologists practicing in CNS. A questionnaire was developed by a team of pediatric nephrologists and was administered to members of the Pediatric Nephrology Research Consortium (PNRC) via Qualtrics. In vitro studies to determine the impact of FOXC1, FOXL1, and GATA3 on NPHS1 transcription and nephron production were performed to determine the effect of these transcription factors on nephron production.

Results: We found the average age of CNS diagnosis was 2.6 months, with 60.3% of patients being female. Sixty-eight percent of patients underwent genetic testing for their CNS. A majority of patients (65.1%) had NPHS1 mutations, whereas 11.6% had NPHS2 mutations. Interestingly, 7.0% had both NPHS1 and NPHS2 mutations and 11.6% had only WT1 mutations. The remaining 4.6% had inconclusive results. We noted that the average age of onset for NPHS1-only mutations was 2.1 months, whereas patients with NPHS2 mutations had an average age of onset of 4.5 months. Interestingly, patients with either WT1 mutations or a combination of NPHS1 and NPHS2 mutations had younger ages of onset of 1.35 months and 1.25 months, respectively. In our in vitro studies, siRNA knockdown of FOXC1, FOXL1, and GATA3 resulted in alterations in the expression of nephron.

Conclusions: The results of this study not only demonstrate the distribution of genetic causes for CNS in North America, but also show that transcription factors may play a role in NPHS1 transcription.

POI995

Genetic Testing in Children with Nephrolithiasis and Nephrocalcinosis

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Background: Genetic Causes for Congenital Nephrotic Syndrome: North American Mutations and the Contribution of Regulatory Factors

POI996

Mendelian Causes Are Identified at a Relatively Low Rate and Show a Unique Pattern in Brazilian Pediatric Patients with Steroid-Resistant Nephrotic Syndrome or Focal Segmental Glomerulosclerosis

Andres Wilhaha,¹ Precil D. Neves,¹ Eliser H. Watanabe,¹ Antonio M. Lerario,¹ Denise M. Malheiro,¹ Maria H Vaisbich,¹ Friedhelm Hildebrandt,² Matt G. Sampson,² Luiz F. Onuchic,³ ¹University of Sao Paulo, Sao Paulo, Brazil; ²Boston Children’s Hospital, Boston, MA; ³University of Michigan, Ann Arbor, MI.

Background: Genetic and non-genetic factors have been associated with faster progression to chronic kidney failure (CKF) in children with steroid-resistant nephrotic syndrome (SRNS). The contribution profile of such factors in adnexed populations, however, is still not well characterized.

Methods: 101 patients/98 families with idiopathic SRNS, age of onset <18yr, were sequenced for 62 NS genes or submitted to whole exome sequencing. Causative variants and APOL1 risk alleles were confirmed by Sanger sequencing. Clinical data were retrospectively reviewed.

Results: Age of NS onset was 2.9yr (1.5-6.8), 61 (60.4%) were male, 61 (60.4%) self-declared white, 6 (5.9%) had parental consanguinity, and 14 (13.9%) familial disease. Focal segmental glomerulosclerosis (FSGS) was diagnosed in 54/95 (56.8%), minimal change disease (MCD) in 20/95 (21.1%) and collapsing glomerulopathy in 12/95 (12.6%). 43/101 (42.6%) progressed to CKF in 29 months (12.0-61.9) and 9/29 (31%) had recurrence after kidney transplantation (KT). APOL1 high risk genotypes (HRG) were identified in 8/98 (8.2%) and were associated with later NS onset [11.0 (10.0-14.5) vs 2.7 (1.4-4.9) yr, p<0.001]. Mendelian causes were found in other 14/98 (14.3%) families: NPHS1=4, NPHS2=3, PIKE=2, WTI=2, COQ2=1, and phenocopies in CUBN=1 and COL4A3=1, all APOL1 G0/G0. Poorer renal survival was observed in APOL1 HRG vs non-Mendelian/non-APOL1 HRG (p=0.001), and a trend in Mendelian vs non-Mendelian/non-APOL1 HRG (p=0.06). The APOL1 or Mendelian cases had no post-KT recurrence. Using Cox regression, age of onset <1yr (OR=6.5, CI:2.3-16.9, p=0.0007) or a 9yr (OR=3.3, CI:1.3-7.9, p=0.015) were associated with reduced renal survival, independently of genetic findings, as well as self-declared non-white (OR=2.6, CI:1.3-5.6, p=0.01) and non-MCD histology (OR=14.2, CI:2.1-94.8, p=0.002).

Conclusions: Mendelian causes of SRNS/FSGS were identified in 14.3% - a lower rate than in PodoNET, SRNS Study Group and RaDar - and APOL1 HRG in 8.2% of patients in this adnexed population with a low frequency of parental consanguinity. Genetics factors, age of NS onset, ethnicity and biopsy pattern were independently associated with progression to CKF.
PO1996

Experience from a Single Centre Following a Large Cohort of Children with Cystinuria (1996-2019)
Sergio Camilo Lopez Garcia,1,2 Naima Smeluders,1 Wesley N. Hayes,1 Alexander Cho,1 Tom A. Watson,1 Alex Barnacle,1 Marina J. Easty,1 Deltef Bockenhauer,1,2 Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom; 3University College London Department of Renal Medicine, London, United Kingdom.

Background: Cystinuria is a rare monogenic disorder accounting for 5-10% of all pediatric urolithiasis cases. This study reviews epidemiologic, clinical and management data of a large, single centre cohort of cystinuric children.

Methods: Request data collection from children with cystinuria between June 1996 to April 2019 in our centre.

Results: A total of 52 (54% female) patients were identified with a median (IQR: interquartile range) age at presentation of 6.2 (1.9-10.3) years. 24/52 (46%) had affected family members. Common presenting symptoms were abdominal pain 21/51 (41%), urinary tract infection 39%, haematuria (18%); 14/51 (28%) cases were diagnosed by family screening or incidentally. 9/52 (17%) had cystinuria but did not form a stone. At the end of follow up eGFR<90 was present in 12/35 (34%).

Conclusion: Cystinuria is a rare monogenic disorder accounting for 5-10% of all pediatric urolithiasis cases. The study reviews epidemiologic, clinical and management data of a large single centre cohort of cystinuric children.

PO1997

Systemic Oxalate Deposition in Patients with Primary Hyperoxaluria
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Background: Primary hyperoxaluria (PH), a rare inborn error of metabolism resulting in systemic overproduction of oxalate, causes kidney stones and, for some end-stage renal disease and systemic oxalosis. Our objective was to determine the timing of dialysis, renal transplant, and use of medications to treat PH manifestations in children relative to their diagnosis.

Methods: A retrospective cohort study was conducted in PEDISnet, a clinical research network of 7 US pediatric health systems. Data from PEDISnet were queried to identify patients <18 years old with a diagnostic code for or related to PH between 2009 – 2020. Outcomes queried were renal transplantation, initiation of dialysis, first prescription for medications used to treat end-organ manifestations of PH, and specialty care visits.

Results: Of 341 patients identified. Median age at CED was 9.4 years (IQR 5.0, 13.0). Median follow-up was 2.9 years (IQR 1.1, 6.0). Median eGFR was 117.33 ml/min (IQR 95.75, 139.79). Most patients with renal transplant were transplanted prior to CED. Similarly, dialysis (n=14) was initiated in the majority before CED and at a younger age than those starting dialysis after CED. Prescription drug therapy before CED was high (29% patients with B6 use, Table). Nephrology was the specialty most commonly responsible for initial PH diagnosis (69% on CED).

Conclusions: In one of the largest cohorts of children in the US with PH, dialysis and renal transplant occurred before diagnosis, suggesting significant morbidity when diagnosis is delayed. Medications for the organs affected by PH were consistently prescribed before diagnosis, suggesting an opportunity for earlier PH identification to enable tailored therapy to potentially delay or prevent need for dialysis and transplant.

Funding: Commercial Support - Dicerna Pharmaceuticals

PO1998

Temporal Relationship of Transplant, Dialysis, and Medications for Children with Primary Hyperoxaluria

Results: At GHC we see 12 pediatric and 4 adult patients on a regular basis, at least twice a year. All 16 patients are in no less than CKD 2. For the following examinations were performed: an eye exam was performed in 8 patients, it was normal in all. Speckle tracking echocardiography was done in 8 patients, it was abnormal in one (GLS – 17.3% and left ventricular hypertrophy) and borderline in another (GLS – 18.6%) in 2020. During 2019, GLS values returned to normal in both under increased treatment awareness (~23% and ~21%, respectively). X-ray left hand was taken in 6 patients, one patient (multiple stone removal procedures, decline in GFR) had tiny sclerosing areas at caput MCP IV and the thumb. MRI of left knee and proximal tibia was performed in 6 patients, eventually visible structural changes as patchy areas of low signal intensity were found in one patient. Two patients had salivary stones in the parotid gland, found in a routine x-ray of the jaw before orthodontic treatment.

Conclusions: Although this is currently only data of a small cohort, systemic oxalate deposition may also occur in PH3. Of course, data in more patients are needed to elucidate the true risk of systemic oxalate deposition and we therefore recommend to screen all known PH3 patients.

PO1999

Oxalate and Glycolate in Urine and Plasma Related to Kidney Function, Dialysis, or Transplantation in Patients with Primary Hyperoxaluria
Type 1
Bernd Hoppe,1,2 Julia Pick,3 Cristina Martin Higuera,1 1German Hyperoxaluria Center, Bonn, Germany; 2University Hospital Bonn, Center for Rare diseases, Bonn, Germany; 3Zentrum fur Kinderheilkunde der Universitat Bonn, Bonn, Germany.

Background: Primary hyperoxaluria type 1 (PH1) is characterized by endogenous oxalate overproduction in the gut and subsequent deposition in blood and urine, causing recurrent urolithiasis, end-organ disease and early death. It results from deficiency of alanine:glyoxylate aminotransferase (AGT), the enzyme that catalyzes the conversion of glycine (gly) and glyoxylate (glyox) to serine and oxalate (oxa). Surrogate markers such as oxalate and glycolate (glycol) are used as biochemical markers for diagnosis, treatment and follow up, but also as primary endpoints in studies.

Methods: We retrospectively analyzed these parameters in urine and plasma of 87 genetically confirmed PH1 patients over the last 15 years. All parameters were analyzed by ion chromatography using spectrometry and an automated lab. Correlation and comparative analyses were performed within groups of different renal function (normal,
CKD 1-5; n=48 patients), hemodialysis (HD; n=31), transplantation (Tx; n=32) and related to vitamin B6 medication.

**Results:** From normal kidney function to CKD3-4 Pox remained stable (median Pox 17 μmol/l), while Pglyc was more markedly elevated (median 90.12 μmol/l). Both were significantly higher in non-B6 versus B6 sensitive patients. Pox and Pglyc did not correlate with kidney function, except for Pox and CKD5. Highest Pox and Pglyc was found in HD (91 and 211 μmol/l, respectively), not related to B6. Uox and Uglyc remained stable at all CKD stages in B6 sensitive, but increased progressively in B6 unsensitive patients. Pox and Uox slowly declined post combined and sequential liver-kidney, but also in isolated kidney Tx, which was performed in adult B6-sensitive patients. In the contrary, Pglyc remained elevated post Tx.

**Conclusions:** Our findings are in many ways contradictory to previously published observations. Pox or Uox did not correlate to GFR. Pox was surprisingly low until HD and increased in HD until CKD3-4 in non-B6 sensitive patients. Pglyc remained elevated even years after transplantation, but no data are available to compare. Glycolate is widely increased until CKD3-4 in non-B6 sensitive patients. Pglyc remained elevated post Tx.

**Funding:** Government Support - Non-U.S.

**PO2000**

**Compassionate Use Treatment with RNAi Medication (Nedosiran) in Two Patients with Primary Hyperoxaluria Type 1 and Maintenance Hemodialysis**

Bernd Hoppe, Gesa Schalk, Cristina Martin Higuera, 1 German Hypoxaluria Center, Bonn, Germany; 2 Kinderinernenzentrum, Bonn, Germany.

**Introduction:** The primary hyperoxalurias (PH) are three ultra-rare, autosomal recessive genetic disorders characterized by oxalate overproduction in the liver. Hyperoxaluria induces recurrent kidney stones, nephrocalcinosis, progressive renal impairment, and systemic oxalosis, especially in PH1. Nedosiran is an investigational RNA interference (RNAi) therapeutic administered monthly by subcutaneous injection. It reduces hepatic LDHA protein thereby inhibiting the final step responsible of oxalate production in all types of PH1.

**Case Description:** We report on two PH1 patients, a 40 year old woman (a) on hemodialysis (HD) 6 x 3 hours weekly, and a 6.5 year old boy (b) receiving 5 x 5 hours HD, both homozygous for AGXT c.508G>A and treated with pyridoxine. Patient (a), global longitudinal strain (GLS), an index of left ventricular contractibility, was impaired (-13%; normal -18%). Patient (b), has massive oxalate osteopathy, myocardial hypertrophy and cardiac insufficiency (GLS of – 9.98). They received Nedosiran as compassionate use medication for now 6 months. Monthly plasma oxalate (Pox in μmol/l, normal 10.4) was measured, Speckle Echo and/or 3 Tesla bone MRI (left knee) were repeated. Speckle echo improved significantly in both (a: GLS -23%; b: GLS -16.5%). Bone MRI ameliorated in patient (b) showing a midus of normal trabecular structure.

**Discussion:** Clinics improved and Pox declined over the six months of treatment. Pox was influenced in (b) by severe oxalate osteopathy and therefore possibly dissolving oxalate and in (a) when dialysis regimen was reduced to 4 x 3 hours at month 6. We cautiously conclude, that Nedosiran treatment reduces plasma oxalate levels in a way, that liver transplantation may be avoidable in PH1 patients.

**Funding:** Government Support - Non-U.S.

**PO2001**

**Functional Analysis of Novel CNNM2 Mutation in Autosomal Dominant Hypomagnesemia with Seizure**

Min-hua Tseng, Chang Gung Medical Foundation, Taoyuan, Taiwan.

**Background:** CNNM2 has been identified to be the responsible gene for patients with hypomagnesemia, seizure, intellectual disability (HSMR) syndrome. The functional impact of mutations in CNNM2 remains unknown.

**Methods:** We have identified 1-year-old infant with HSMR featuring severe hypomagnesemia with renal magnesium wasting requiring higher dose of Mg²⁺ replacing.

**Results:** With WES, we identified a de novo heterozygous mutation c.14347T>R480L in CNNM2 gene. Direct Sanger sequence was performed to identify the responsible gene. The functional assay of this identified mutant was examined in vitro studies.

**Conclusions:** This novel R480L mutation in CNNM2 gene diminishes the Mg²⁺ influx probably through the impaired binding between Mg²⁺-ATP and CNNM2, accounting for refractory hypomagnesemia.

**Funding:** Government Support - Non-U.S.

**PO2002**

**Long-Term Outcome of Bartter Syndrome**

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**Background:** Bartter syndrome (BS) is a rare salt-wasting tubulopathy caused by mutations in genes encoding sodium, potassium, or chloride transporters of the thick ascending limb of Henle and/or the distal convoluted tubule of the kidney. BS is characterized by polyuria, failure to thrive, hypokalemia, metabolic alkalosis, hyperreninemia and hyperaldosteronism. Previously, potassium and/or sodium supplements, potassium sparing diuretics and NSAIDs were known as possible treatment options for BS. While presenting symptoms and initial managements of BS are relatively well known, long-term outcomes and treatments are still unclear.

**Methods:** Through a survey for the members of Genetic Kidney Disease Working Group of the Korean Society of Nephrology, clinically and/or genetically diagnosed 54 Korean BS patients were recruited. We retrospectively reviewed their medical records between 1992-2020 for presenting symptom, laboratory findings, genotype, medication, and their final height and renal function.

**Results:** There were clinically and/or genetically diagnosed with BS at median age of 5 months old (range 0-271) and their median follow up was 8 years (range 0.5-27). Genetic diagnosis of BS was made in 40 patients; 4 patients with SLC12A1 gene mutations, 2 patients with KCNJ1 gene mutations, 33 patients with CLCNKB gene mutations, and 1 patient with BSN1 mutation were revealed, respectively. Potassium chloride supplementation was administered in 94% of patients and potassium sparing diuretics were administered in 68% of patients. Average dosage of potassium supplementation was equivalent to 4.30 mEq/day/kg (body weight). At the last follow-up of 8 years after the initial diagnosis, 41% had short stature (height less than 3rd percentile) and CKD was observed in six patients (CKD stage 3 in four and stage 5 in two patients).

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

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PO2003

Walking in Patients’ Shoes: Novel Approach to Increase Staff Empathy Through Adherence to Dietary Restrictions

Randa Razzouk, Mary Cazzell, Amanda Marroquin, Barrett Brown. Cook Children’s Medical Center, Fort Worth, TX.

Background: Dietary recommendations for children with end-stage renal disease (ESRD) on dialysis include restrictions in potassium, phosphorus, and sodium. Children must take phosphate binders with meals and snacks. Renal diet compliance can be challenged by adherence difficulties. Patient perceptions of health care professionals (HCPs) levels of empathy play an important role in improved patient satisfaction. Higher perceived empathy levels lead to improved patient compliance to treatment, diet, and overall positive health. The purpose of this study was to explore the impact of a novel intervention (adherence to a two-week renal diet) on levels of empathy among HCPs directly caring for children with ESRD on dialysis.

Methods: A quasi-experimental comparative interventional study design was utilized with a convenience sample of 37 HCPs who directly cared for children with ESRD on dialysis Through self-assignment, 14 HCPs completed a renal diet education class (control group), 23 completed the class and two-week renal diet and “phosphate binders” intake with logs (experimental group). Pre- and post-intervention levels of empathy were measured using the Jefferson Scale of Empathy. Renal diet logs were reviewed to calculate percentages of adherence to compliance and “phosphate binder” use.

Results: Baseline empathy scores for each group were matched (p = 0.825). Within the experimental group, post-intervention results showed statistically significant increases in empathy levels after adherence to a two-week renal diet (p = 0.004). No significant differences in control group pre- and post-empathy levels were noted. Percentages of compliance to a two-week renal diet were 82% and to “phosphate binders,” 83%.

Conclusion: Levels of empathy increased when HCPs followed a two-week renal diet, discovering similar patient adherence issues. HCPs reported less-than-perfect renal diet compliance and use of “phosphate binders.” This study can be implemented in various pediatric settings, such as specialty areas treating patients on therapeutic dietary restrictions (e.g. diabetes, celiac disease, epilepsy).

Results from experimental group

PO2004

Outcome of a 30-Month Screening, Education, and Treatment Program of Lower Urinary Tract (Dys)Function in Pediatric Kidney Recipients


Background: Graft survival of pediatric kidney recipients increased dramatically over the past decades. Lower urinary tract dysfunction (LUTD), as one of the factors that might contribute to graft function and survival, is seen in the majority of all recipients despite cause of kidney failure. This study presents the 30 months outcomes of a screening and early intervention program of all pediatric kidney recipients.

Methods: Since June 2018 all pediatric renal recipients underwent an active screening and education for LUTD pre-and post-transplant by our nurse specialist. Personalized education was given to all and uterotherapy in case of LUTD. Those without LUTD, received yearly re-evaluation.

Results: A total of 56 recipients are screened thus far, aged 11.8 ± 4.7 years. MeanSD time after transplant was 4.4 ± 3.9 years. After initial screening, LUTD was present in 71% of the patients (Table 1). Maximal bladder capacity exceeded in 59%, abnormal uroflowmetry was present in 58%, and residual voiding was present in 37% of the children. Longitudinal data showed that 16% remained dysfunctional despite uterotherapy. In addition, 60% switched between a functional and dysfunctional pattern. Overall, after 30 months, 48% of the children with LUTD developed a persistent functional voiding pattern. Recipients with LUTD significantly more health care activities (2-6 times more compared to patients without LUTD). By consequence economic burden rises with €600,- per patient each year.

Conclusions: LUTD is present in the majority of pediatric kidney recipients, regardless of the cause of kidney failure. Due to LUTD, patients need more health care. Resulting in a significant economic and psycho-social burden. This pro-active screening, treatment and education uro-transplant program was effective in 48% of the children with LUTD in the long term. A longer follow-up time is needed in order to analyze the impact of early childhood urological treatment.

Funding: Government Support - Non-U.S.

PO2005

Machine Learning Can Predict the Individual Risk of Acute Pyelonephritis in Children

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Background: Acute pyelonephritis (AP) is a common infection in children. Timely diagnosis of pediatric AP is necessary, since under-diagnosed AP increases infectious morbidity, whereas over-treatment of AP is responsible for an increase in antibiotic resistance and health costs. However, confirmed AP diagnosis requires validated urine cultures, which can take up to 3 days. Here we propose to use machine learning algorithms to predict the risk of AP in febrile children, using simple parameters available within the first hours of medical care.

Methods: We performed a retrospective study of medical and laboratory files of 102 pediatric patients with a suspected diagnosis of AP, treated between 2014 and 2020 at the pediatric National Reference Hospital of Luxembourg. Based on the results of urine cultures, patients were allocated to the AP or non-AP group. All patients were then randomly split into training and testing batches, used by a Random Forest machine learning algorithm to predict the individual risk of AP, using clinical (age, sex), blood (CRP, white blood cell and neutrophil counts) and urine (red and white blood cell counts) parameters.

Results: Patients’ demographic and clinical characteristics were comparable between groups. In particular, sex ratios were not significantly different between AP and non-AP patients (0.66 versus 0.74). Random Forest algorithm mean performance metrics were: accuracy 90.48% [85-95%], sensitivity 91.67% [90-95%], specificity 88.89% [90-90%]. Given a prevalence of AP of 60%, positive predictive value was 92.52% [88-95%], negative predictive value 87.67% [82-89%]; mean AUC-ROC was 0.92. Predictions performed with a neural network or a support vector machine algorithm on the same population obtained comparable performance metrics.

Conclusions: Timely diagnosis of pediatric AP is necessary to minimize infectious morbidity, antibiotic resistance and health costs; however, it requires validated urine cultures, which can take several days. Here we showed that machine learning algorithms can accurately predict the individual risk of AP in pediatric patients within the first hours of medical care, helping pediatricians in daily clinical decision making.

PO2006

Associations Between Clean Intermittent Catheterization, Quality of Life, and Emotional-Behavioral Functioning in Children with CKD

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Background: Need for clean intermittent catheterization (CIC) can affect quality of life (QOL) and emotional functioning in pediatric populations, with some evidence that urethral catheterization is associated with poorer emotional adaptation than use of Mitrofanoff. Little is known about the impact of CIC on QOL and emotional functioning for children with chronic kidney disease (CKD).

Methods: Data from the CKD study were used to evaluate QOL, emotions/behavior, and CIC in children age 6+ years with mild to moderate CKD (non-glomerular disease). We hypothesized that CIC would be associated with poorer QOL and more internalizing and behavioral symptoms (using ratings from BASC2, PedQOL), and that urethral CIC (versus Mitrofanoff) would predict worse outcomes. Linear mixed models adjusted for sociodemographic and disease-related covariates were used and included predictors for CIC use (vs non-users) as well as for urethral catheterization (vs Mitrofanoff) to predict worse outcomes. Linear mixed models adjusted for sociodemographic and disease-related covariates were used and included predictors for CIC use (vs non-users) as well as for urethral catheterization (vs Mitrofanoff).

Results: The sample included 1484 records (466 CIC non-users, median age 10 years, 66% male, median eGFR 52 ml/min/1.73m²; 115 CIC users, median age 12 years, 67% male, median eGFR 45, 43% urethral, 48% Mitrofanoff). Median BASC2 scores...
were in the average range for both CIC users and non-users. Median PedoQol scores were slightly lower than that of healthy populations for CIC non-users (parent-report 80 [IQR=66,89]; child-report 79 [IQR=70,88]) and even lower for CIC users (parent-report 73 [IQR=59,83]; child-report 76 [IQR=65,85]). CIC predicted higher scores on the BASC2 Internalizing Composite (β=3.33, CI=1.13, 5.54; p<0.003), and Behavioral Symptoms Index (β=2.13, CI=0.08, 4.18; p=0.04), and lower parent- and child-reported QOL (β=−5.11, CI=−8.46, −1.75; p<0.003; β=−3.75, CI=−6.98, −0.52; p<0.02). However, urethral CIC predicted lower scores compared to Mitrofanoff on the Internalizing Composite (β=−3.94, CI=−6.65, −1.22; p<0.005).

Conclusions: For children with mild to moderate CKD, CIC is associated with poorer QOL and more parent-reported emotional-behavioral symptoms. Urethral CIC (versus Mitrofanoff) is associated with fewer internalizing symptoms. Additional research is needed to determine if other characteristics associated with need for CIC influence emotions and QOL.

Funding: NIDDK Support, Other NIH Support - National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI).

**PO2007**

Pneumococcal Vaccination in High-Risk Pediatric Nephrology Patients
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Background: Children with nephrotic syndrome (NS), chronic kidney disease (CKD) and immunosuppression (IS) are at high risk of invasive pneumococcal infection but are often undertreated.

Methods: Cross-sectional survey of 374 patients (20% up-to-date (UTD), 5% missing PCV13, 32% missing PPSV23, 34% missing both) were identified. Sources of failure to vaccinate with initial interventions were single stakeholder reliance, lack of follow-up and vaccine supply. Primary drivers were patient identification, vaccine administration and rate determination.

Results: 374 patients (20% up-to-date (UTD), 5% missing PCV13, 32% missing PPSV23, 34% missing both) were identified. Sources of failure to vaccinate with initial interventions were single stakeholder reliance, lack of follow-up and vaccine supply. Primary drivers were patient identification, vaccine administration and rate determination. All physicians and nurses were taught to identify patients, check vaccine history and use a vaccine algorithm. Study of our interventions revealed unanticipated obstacles with monetary cost, vaccine refusal and shared responsibility. To aid monetary issues a new stakeholder (manager) was created. Vaccines were re-offered at subsequent visits if initially refused. Reminders were sent to physicians on the importance of patient identification in clinic. Vaccination increased to >75% and has been sustained for 4 months (Figure 1). Percent UTD increased to 39%.

Conclusions: Incorporating and educating multiple stakeholders and adequate vaccine access improved vaccination rates at our center. Our methods appear successful without excess time expenditure. Further study is underway to ensure sustainability without excess monetary cost.

Figure 1: Run chart

**PO2008**

Psychosis in Adolescence and Young Adulthood with a Kidney Disease Diagnosis in Childhood
Megan Dunleavy,1,2 Christopher B. McFadden,1,2 Rowan University Cooper Medical School, Camden, NJ; 2Cooper University Health Care, Camden, NJ.

Background: Advances in medical technology & management continue to improve the lifespan of children with kidney disease; yet, enhanced understanding of this population shows a relative lag. Prior studies examining pediatric kidney disease have repeatedly found neurocognitive deficits in areas of attention, memory, complex cognition, emotion identification, and inhibitory control. Such deficits, when considered alongside nervous system injuries resulting from toxin retention and electrolyte aberrations, warrant further investigation. This study seeks to explore for any association among experiences of acute psychosis in adolescence and young adulthood (AYA) and defined history of childhood kidney disease.

Methods: To explore this, a retrospective cohort study using electronic medical records (EMR) was conducted. EMR queries were run to identify & categorize study samples into two groups: ICD-coding defined kidney disease vs healthy peer control. Data collection ranging from July 1, 2012, to February 13, 2021, was then queried for episodes of psychosis in both arms.

Results: Results identified 1192 patients as qualifying for study inclusion. Twenty-one (Prevalence= 1.76%; OR= 0.018) patients qualified for inclusion in the kidney disease group. 1711 (Prevalence= 98.24%; OR= 55.76) patients qualified for inclusion in the control group. Data analysis uncovered ten of 1192 (Prevalence= 0.84%; OR= 0.008) cases experienced acute psychosis throughout AYA. One of these ten cases occurred in CKD sample, representing a 4.76% prevalence (OR= 0.05). The remaining nine cases of AYA psychosis occurred in the control sample, representing a prevalence of 0.77% (OR= 0.008).

Conclusions: Preliminary data demonstrate, those with kidney disease had an increased likelihood of 6.46 (CI= 0.78-54.05) times that seen in control sample for development of acute psychosis in AYA. While unable to rule out the observed effect being due to random chance, acknowledgement of the limitations made by restful and data quantities are held. This pilot study, highlights a novel association deserving of further investigation in a large-scale, multicenter format. Establishing a significant association among childhood kidney disease and psychosis in AYA, would therefore prompt initiation of early education efforts aimed to persuade patient self-awareness, and ignite help-seeking mindsets prior to symptom onset.

**PO2009**

Pediatric Nephrologists’ Perspectives on Palliative Care: A National Survey Study
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Background: Integration of palliative care (PC) within nephrology practice offers the chance to lessen the burdens experienced by children with chronic kidney disease (CKD) and their families. Yet, little is known about pediatric nephrologists’ attitudes regarding early recognition in and seeking PC services for children with CKD. We sought to ascertain pediatric nephrologists’ perspectives in routine integration of PC for children with CKD.

Methods: A cross-sectional web-based survey was administered to pediatric nephrologists associated with the American Society of Pediatric Nephrology listserv. Three invitations were sent from May 3, 2021 to May 28, 2021. The survey was adapted from a previously validated instrument and pretested by stakeholders; studied areas included institutional and personal experience with PC, training, and education, and confidence. Data were summarized descriptively.

Results: There were 64 participants (17.7% response rate). Most participants were female (62.5%), Caucasian (64.1%), and practice in urban (76.4%), academic centers (89.1%) with access to subspecialty PC teams (93.8%). Perceived institutional barriers to subspecialty PC consultations were low, and prior consultations were found to be helpful. However, nephrologists expressed concern that consultation may imply to parents that the team is “giving up” on their child. Though 63.6% indicated that consultation should happen at diagnosis for life threatening conditions where cure is feasible but may fail, 59.6% of nephrologists reported that PC is rare or never consulted for ESKD patients at their center. Confidence in engaging in challenging communication was high, yet only 26.4% and 30.2% of participants, respectively, were comfortable managing pain or psychological distress of children with CKD.

Conclusions: Pediatric nephrologists are receptive to PC consultations for children with CKD, but utilization is low. Parental perception of the implications of consultation are of concern. Among primary PC skills, challenging communication is seen as a strength of pediatric nephrologists, but confidence is low in managing some physical and psychological symptoms. Routine integration of PC will require efforts to assess patient and family impacts of PC and shift that of providers, as well as targeted education to increase skills.

Funding: Other NIH Support - Dr. House is supported by a National Institutes of Health training grant (ST32DK07662-30, PI Hingorani).

**PO2010**

Palliative Care Training in Pediatric Nephrology Fellowship: A Cross-Sectional Survey
Patient Safety House,1,2 Aaron G. Wightman,1,2 Jodi M. Smith,1,2 Abby R. Rosenberg,1,2 1University of Washington, Seattle, WA; 2Seattle Children’s Hospital, Seattle, WA.

Background: The integration of primary palliative care (PC) in pediatric nephrology provides an opportunity to address the burdens faced by children with chronic kidney disease (CKD) and their families. Incorporation of PC education in training programs is recommended, but adult nephrology fellows report inadequate preparation to engage in primary PC. Similar experience of pediatric nephrology fellows is unknown. We sought to describe pediatric nephrology fellows’ knowledge and confidence in providing primary PC and education received during training.
**PO2011**

**Correlation Between Kidney Sodium and Potassium Handling and the Renin-Angiotensin-Aldosterone System in Children with Hypertension**

**Ella C. Perrin, Andrew M. South. Wake Forest University School of Medicine, Winston-Salem, NC.**

**Background:** Urine sodium and potassium concentrations are used as surrogate markers for dietary sodium and potassium consumption in adults with hypertension, but their association with components of the renin-angiotensin-aldosterone system (RAAS) is incompletely characterized. Some individuals with hypertension may have an abnormal RAAS response to dietary sodium and potassium intake, though this is incompletely described. Our objective was to investigate if plasma renin activity and serum aldosterone are associated with urine sodium and potassium in youth with hypertensive disorders.

**Methods:** This pilot study was a cross-sectional analysis of baseline data from 44 youth being evaluated for hypertensive disorders in a Hypertension Clinic. We recorded serum sodium and potassium, albuminuria, and aldosterone to sodium/potassium (UNaK) and aldosterone/potassium (A/PK) ratios. We used multivariable generalized linear models to estimate the associations of renin, aldosterone, sodium, and potassium.

**Results:** Our cohort was diverse (37% non-Hispanic Black, 14%, Hispanic, 66% were male, and median age was 15.3 years; 9% had a secondary etiology and 77% had hypertension phenotypes and guide treatment).

**Funding:** NIHHDK Support, Other NIH Support - Dr. House is supported by a National Institutes of Health training grant (5T32DK007662-30, PI Hingorani).

**Conclusions:** Few pediatric nephrology fellows receive PC education and experiences during training, resulting in low rates of knowledge and confidence across care domains. Fellows indicate a need and desire for improved PC training.

**PO2012**

**Aldosterone Producing Adenoma in an Adolescent Black Female**

**Kristie R. Searcy,1 Celso E. Gomez-Sanchez,2 Rohit Ranganath,3 Radhakrishna Baliga,1 1LSU Health Shreveport, Shreveport, LA; 2The University of Mississippi Medical Center, Jackson, MS.**

**Introduction:** Aldosterone-producing adenoma (APA) is a rare clinical entity in the pediatric population resulting in severe hypertension and/or hypokalemia. Limited number of cases have been reported with somatic KCNJ5 mutation being described in only one case. We report a case of a somatic CACNA1D mutation more prevalent in the male black patients unlike KCNJ5 which is considered the most frequently mutated gene in black females.

**Case Description:** A 16-year-old black female was noted to be hypertensive while being evaluated for diabetes. She was referred to us a year later for recurrent headaches, chronic drug resistant hypertension and persistent hypokalemia. Family history was positive for a maternal uncle with hypertension. On examination, her wt was 98 kg [>99%], ht 178 cms [94%], heart rate 88 per minute and blood pressure 155/94 mmHg [95%]. Pertinent labs: serum sodium 142, potassium 2.8, chloride 106, and CO2 content 26 mEq/L. Serum creatinine was 0.80, and BUN 10 mg/dL. Plasma aldosterone concentration (PAC) was 27.2 ng/dL and plasma renin activity (PRA) [0.6 ng/mL/ h with PAC/PRA ratio of 45 [significant > 20]. Cortisol level was 8.7 [N 1-7.14] mg/dL. Timed urine aldosterone for estimated urine creatinine of 1980 mg was 20 ng/dL [N <15.6]. Cardiac echocardiogram showed compaction cardiomyopathy. CT abdomen indicated a right adrenal nodule suggesting an adenoma. Robotic right adrenalectomy was performed and pathology was consistent with APA. Blood and right adrenal tissue was sent for germline and somatic mutations. Post-operatively PAC was <3.0 ng/dL. Her headaches resolved, her blood pressure significantly improved to 124/89 mmHg with normalization of her serum potassium. One month after right adrenalectomy her blood pressure continues to be well controlled on two antihypertensive medications and her serum potassium levels remain normal.

**Discussion:** Unilateral APA should be considered in any child who presents with drug resistant hypertension and/or hypokalemia as early diagnosis and prompt adrenalectomy would prevent significant cardiovascular sequelae. The identification of somatic and germline mutations will provide further insight into the mechanisms of APA and assist in tailoring appropriate therapy especially in blacks who have high cardiovascular disease morbidity and mortality.

**PO203**

**Rare Case of Atypical Hemolytic Uremic Syndrome in a Child**

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**Introduction:** Atypical hemolytic uremic syndrome (aHUS) is rare with an incidence of 0.26-0.75 cases/million/year for individuals less than 20 years of age. Little is known about the course of the disease and its clinical episodes. Individuals typically harbor genetic mutations and/or complement autoantibodies.

**Case Description:** A 7-year-old male presented with 2 weeks history of fatigue, pallor, and emesis. Laboratory findings were consistent with HUS; serum creatinine 1.35 mg/dL, hemoglobin 7.5 g/dL, and platelets 86 thou/mcL. Schistocytes were identified on peripheral smear. Stool culture was negative for O157 STEC. Stool PCR was positive for Shigella Enteroaggregative E. coli. e.coli STEC PCR was negative. Patient was hemolysis dependent. Given severity of his course and persistent evidence of hemolysis and thrombocytopenia at 5 weeks, Eculizumab was initiated with improvement of hematological parameters. Laboratory workup was done at the same time and came back positive for homoygous deletion of CFH3-CHR1 and complement factor H (CFH) autoantibodies (2140 AU). Eculizumab was continued for 8 doses with additional 2 doses of Rituximab followed by Mycophenolate Mofetil (MMF) before transition to Ravalizumab which was discontinued after 7 doses. He remained on MMF with no evidence of relapse. He has continued to be off dialysis 11 months after cessation of Ravalizumab at CKD stage III.

**Discussion:** To our knowledge, this is the first published pediatric case with CFH autoantibodies that achieved partial kidney recovery after prolonged dialysis dependent course. aHUS should be considered in children with severe and prolonged course of HUS even if laboratory results are suggestive of STEC-HUS. Aggressive therapy should be considered even if patients are dialysis dependent as this may reverse the course of the disease. There is limited published data on the course and effect of complement blockade therapy (Eculizumab or Ravalizumab) and immunosuppression (Rituximab and MMF) on the course of aHUS due to C3 and factor H autoantibodies. There are variable reports on the efficacy of other therapies, like plasmapheresis, on the course of this specific aHUS entity. Our case highlights the importance of considering these therapies in this population even after prolonged dialysis as this may alter the course of the disease and help kidney recovery.

**PO204**

**Prenatal Nephrology Consultations and Neonatal Dialysis Survey**

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**Background:** Little is known about pediatric nephrology (PN) prenatal consultations for congenital anomalies of the kidney & urinary tract (CAKUT) or possible initiation of kidney replacement therapy (KRT) in neonatal end stage kidney disease (N-ESKD).

**Introduction:** The purpose of this study was to determine the prevalence of prenatal nephrology (PN) consultations for congenital anomalies of the kidney & urinary tract (CAKUT) or possible initiation of kidney replacement therapy (KRT) in neonatal end stage kidney disease (N-ESKD).

**Methods:** A cross-sectional web-based survey was administered to pediatric nephrology fellows associated with the American Society of Pediatric Nephrology. Three invitations were sent from May 3, 2021 to May 28, 2021. The survey was distributed to fellows who had participated in a PC rotation during fellowship, and 46.4% of respondents completed a rotation in medical school or residency. On a scale of 1-5, with 1 being ‘no knowledge’ and 5 being ‘extensive knowledge’ of PC principles, fellows reported a mean knowledge of 2.33 ± 1.04. A single fellow had performed over 10 family meetings to elicit goals of care compared to 64.3% of fellows who had performed over 10 kidney biopsies. A quarter of fellows had never led such a meeting. Confidence in ability to discuss goals of care or address psychological distress in a child with CKD or parent were low, with only 30.8% and 26.9%, respectively, feeling moderately or very confident in their ability. Many fellows (44%) felt low confidence in managing pain in a child with CKD. A desire for additional training was prevalent, with 96.2% of fellows indicating that this training should happen during fellowship.

**Conclusions:** Few pediatric nephrology fellows receive PC education and experiences during training, resulting in low rates of knowledge and confidence across care domains. Fellows indicate a need and desire for improved PC training.

**Funding:** Other NIH Support - Dr. House is supported by a National Institutes of Health training grant (5T32DK007662-30, PI Hingorani).
The aims were to evaluate PN practice patterns for prenatal counseling of fetal CAKUT & to describe criteria used by PN to offer KRT in N-ESKD.

Methods: A 35 question Qualtrics® survey was distributed via the North American Pediatric Renal Trials and Collaborative Studies email list between 1/1/2021-3/31/2021. 39 of 108(36%) participating pediatric sites in the US & Canada responded. Median number of faculty (MDs, APPs, APRNs) per center was 7. Median chronic hemodialysis (HD) and peritoneal dialysis (PD) patients per center were 8 & 8, respectively. Of those 38 centers, 71% report only a select number of non-trainee workforce members. Only 50% of centers use written/unwritten criteria for decisions about KRT initiation in N-ESKD. The most common contraindications to KRT was parental refusal (61%;Table 1). The most common birth weight contraindication was <1500g(52%). 82% of centers reported <5 neonates with ESKD were started on KRT within the past year. 58% of centers use HD therapies as a bridge to PD in N-ESKD(Figure 1); 100% of centers report PD as the primary modality at discharge.

Conclusions: Many PN programs provide prenatal consultations for CAKUT diagnoses by a select group of non-trainee workforce members. Only 50% of centers use written/unwritten criteria for decisions about KRT initiation in N-ESKD. Further multi-center research regarding prenatal consultations and neonatal KRT outcomes is necessary to provide greater evidence based practice.

Table 1: Reported contraindications to dialysis initiation in neonates with ESKD amongst surveyed PN centers (n=38 centers)

<table>
<thead>
<tr>
<th>Condition</th>
<th>% of Centers Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parental refusal</td>
<td>61%</td>
</tr>
<tr>
<td>Birth weight &lt;1500g</td>
<td>52%</td>
</tr>
</tbody>
</table>

Figure 1: Reported use of hemodialysis/CRRT/IRRT/modified Aquapheresis as a bridge to PD initiation in the neonate with ESKD (n=38 centers)

PO2016

Impending Uremic Cardiac Tamponade in an Infant with ESKD


Introduction: Uremic pericarditis (UP) occurs in patients with advanced chronic kidney disease (CKD) prior to dialysis initiation. The incidence of UP is rare due to advances in CKD management by providing adequate and early dialysis. Additionally, it is extremely rare in children. We present a case of a toddler with advanced CKD presenting with UP and impending cardiac tamponade. Daily intensive hemodialysis resulted in a complete resolution of the pericardial effusion.

Case Description: A 2-year-old female presented with a 3-day history of dry cough and low-grade fever. Her medical history was significant for CKD stage 5 related to branchio-oto-renal dysplasia. Her physical examination was remarkable for increased respiratory rate and the presence of pericardial friction rub. A chest radiograph demonstrated enlargement of the cardiac silhouette. An electrocardiogram (ECG) showed sinus rhythm without ST-segment changes and an echocardiogram demonstrated a large circumferential pericardial effusion. The following day, she developed low oxygen saturation and a repeat echocardiogram demonstrated features of early tamponade physiology. Pericardiocentesis was considered but not performed because the amount of apical fluid was deemed insufficient to safely perform the procedure. Daily intensive hemodialysis was initiated and resulted in a complete resolution of the pericardial effusion within a week.

Discussion: Our case of UP in a pediatric patient is exceptionally rare. The most common presentations of this condition are fever, chest pain, and pericardial friction rub. As seen in this case, a characteristic ECG in UP does not show the diffuse ST and T wave elevations often seen in other forms of pericarditis. UP is an absolute indication for dialysis which usually results in rapid resolution of the pericardial effusion.
PO2017
When Less Is More: Phosphate Homeostasis Insights from a Micrillus Inclusion Disease Patient
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Introduction: Micrillus inclusion disease (MVID) is a rare, severe congenital secretory diarrhea caused by recessive MYO5B or STX3 mutations. Multiple cases of MVID with partial proximal tubule (PT) defects are reported (mostly hyperphosphaturia). While MYO5B is expressed in PT cells, MVID patients have normal PT brush border on kidney biopsy, and the PT defect resolves after intestinal transplant. Therefore, it is unlikely that the MYO5B genotype is causally related to the proximal tubulopathy.

Case Description: A 10-year-old patient with MYO5B-MVID, our patient required cyclized total parental nutrition (TPN). She was referred to nephrology at age 2 for persistent hypophosphatemia despite escalating TPN phosphate (PO4) content, and nephrocalcinosis. Urinary PO4 wasting was confirmed given the low (<65%) tubular reabsorption of phosphate (TPR). FGF-23 and PTH were elevated. A 24 h balance study (on/off TPN) revealed that TPR was lowest and FeNa highest (~2%) while on TPN (these values were improved after 6h without TPN). It also confirmed that the negative PO4 balance was only due to renal losses. We hypothesized that high TPN electrolyte concentrations caused an obligate phosphaturic response. Gradual reductions of TPN sodium (Na+) (by 13%), then TPN PO4 (by 70%) over 4 mo led to normalization of serum PO4 (Figure), TPR (83-91%) and FeNa (~0.3%).

Discussion: We propose that excessive TPN Na+ and PO4 promoted a strong phosphaturic response: the combination of several physiologic factors likely explains this unusual phenomenon. Of interest, the intermittently negative TPR suggest that tubular phosphate secretion must have contributed to the massive phosphaturia. A counterintuitive reduction in TPN Na+ and PO4 reduced renal PO4 wasting without impacting serum Na+. We surmise that other MVID cases of PO4 wasting were also probably due to unusually high TPN electrolyte concentrations. Detailed balance studies are invaluable tools to assess complex fluid/electrolyte disorders.

PO2018
Occurrence of Nephrogenic Systemic Fibrosis with Group II Gadolinium-Based Contrast Agent in a Pediatric Oncology Patient with AKI
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Introduction: Nephrogenic Systemic Fibrosis (NSF) is a rare systemic disorder occurring in patients with chronic kidney disease (CKD) stage IV or V, end-stage renal disease (ESRD), or acute kidney injury (AKI). It is triggered by gadolinium-based contrast agents (GBCAs) and characterized by sclerodermic skin changes from fibrosis and internal organ damage. Almost all NSF cases are associated with group I GBCAs, and only extremely rare, unconfounded cases are reported with group II agent exposure including none in children. We present a case of a female child with acute myelogenous leukemia (AML) in remission and AKI on hemodialysis who presented with NSF six years following a magnetic resonance imaging (MRI) with group II GBCA.

Case Description: A 19-year-old female with intermediate risk AML in remission, complicated by prolonged neutropenia with colitis, invasive fungal sinus and pulmonary infection, and AKI with a renal biopsy-proven acute tubular necrosis on intermittent hemodialysis three times a week presented to the dermatology clinic for evaluation of progressive hardening of her skin. Dermatological examination revealed diffuse, indurated, and compressible plaques involving the lower back, buttocks, posterior thighs, and lateroposterior aspects of the arms. A skin biopsy showed findings consistent with NSF. Six weeks prior to her presentation, she underwent an MRI of the brain and orbits for ependymoma and received intravenous gadobutrol injection, a group II GBCA. Treatment with photopheresis twice weekly over a 2-month period resulted in a gradual improvement of her condition.

Discussion: Our case of group II GBCA induced NSF is exceptionally rare, with no published cases from group II GBCA exposure reported to date. While NSF has been reported rarely in children who received group I GBCAs, the risk of NSF in children exposed to group II or even group III GBCAs is unknown. We strongly recommend that physicians continue kidney function screening prior to group II GBCAs administration in children and carefully evaluate the risk versus benefit of using or withholding group II GBCAs for clinically indicated MRIs in patients with CKD stage IV/V, ESRD, or AKI.

PO2019
Exploring Population Pharmacokinetic Models in Patients Treated with Vancomycin During Continuous Venovenous Hemodiafiltration (CVVHDF) on Different Anticoagulant Modalities
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Background: Achievement of target concentrations for antibiotics using therapeutic dose monitoring (TDM) is particularly challenging in septic patients requiring renal replacement therapy.

Methods: We conducted an exploratory population pharmacokinetic (PK) analysis in our tertiary level intensive care unit (ICU) on PK of vancomycin following intermittent infusion in critically ill patients receiving continuous venovenous haemodiafiltration (CVVHDF). Clinical, laboratory and dialysis data were extracted from the electronic healthcare record (EHR) using strict inclusion criteria. A population PK analysis was conducted with a one compartment model using the PMetrics population PK modelling package. A base structural model was developed and further analyses were performed with clinical and dialysis-related data, including regional citrate anti-coagulation (CVA) or non-CVA, to improve model prediction through covariate inclusion. The final selected model simulated patient concentrations using probability of target attainment (PTA) plots to investigate the probability of different dosing regimens achieving target therapeutic concentrations.

Results: 107 vancomycin dosing intervals (155 levels) in 24 patients were examined. An acceptable base model was produced (Plots of observed vs. population predicted concentrations (Obs-Pred) R2=0.78). No continuous covariates explored resulted in a clear improvement over the base model. Use of anti-coagulation modality and vasopressor use as categorical covariates resulted in similar PK parameter estimates, with a trend towards lower parameter estimate variability both with use of CVA and without vasopressor use. Simulations using PTA plots suggested that a 2 g vancomycin loading dose followed by 750 mg 12 hourly as a maintenance dose, commencing 12 hours after loading, is required to achieve adequate early target trough concentrations (>15 mg/L).

Conclusions: Using robust EHR data to construct a base model from a population known to have highly heterogeneous antimicrobial PK, simulations based on PTA plots showed that we could achieve acceptable trough vancomycin concentrations early in treatment with a 2 g loading dose and a maintenance dose of 750 mg 12 hourly for ICU patients on CVVHDF.

PO2020
Evaluation of Gabapentinoid Dosing and Adverse Events in Patients with Advanced CKD
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Background: Gabapentinoids (GP, gabapentin and pregabalin) are frequently prescribed in individuals with chronic kidney disease (CKD); however, their exclusive renal elimination warrants dose adjustments to decrease the risk of toxicity. Data to describe prescribing patterns and incidences of adverse events in advanced CKD is limited. This study evaluated prescribing patterns for GPs and whether excessive dosing was associated with increased incidence of gabapentinoid-related adverse events (GRAEs).

Methods: A retrospective analysis of adult patients admitted to the Methodist LeBonheur Healthcare system from January 2014 – October 2020 with CKD stage 4, 5, or end-stage kidney disease (ESKD) receiving GPs prior to admission or during hospitalization for at least two days was conducted. Patients were grouped based on whether the average daily dose prescribed was higher than recommended [inappropriately dosed, (ID)] or as recommended [appropriately dosed (AD)] for CKD stage. The occurrence of GRAEs (altered mental status, respiratory depression, and falls) was compared between groups. Patient characteristics and CKD stage were evaluated to determine any association with GPs. Hospital length of stay (LOS) was also evaluated.

Results: The 200 patients included were predominantly female (51%), black (72%), CKD 5/ESKD (84%) with a mean age 61±14 years, and prescribed gabapentin (90%) with 111 (55%) in the AD group and 89 (45%) in the ID group. Baseline characteristics were similar between groups except type 2 diabetes and neuropathy were more common in the ID group. For the primary outcome, there was no statistically significant difference in GRAEs (18% vs. 19%, p=0.84). GRAEs were associated with older age (mean age 65±11 years for GRAEs vs. 60±14 years for no GRAE; p<0.001) and seizure history (14% for GRAEs vs. 6% for no GRAE; p=0.02), but not with CKD severity. LOS was significantly longer for patients who experienced a GRAE than for those who did not (8.5 vs. 5.3 days; p=0.04).

Conclusions: In patients with advanced CKD, appropriate dosing of gabapentinoids is important to minimize the risk of adverse events, particularly in patients of older age or with a history of seizures. There is a need for prescriber education given the high frequency of inappropriate gabapentinoid dosing in patients with advanced kidney disease.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO2021

Chronic Dosing of Voclosporin at Clinically Relevant Exposure Levels Does Not Induce Renal Fibrosis Markers in Rats

Background: Although prognosis of lupus nephritis (LN) has improved, the long-term outcome is still poor, with many patients progressing to end-stage renal disease. Calcineurin inhibitors (CNIs) like cyclosporine A (CsA) and tacrolimus have demonstrated benefit in LN; however, prolonged use is associated with renal fibrosis. CsA-induced fibrosis has largely been in the context of high doses required for immunosuppression in transplant patients. Voclosporin (VCS), a potent, novel CNI with a predictable PK/PD profile, is approved for treatment of LN. This study tested the hypothesis that the clinically effective dose of VCS used in LN patients, would not induce fibrosis markers in the chronic dosing rat model compared to CsA and vehicle controls.

Methods: Sprague Dawley rats (n=10/group) on a low sodium (0.05%) diet were treated by oral gavage (QD) with VCS (4 mg/kg), cyclosporine A control (10 mg/kg) or vehicle control (5 mL/kg) for 3 or 6 weeks. Clinical chemistry was performed on serum, and overnight urine. Gene expression (RT-qPCR) and histology were performed on kidneys. Data were analyzed as change from baseline.

Results: There were no significant differences in clinical measures of renal or liver function. There were no significant changes in urine protein/creatinine or fractional excretion. Serum total bilirubin and cholesterol were significantly increased in the CsA treated group compared to vehicle and VCS. At 3 weeks, there was a significant decrease in expression of Tgfb1 and the epithelial-mesenchymal transition (EMT) marker Cadh2 (N-cadherin) in VCS treated animals compared to vehicle and CsA, and significant decreases in expression of the EMT regulators, Snail (SNAIL) and Snai2 (SLUG), and the extracellular matrix components (ECM) Col1a1, Col3a1 and Vim in the VCS treated group. At 6 weeks, trends between groups remained, and there were significant decreases in Tgfb2 and Col3a1 in the VCS treated group. At 6 weeks, there were no differences in renal histopathology.

Conclusions: This study shows that the clinically relevant dose of voclosporin does not induce renal fibrosis markers in rats, in contrast to the CsA control. Additionally, voclosporin may protect against renal EMT and fibrosis, which is associated with CsA. Collection of data from a two-year-continuation renal biopsy sub-study of AURORA-1 is ongoing.

Funding: Commercial Support - Aurinia Pharmaceuticals Inc.

PO2022

The Effect on Renal Function of Patients on HIV Pre-Exposure Prophylaxis (PrEP)
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Background: Tenofovir, a nucleotide reverse transcriptase inhibitor, is used in management of hepatitis B and as part of a highly active antiretroviral medication regimens for HIV infected individuals. Tenofovir disoproxil fumarate (TDF) is one of two tenofovir nucleotide analog. The U.S. Food and Drug Administration (FDA) recommended on 16 July 2012 the use of tenofovir-emtricitabine combination medication as pre-exposure prophylaxis (PrEP) against HIV. TDF is cleared through glomerular filtration and tubular secretion. Its nephrotoxicity includes renal tubular acidosis type 2, acute tubular necrosis, and tubulointerstitial disease. Reported data regarding effect of renal function from tenofovir based PrEP are less than 24 months of follow-up. This study evaluates the effect on renal function in patients receiving TDF for PrEP over more than 24 months because it can affect the future of PrEP with more expensive analog of tenofovir (TAF) promoted as less nephrotoxic and other PrEP medications.

Methods: VA San Diego database on adults receiving PrEP is the source for this data. Serum creatinine and estimated glomerular filtration rate (eGFR) are obtained as part of PrEP protocol which started in 2014. The PrEP protocol follows the Centers for Disease Control and Prevention (CDC) recommendations of pre-initiation serum creatinine and the PrEP protocol which started in 2014. The PrEP protocol follows the Centers for Disease Control and Prevention (CDC) recommendations.

Results: Since 2014, 103 individuals are in the PrEP program. At one year, there are 87 participants and none meet the criteria for AKI. After 2 years, there are 73 participants and 2 meet the criteria of AKI. Their kidney function returned back to baseline creatinine one month later. 55 individuals completed 3 years on PrEP and none meets the criteria for AKI. 41 individuals completed 4 years of PrEP and none meets criteria for AKI. The average change of eGFR at one year is 7.1%, 7.5% at 2 years, 8.6% at 3 years and 8.1% at 4 years.

Conclusions: Serum creatinine is stable on PrEP and none meet KDIGO AKI definition. The decrease in eGFR is not significant to warrant a change of TDF based PrEP.

PO203

Tenofovir Kidney Clearance Predicted by Glomerular and Tubular Secretory Functions

Background: Proximal tubule secretion is the primary kidney mechanism for eliminating most prescribed medications. Yet, kidney drug dosing is based on estimates of the glomerular filtration rate (GFR). In an empiric pharmacokinetic study, we compared pharmacokinetic measurements of endogenous secretory solutes for predicting the kidney elimination of tenofovir disoproxil fumarate (TDF), a drug with complex kidney handling.

Methods: We recruited 27 adult patients across a wide range of kidney function. Exclusion criteria were use of tenofovir or a secretory antagonist (cimetidine, digoxin, probenecid, diltiazem, diazepam, or fosinopril). We administered a single 125mg oral dose of TDF and estimated its kidney clearance from the area under the plasma time concentration curve and urine drug recovery. We measured GFR by iohexol clearance (GIFR) and estimated secretory function from a 10-hour urine collection with mass-spectrometry measurements of endogenous secretory solutes. We used linear regression, leave one out cross-validation, root mean squared error, and mean percentage error to describe agreement between kidney functions and TDF clearance.

Results: Mean age of the study population was 55 ±15 years, 63% were male, and mean GFR was 78 ml/min/1.73m² (IQR 52, 99 ml/min/1.73m²); ten participants (37%) had an GIFR <60 ml/min/1.73m². The mean percentage error (MPE) between observed and GIFR-predicted TDF kidney clearance was 26.7% (Table). The clearances of four endogenous secretory solutes improved the prediction of TDF clearance beyond that of GIFR: cinnamoylglycine, indoxyl sulfate, isovaleryl glycine, and tiglicyglycine. Combining solute clearance and GIFR results in a lower overall mean percentage error in TDF kidney clearance prediction.

Conclusions: Measurements of secretory solute clearance represent a potential future strategy for improving kidney drug dosing.

Funding: NIDDK Support

PO204

Subcutaneous VIS649, an APRIL-Neutralizing Antibody: Preliminary Pharmacokinetic (PK) and Pharmacodynamic (PD) Results of VIS649-102, a Phase 1, Single Ascending Dose Study in Healthy Volunteers
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Background: Immunglobulin A (IgA) nephropathy (IgAN) is in part driven by A proliferation-inducing ligand (APRIL). VIS649, a humanized immunoglobulin G (IgG2) monoclonal antibody that blocks APRIL, is currently in Phase 2 clinical development as a potential treatment for IgAN. The preliminary results of VIS649-102, a Phase 1 single ascending dose study of subcutaneously (SC) administered VIS649 in healthy volunteers is reported here.

Methods: VIS649 (200 mg/ ml) liquid was administered as a single dose via the SC route to four cohorts of 12 healthy adult volunteers each. Doses were 200 mg (1x1 mL SC), 400 mg (2x1 mL SC injections), 400 mg (1x2 mL SC injection), and 600 mg (2x2 mL SC injections). Studies show bioavailability of approximately 75% compared to intravenous (IV)-administered VIS649 (Y. Suzuki et al, ERA-EDTA 2021). Single SC doses of either 400 mg or 600 mg suppress total IgA by up to approximately 50-55% from baseline values at 8 weeks post-dose. This is a dose of 200 mg per 1 mL SC injection. Currently, 8 weeks post-dose.

Results: SC-administered VIS649 was well tolerated, with no adverse events that led to study discontinuation, and no injection site reactions. Treatment Emergent AE’s (TEAEs) were all mild and all resolved. There was no clinically relevant effect of treatment on laboratory tests, vital signs or physical examinations. Preliminary PK results show bioavailability of approximately 75% compared to intravenous (IV)-administered VIS649 (Y. Suzuki et al, ERA-EDTA 2021). Single SC doses of either 400 mg or 600 mg suppress total IgA by up to approximately 50-55% from baseline values at 8 weeks post-dose. Overall, these preliminary results with SC VIS649 indicate a similar degree and
trajectory of IgA suppression as that achieved by the IV formulation in healthy volunteers, in which all patients were pre-treated with IgA by approximately 50% from baseline values at 8 weeks post-dose (Figure 1).

Conclusions: Preliminary results of this Ph1 study of SC-administered VSY649 demonstrated acceptable safety, tolerability, and bioavailability, and suppressed total IgA by approximately 50-55% from baseline, comparable to IV doses.

Funding: Commercial Support - Visterra Inc, Otsuka Pharmaceuticals Inc

Figure 1. Total IgA Mean Percent Suppression From Baseline Following Single Dose VSY649 Administered Via SC or IV Route

PO2025

Association of Oxypurinol Exposure with Progression of CKD: Pre-Specified Substudy Results from the CKD-FIX Trial

Poster

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Background: The CKD-FIX trial evaluated the effect of allopurinol on eGFR slope over 104 weeks in patients with chronic kidney disease (CKD) and risk of progression. The aim of this pre-specified sub-study was to assess whether exposure to oxypurinol, the active metabolite of allopurinol, predicts change in eGFR.

Methods: Adults with CKD stage 3 or 4 (n=369), no history of gout, and high risk of progression (urinary albumin-to-creatinine ratio ≥ 265 mg/g or eGFR decrease ≥ 3.0 mL/min/1.73 m2 in the preceding year) were randomized to receive allopurinol (n=190) or placebo (n=184). Plasma oxypurinol concentrations were determined at weeks 16, 24, 40, 56, 72, 88 and 104 post-initiation of allopurinol. Non-compartmental pharmacokinetic analysis of oxypurinol concentrations was performed to determine oxypurinol exposure (area under the concentration-time curve) using the SimBiology module of MATLAB. The association between eGFR slope and oxypurinol exposure was assessed using least-squares estimates linear regression.

Results: Overall 155 (84%) patients (mean eGFR 31.7 mL/min/1.73 m2, mean serum urate 8.0 mg/dL) received allopurinol and had a plasma oxypurinol concentration available. At the end of the 12-week dose-escalation phase, the majority of patients (123; 79%) were prescribed allopurinol 300 mg and the remainder 100 mg (13; 8%) or 200 mg (19; 12%). The mean (standard deviation) eGFR slope and reduction in serum urate concentration were -3.32 (5.02) mL/min/1.73 m2/year and 2.6 (0.14) mg/dL, respectively. Based on a total of 319 plasma oxypurinol concentrations (median n=6 per patient), there was no correlation between eGFR slope and total oxypurinol exposure (P=0.93), including after adjusting for allopurinol dose (P=0.99). These results were consistent across the three allopurinol dosing regimens. Greater oxypurinol exposure was associated with larger reduction in serum urate concentrations (P<0.0001).

Conclusions: In CKD-FIX participants, exposure to oxypurinol was not associated with change in eGFR. However, reduction in serum urate concentration was dependent on plasma oxypurinol exposure.

Funding: Private Foundation Support, Government Support - Non-U.S.

PO2026


Poster

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Background: Background: High urinary oxalate levels (UOx) in patients with enteric hyperoxaluria (EH) can lead to recurrent kidney stones, nephrocalcinosis and chronic kidney disease. SYN8802 is an engineered E. coli Nissle 1917 that contains an oxalate overproducer. This strain seeks proof-of-concept in patients with enteric hyperoxaluria.

Methods: In Part A of this study [NCT04629170] hyperoxaluria was induced in adult kidney transplant recipients with history of hyperoxaluria and with serum urate levels ≥ 8 mg/dL and ≤ 16 mg/dL. Patients were randomized to receive SYN8802 (3x11 live cells/dose) or placebo, up to 18 months post-dose.

Results: In Part A, a well-tolerated dose of 3x11 live cells/dose was identified in HV. At this dose, the percent change from baseline UOx levels was -28.6% (90% CI: -42.4 to -11.6) compared to placebo in diet-induced hyperoxaluria. This dose is being studied in Roux-en-Y patients with hyperoxaluria in Part B. The results from the RYGB population will be reported.

Conclusions: These results provide proof of mechanism for UOx lowering by GI consumption of oxalate in diet-induced hyperoxaluria. Part B seeks proof-of-concept in patients with enteric hyperoxaluria.

Funding: Commercial Support - Sylogic Inc.

PO2027

Tacrolimus Induces Ligand-Independent TGF-β Receptor Signaling to Promote Renal Fibrosis

Poster

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Background: Although calcineurin inhibitors (CNIs) such as tacrolimus and cyclosporin A dramatically improved the quality of patient care, long-term therapy causes irreversible damage to the kidneys in the form of renal fibrosis. These morphologic changes ultimately lead to a decline in renal function and can progress to end-stage renal failure. These detrimental outcomes present a critical need to identify mechanisms by which CNIs cause renal damage. It is well established that TGFβ is a major contributor to CNI-induced renal fibrosis. However, the underlying mechanisms remain unknown. The objectives of this study are to 1) investigate whether TGFβ secretion is required to stimulate TGFβ receptor signaling in a model of CNI-induced renal fibrosis and 2) investigate whether calcineurin plays a critical role in regulating TGFβ receptor activation.

Methods: To examine the role of calcineurin inhibition in altered TGFβ receptor signaling, wild type mice were treated with either vehicle (100% ethanol) or 10 mg/kg tacrolimus for 7 days. To confirm in vivo findings, wild-type mouse renal cortical fibroblasts were treated with either vehicle (100% ethanol) or 10 µM tacrolimus for 24 hours in the presence and absence of anti-TGFβ neutralizing antibodies. TGFβ receptor expression and activation, TGFβ receptor downstream signaling mediators, profibrotic markers and calcineurin activity were analyzed.

Results: Findings demonstrated that calcineurin-inhibited loss of calcineurin activity is accompanied with enhanced TGFβ receptor activation and signaling. Notably, increasing concentrations of anti-TGFβ neutralizing antibodies failed to abolish aberrant TGFβ signaling and increased expression of profibrotic markers.

Conclusions: Together, these results demonstrate that 1) CNIs promote ligand-independent TGFβ signaling and 2) calcineurin plays a functional role in regulating TGFβ receptor activity.

Funding: NIDDK Support, Other U.S. Government Support

PO2028

Immuneautoimmunity of CD3+CD4+ in Stable Young, Middle Aged, and Elderly Kidney Transplant Recipients Receiving Maintenance Tacrolimus and Mycophenolic Acid Immunosuppression

Poster

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Background: Tacrolimus and mycophenolic acid are the standard of care in most stable kidney transplant recipients (KTR) at U.S. transplant centers. However, there are limited data that determine within subject immunophenotypic responses over the adult age range. This study examined ex vivo immunoreactivity of CD3+CD4+ lymphocytes in stable young, middle age and elderly KTR receiving tacrolimus and mycophenolic acid.

Methods: Fifteen stable KTR greater than 1 yr post-transplant completed a 12-hour study with serial collections at pre-dose (t0) 3, 4, 8 and 12 hours. The immune repertoire as measured was evaluated by Interferon-2 (IL-2) and TGFβ reporter production by CD3+CD4+ T cells after ex-vivo treatment with PMA/lonomycin with Brefeldin-A. Data was represented as within individual, timed collection and the mean for all time points of ex-vivo stimulation by cell sub-populations stratified by young, middle age and elderly. Comparisons were made using Kruskal-Wallis test.

Results: Table summarizes the major findings. There were no group differences between tacrolimus and mycophenolic acid troughs with all tacrolimus troughs within the therapeutic range. Increased IFNγ from CD3+CD4+ T cells was quantitated by ex vivo mycophenolic acid immunoreactivity in middle age recipients at the 4 and 8 hours during the 12-hour study period. No significant differences were noted for interleukin-2 quantitated from CD3+CD4+ T cells.

Conclusions: These data indicate increased IFNγ from CD3+CD4+ T cells for ex vivo mycophenolic acid over a 12-hr dosing interval in middle age KTR receiving long-term maintenance immunosuppression. Variable immunodynamics and the implications of intra- and interpatient variability in immunoreactivity across the range of adult KTR require further investigation of clinical and allograft outcomes.

Funding: Other NIH Support - National Institute of Aging
PO2029

Urinary Proteomics and Effects of Dagapilozin Treatment in Persons with Type 2 Diabetes and Kidney Disease

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Background: About 40% of persons with type 1 (T1D) or type 2 diabetes (T2D) develop diabetic kidney disease (DKD) posing a major economic burden on health care systems. Sodium Glucose Co Transporter 2 inhibitors (SGLT2i) have emerged as a novel treatment option for T2D and DKD. Although the kidney-protective effects of SGLT2i are well documented, the mechanisms remain unclear. The current study aims to investigate SGLT2i function through urinary proteomics.

Methods: A double-blinded, randomized, placebo-controlled, crossover trial comprising 36 persons with T2D was treated with 10 mg of dapagliflozin for 12 weeks or matching portion of placebo on top of their standard diabetes treatment at the Steno Diabetes Center Copenhagen, Denmark. All participants had albuminuria (UAER > 30 mg/g) and received RAAS medication. Clinical factors like BMI, blood pressure (BP), estimated glomerular filtration rate (eGFR), LDL and HDL cholesterol, were measured at baseline, and after trial. Changes in clinical factors were modelled using linear mixed effects model adjusting for relevant clinical covariates. Urinary proteomics data in pre and post treatment groups (n=32) were analyzed using paired Mann Whitney U test. Multiple testing correction was performed and p < 0.05 was considered significant. We further verified whether identified peptide levels differed significantly between T1D DKD vs. healthy controls (n=210) and performed pathway enrichment analysis with STRING database.

Results: Trial participants had a mean (SD) age of 63.8 (8) years, 88% males, diabetes duration 15.9 (4.7) years, BMI 33.7 (5.4) kg/m², HbA1c 8.8 (1.2%) median (IQR) UACR 154 (94–329), eGFR 85.5(19.1) ml/min/m², respectively, 19 proteins significantly changed after treatment. Type I and III collagen α1 (I), (II), and (III) chains, α2-HS-glycoprotein, and polymeric immunoglobulin receptor peptides increased while albumin, α1–antitrypsin, and αβ–glycoprotein peptides decreased multifold. This was reflected in the DKD-control cohort.

Conclusions: The identified differential urinary peptide patterns in response to SGLT2i (Dagapilozin) treatment on individuals with T2D and DKD. Extracellular matrix organization, inflammation, coagulation, renal fibrosis, and wound healing pathways were enriched. We suggest the involvement of expected and novel proteins.

PO2030

Antifibrotic Effects of Low-Dose SGLT2-Inhibition in Comparison to Standard Angiotensin II Receptor Blockade in 5/6 Nephrectomised Rats

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Background: The kidney is an important target organ and the glomerular filtration rate (GFR), as well as the systemic blood pressure (SBP) are key determinants of the progression of renal failure. Using high salt diet (HSD), as follows: Sham operation (Sham) with sodium and placebo; 5/6 Nx with 2% HSD and placebo; 5/6 Nx with HSD and empagliflozin (0.6 mg/kg/day, bid); 5/6 Nx with HSD and telsiramitin (5 mg/kg/day, qd).

Results: Empagliflozin treatment increased urinary glucose excretion in parallel to empagliflozin plasma levels in a dose-dependent manner starting at doses of 1 mg/kg. 5/6Nx rats on HSD treated with this low empagliflozin dose showed significantly reduced cardiac (-34.85%; p<0.05) and renal (-33.68%; p<0.05) fibrosis in comparison to 5/6Nx rats on HSD and placebo. These antifibrotic effects were comparable to the effects of a standard dose (5mg/kg/day) of telsiramitin (cardiac fibrosis: -36.37%; p<0.01; renal fibrosis: -43.96%; p<0.01). RNA-sequencing followed by confirmatory qRT-PCR revealed that both telmisartan and empagliflozin exert their cardiac effects on genes involved in vascular cell stability and cardiac iron homeostasis, whereas in the kidneys expression of genes involved in endothelial function and oxidative stress were differentially expressed. Urinary adenosine excretion, a surrogate marker of the tubuloglomerular feedback (TGF) mechanism, was not affected.

Conclusions: The antifibrotic properties of low dose empagliflozin were comparable to a standard dose of telsiramitin. The underlying pathways seem to be TGF independent.

Funding: Commercial Support - Boehringer Ingelheim Pharma GmbH & Co. KG

HIF Prolyl-4-Hydroxylase Inhibitor AKBX27922 Induces Cellular Metabolic Adaptation

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Background: Inhibition of prolyl-4-hydroxylase (PHD) enzymes leads to the stabilization of hypoxia inducible factor (HIF) and the expression of HIF target genes. Because of effects on erythropoiesis, several PHD inhibitors are undergoing clinical evaluation for the treatment of anemia with chronic kidney disease. However, the impact on other biological functions is not well investigated. We demonstrate that AKBX27922, a novel small molecule PHD inhibitor, can shift cellular metabolism from mitochondrial oxidative phosphorylation to glycolysis, mimicking adaptation to hypoxia.

Methods: Inhibition of PHD enzymatic activity was determined using the time-resolved fluorescence resonance energy transfer assay. HIF 1α stabilization in Hep3B cells was measured by meso scale discovery technology and protein expression of HIF target genes by enzyme linked immunosorbent assay. Oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) were measured in HepG2 cells with the Seahorse technology. Pharmacodynamics of the formulation were confirmed in vivo.

Results: In vitro, AKBX27922 potently and in a concentration-dependent manner, and without chelating iron, inhibited PHD1 and PHD2 enzyme activity, leading to HIF 1α stabilization and expression of HIF target genes implicated in erythropoiesis, angiogenesis, cell survival, and cell survival. Pretreatment of HepG2 cells with AKBX27922 dose-dependently reduced both basal and maximal OCR without affecting cellular viability, while ECAR was significantly increased. Reactive oxygen species production in human primary renal epithelial cells was decreased. In vivo, AKBX27922 stabilized HIF in the liver and kidneys, as measured by luciferase activity in the oxygen-dependent degradation domain (ODD)-luciferase reporter mouse. In rats, AKBX27922 induced time-dependent stabilization of HIF1α in the kidney medulla and papilla, and increased expression of glycolysis related (ALDOC, CAR9, PDK1, PFKFB4, LDH1) and other HIF-target genes (PPO, ADAM, HMox-1) in the kidneys and liver.

Conclusions: PHD inhibitor AKBX27922 mimics hypoxia, leading to HIF-driven metabolic adaptation. This novel small molecule will be useful as an in vitro and in vivo research tool for additional mechanistic studies that probe the pleotropic biology of HIF.

Funding: Commercial Support - Akebia Therapeutics, Inc.

PO2031

Comparative Kidney-on-Chip Toxicity Assessment in Human, Rat, and Dog Kidney Tissue Chips


Background: The projected market comprises of the development of a kidney proximal tubule (KPT) microphysiological system (MPS) from human cells as well as two experimental animal species that are typically used in kidney toxicity screening: rat and dog. These KPT-MPS may serve as an important new tool in chemical toxicity screening, allowing cross-referencing animal-based MPS data within vivoanimal data and with human-based MPS data and clinical outcomes. It also has the potential to result in a significant reduction of the use of live animals in studies.

Methods: The Nortis chip is made from silicone in a polycarbonate casing and is designed to use the “mandrel” method for generating channels within a 3D extracellular matrix using retractable small glass fibers. The fibers serve as starting points for generating tubular tissue structures, such as vessels or kidney tubules. The chip is compatible with high-quality imaging, tissue sampling, and up- and down-stream fluid collection. Multiple publications have documented the suitability of the Nortis system to generate functional human KPTs and how well they resemble the function of in vivo tubules. All KPT-MPS experiments were accompanied by 2D controls for comparison, using a traditional culture dish system. To assess viability of tissue, Live-Dead staining assays were run on canine tubules with Calcein-AM (live) and the nucleic acid stain ethidium homodimer I (dead), the results of which indicated sufficiently viable tubules. Confocal imaging and 3D rendering of these tubules demonstrates presence of key ion and drug transport proteins in their respective basolateral and luminal domains.

Results: Preliminary studies have shown that rat and canine derived KPT-MPS in the Nortis platform produce structurally viable tissue structures that elicit injury markers in response to nephrotoxic insults using in vivo relevant toxic compounds in a differential manner.

Conclusions: Our preliminary data suggests that Nortis kidney chip allows for an ideal predictive platform for comparative toxicity studies, allowing for fast and highly predictive preclinical simulations.

Funding: Other NIH Support - NCATS
PO2033

Forced Saline Diuresis Successfully Treats Lithium Intoxication
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Background: Forced 0.9% normal saline (NS) diuresis (FSD) is not advised by poison control centers for lithium intoxication (LIT) but in papers in 1% & 7.8% showed 350 - 500 mL/hr of FSD treated LIT at 4mEq/L successfully. We studied all pts with LIT over 10 years with both acute (A) overdoses and chronic (C) LIT to compare FSD in both groups to pts requiring hemodialysis (HD).

Methods: We found 20 LI pts seen over 10 years. Our team uses NS at 200-500 mL/hr as FSD in pts w/o CRF. 9 pts had Acute overdoses of L & 5 had C LIT due to reduced gift, ACE drugs or NSAIDS. These 14 got FSD, 200-500 mL/hr until L was < 1 mEq/L. 6 pts needed HD due to severe toxicity (seizures, coma, hypotension). We compared & showed the mean +SEM values for peak L level mEq/L, GFR calculated by the Cockcroft-Gault equation, the rate of L decrease in mEq/hr, the normalized rate of L decrease in mEq/24 hr & time in hrs to reach a L level of 1.0 mEq/L amongst the 3 groups.

Results: The mean peak L levels were: FSD A LI, 2.8±0.2 (range, 2.3-4), FSD C LI, 2.8±0.4 (range, 2.4-2), HD LI 3.5 ± 0.4 (range, 1.8-4.9). There were no differences in L levels. The mean GFR was: FSD A LI, 127±11, FSD C LI, 66±17, HD LI 142±7, p<.05 FSD C LI vs FSD ALL or HD LI. The GFR was significantly lower in the C LI pts. The hourly rate of L decrease in mEq/hr was: FSD A LI, 0.13±0.3, FSD C LI, 0.05±0.1, HD LI, 0.22±0.4. There was no difference in the rate of L decrease in FSD A LI & HD LI but both were much faster than FSD C LI, p<.05. The mean 24 hour decrease (mEq/L) in L was: FSD A LI, 3.1±2.2, FSD C LI, 1.1±0.2, & HD LI, 5.3±1.6. p<.05 FSD C LI vs FSD A LI or HD LI. The time to L level of 1 mEq/L was: FSD A LI, 14.4±1.3 h, FSD C LI, 36±4.3 h, HD LI, 11.5±2.3 h due to rebound after HD. There was no difference in the time to normal L between FSD A LI & HD but FSD C LI was much slower than FSD LI. Linear regression of the rate of L decrease compared to the hourly rate of NS in FSD A LI pts showed greater decreases in L level with greater rates of FSD, r = 82, p=.006. No pt had a serum Na > 145 mEq/L.

Conclusions: FSD with NS at rates of 200-500 mL successfully treats A LI and rates of L decrease in the NS approximates to HD for LI C LI can be treated with FSD but the rates of L decrease are slower possibly due to lower GFRs in these pts. This is the first study in 40 years showing efficacy of FSD LI.

Funding: Clinical Revenue Support

PO2034

Snow White and the Apple: When Drugs Become Poisons
UMASS/Baystate, Springfield, MA.

Commonly used drugs can cause significant toxicity in unfavorable clinical scenarios. We present a case of a pregnant female on a high dose of baclofen which led to significant neurotoxicity as her GFR dropped during an episode of acute pancreatitis.

Case Description: A 29-year-old pregnant Caucasian Female presented to an OSH with abdominal pain of a day’s duration. She was obese and had DM-II, hypertension as well as HD 0 a brain tumor treated when she was 10 years old. She was 29 weeks pregnant. Abdominal pain was sharp, epigastric and radiating to her back with nausea and vomiting. She was found to have severe acute pancreatitis. Her kidney function was normal (creatinine 0.5 mg/dl) on admission but on hospital day 2 it rose to 1.5 mg/dl and was at 2.3 mg/dl the next day. On hospital day #2 she became obtunded without response to naloxone and flumazenil. She was transferred to our hospital. She was comatose with neck muscle spasms. Neurotoxicity due to baclofen was suspected and urgent CVVH was started to treat renal failure. On admission, she was placed on this standing dose and at the same time lost GFR due to poisoning of her kidneys.

After 36 hours of baclofen poisoning, the patient and baby were spared neurotoxic sequelae. Prolonged dialysis may be required to remove baclofen and treat neurotoxic manifestations. This was the more important in the case due to risk of fatal neurotoxicity. It was a careful review of records of medicines dispensed at the OSH that helped clinch the diagnosis clinically, subsequently confirmed with elevated baclofen levels demonstrated on a send out test.

PO2035

Efficacy of Pi-Binder Lanthanum Carbonate in Reversing Systemic Effects of a High-Phosphate Diet in Mice
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Background: Modulating dietary inorganic phosphorus (Pi) is particularly important for patients suffering from chronic kidney disease (CKD) as excess Pi consumption and subsequent elevated serum Pi levels can lead to significant health problems, including increased mortality. Recent data now suggests that high Pi consumption might also have negative health outcomes even in those with clinically normal renal function. The predominant clinical therapy to reduce serum Pi and related health complications of CKD patients is orally administered Pi-binders with meals, including the commonly used Lanthanum Carbonate (LaC). Our study assessed the strategy of binding Pi in the gut to reduce health consequences of a high Pi diet including changes in bone volume, Pi-responsive circulating factors, and gene expression in the kidney.

Methods: Healthy 10-Week-old, female C57BLK/J mice were fed diets with varying Pi for 5 weeks, Low Pi (LDP, 0.2% Pi), Normal Pi (NP, 0.6% Pi), High Pi (HPD, 1.3% Pi), and HPD supplemented with LaC (3%). All diets contained 0.6% Calcium, similar protein, Kcals, and fat%. Circulating Pi-responsive factors (FGF23, OPN) were measured by ELISA, bone volume by micro-computed tomography, and gene expression in the kidney by quantitative real-time (qRT) PCR.

Results: HPD resulted in increased serum FGF23 and OPN, decreased bone volume (trabecular, cortical), and significant changes in kidney gene expression of inflammatory protein Nf2, Pi responsive Klotho, vitamin D synthesis Cyp27b1, and Pi-transporter Pi-MT1. LaC completely reversed HPD-induced increase in circulating Pi-responsive factors, and gene expression changes in the kidney but did not alter HPD-induced bone loss.

Conclusions: The clinically used Pi-binder LaC only reversed certain HPD-induced consequences, suggesting a multifactorial mechanism, and therefore may require a therapeutic strategy beyond reducing gut Pi-absorption. Decreasing Pi consumption was substantially more effective at minimizing physiological repercussions like bone loss. Changes in kidney gene expression after a sustained HPD also reveal potential long-term consequences on kidney health/function in otherwise healthy individuals. Given divergent claims concerning LaC binder efficacy, our study shows LaC corrects some but not all—effects of a high Pi diet.

Funding: Veterans Affairs Support, Private Foundation Support

PO2036

A Meta-Analysis Evaluating the Effect of Sacubitril-Valsartan on Renal Function in Heart Failure Patients

Background: Cardiorenal syndrome (CRS) has been associated with increased morbidity and mortality in heart failure (HF). Sacubitril-Valsartan is the first-in-class angiotensin receptor-neprilysin inhibitor which has been found to reduce all-cause mortality in HF with reduced left ventricular ejection fraction. The effect of sacubitril-valsartan on renal outcomes is unknown. This meta-analysis analyzes recent studies comparing Sacubitril-Valsartan and RAS inhibitors in heart failure patients.

Methods: We performed a comprehensive literature search for all eligible studies comparing Sacubitril-Valsartan and RAS inhibitors in PubMed, EMBASE, SCOPUS, and Google Scholar. Only recent clinical trials were included. All retrospective studies were excluded. Clinical outcomes comprised of all-causes mortality and renal complications.

Results: 5 Randomized clinical trials (RCT) were deemed eligible, which consisted of 7325 sacubitril-valsartan patients and 7333 RAS inhibitor patients. Meta-analysis confirmed that Sacubitril-Valsartan was associated with reduced all-cause mortality (OR = 0.87, p < 0.00001). There was no observed statistically significant differences in in- hospital mortality, HF hospitalization, composite renal outcomes, and HF hospitalization.

Conclusions: Sacubitril-Valsartan reduces the risk of all-cause mortality, diminished renal function, and hyperkalemia compared with RAS inhibitors. Further evaluation is required.
PO2037
Combination Therapy of Neprilysin Inhibitor with AT2R Agonist C21 Provides Superior Renoprotection Compared to its Combination with AT1R Antagonist Valsartan in High-Sodium Diet-Fed Obese Zucker Rats
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Background: The neprilysin (NEP) inhibitor sacubitril (SAC) combined with the angiotensin II type 1 receptor (AT1R) blocker valsartan (VAL) (i.e. Entresto) is clinically approved for the treatment of heart failure (HF) associated with reduced ejection fraction, owing mainly to its ability to preserve atrial natriuretic peptide (ANP), a substrate of NEP. However, many HF patients treated with Entresto have presented with increased albuminuria. We have reported that the agonist of angiotensin II type 2 receptor (AT2R) Compound 21 (C21) prevents proteinuria and is renoprotective in obese Zucker rats (OZR) fed high sodium diet (HSD). Thus, we hypothesized that SAC/C21 combination provides superior renoprotection compared to the current SAC/VAL therapy.

Methods: Male OZR 10-11 wks. old were treated daily via oral gavage with vehicle, SAC (10mg/kg/day) + C21 (21mg/kg/day), or SAC (10mg/kg/day) + VAL (10mg/kg/day) while fed HSD (4%) for 16 days.

Results: Untreated HSD-fed OZR showed reduced plasma ANP and increases in renal cortical Ang II (all p<0.05 vs OZR-fed 0.4% normal sodium diet (NSD)). These changes were associated with a modest increase in kidney weight and kidney dysfunction, evident by increased proteinuria, and reduced urinary excretion of urea nitrogen and creatinine (all p<0.05 vs OZR-fed NSD). Other indices of renal injury include increased cortical expression of nephrin (p<0.05 vs OZR-fed NSD), podocin, megalin, albuminuria, and increased urinary osteopontin (OPN). Treatment with SAC/C21 significantly prevented increases in renal Ang II, proteinuria, albuminuria, nephrin expression and kidney weight (all p<0.05 vs OZR-fed HSD), while SAC/VAL did not affect these parameters. Furthermore, SAC/C21 prevented the decline in the excretion of urinary creatinine and decreased urinary OPN (all p<0.05 vs SAC/VAL). Moreover, SAC/VAL therapy increased plasma renin concentrations –3-fold compared to OZR-fed HSD and SAC/C21.

Conclusions: Together, this study suggests that combination therapy with SAC/C21 afforded superior renoprotection compared to SAC/VAL therapy in HSD-fed OZR.

Funding: NIDDK Support

PO2038
Is Basal Nitric Oxide Activity of the Renal Vasculature Altered? Analysis of a Randomized Controlled Trial Comparing Two Combination Therapies
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Background: Recently we demonstrated that a combination therapy with empagliflozin and linagliptin in patients with type 2 diabetes mellitus (T2DM) induce changes in renal hemodynamics. The purpose of this study was to analyze the influence of basal nitric oxide (NO) activity of the renal vasculature on the described changes of the renal hemodynamic profile.

Methods: In this study patients with T2DM were randomized to receive either empagliflozin and linagliptin (E+L group, n=50) or metformin and insulin glargine (M+I group, n=46), for 3 months. Renal hemodynamics were assessed with constant-infusion input-clearance technique with p-aminohippuric acid and inulin at baseline and after treatment. Due to withdrawal of inulin from the market during the study, glomerular filtration rate and filtration fraction (FF) were measured only in a sub-group of patients (E+L: n=34; M+I: n=31). Intraglomerular hemodynamics were calculated according the model established by Gomez. The basal NO activity in the renal circulation has been assessed by analyzing change in renal plasma flow (RPF) in response to intravenously administered NG-monomethyl-L-arginine (NO inhibitor).

Results: After 3 months of treatment, we did not observe any change in basal NO activity compared to baseline in either of the groups. In the E+L group, we found a correlation between basal NO activity of the renal vasculature after 3 months of treatment and change in RPF (r=−0.535, p<0.001), renal blood flow (r=−0.468, p=0.001) and renal vascular resistance (r=−0.377, p=0.007) induced by treatment. Similar correlations with change in FF (r=0.639, p=0.001), preglomerular (r=−0.350, p=0.046) and postglomerular resistance (r=−0.588, p=0.001) have been found. No such relationships were found in the M+I group after 3 months and with basal NO activity at baseline in both treatment groups.

Conclusions: Basal NO emerged as a determinant of the renal hemodynamic response in the combination therapy of empagliflozin and linagliptin, but not in the combination therapy of insulin and metformin.
Preserved Kidney Allograft Function and Unique Urinary Biomarker Profiles in Living Donor Kidney Transplant (LDKT) Patients Tolerized with an Investigational Allo-Hematopoietic Stem Cell Transplantation Therapy

**Methods:** The protocol was based on tolerogenic CD8+ TCRαβ-facilitating cells (FCR001), nonmyeloablative conditioning and enrollment agnostic to the degree of HLA mismatch. Tacrolimus/MMF based immunosuppression (IS) was weaned and discontinued at one year if durable chimerism and normal kidney function and transplant biopsy were confirmed.

**Results:** Durable chimerism enabled complete withdrawal of IS in 26/37 patients. Comparison of clinical outcomes in FCR001 and a SOC cohort showed comparable patient survival and graft survival at two, three and five years. Cardiovascular medication safety and durability of immune tolerance and graft function. We are currently enrolling patients identified a potential signature of tolerance, characterized by increased levels of CTLA4 mRNA, and a higher ratio of CTLA4 mRNA to mRNA for granzyne B and perforin mRNA. If validated, such a signature of tolerance might help identify kidney transplant patients in whom reduction of IS drugs might be safely undertaken. To date, we have accumulated approximately 235 patient-years of exposure to FCR001 in LDKT, and the safety profile is consistent with that expected if a patient were to receive both a kidney transplant and an allo-HSC with nonmyeloablative conditioning.

**Conclusions:** We continue to monitor the patients in the Phase 2 trial for long-term safety and durability of immune tolerance and graft function. We are currently enrolling patients in FREEDOM-1, a randomized, controlled, open-label Phase 3 trial in the US in adult LDKT recipients.

**Funding:** Commercial Support - Talaris Therapeutics

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**Urinary T Cell Subsets and Tubular Epithelial Cells as Biomarkers for Kidney Transplant Rejection**

**Methods:** Urine samples of 275 KT patients were analyzed. Cell population were quantified in 125 and 125 cases by epigenetic analyses and FC, respectively. Professional diagnoses from renal biopsies served to uniquely group graft deterioration into borderline rejection (BR), T cell mediated rejection (TCMR), and antibody mediated rejection (ABMR), other specific pathohistological diagnosis (other) or no rejection (NO RX). For FC analyses urine sediments were stained for T cells (anti-CD3, -CD4, -CD8, -CD45R0, +CD45, -CCR7, -HLA-DR, -CD28) and tubular epithelial cells (TECs) (anti-Cytokeratin, -Vimentin, -CD10, -CD13, -CD227, -CD26). Epigenetic qPCR approach was used to determine T cells and TECs based on specific DNA methylation patterns identified by bisulfite sequencing.

**Results:** Absolute numbers of urinary T cells and TECs discriminated patients with and without TCMR. Most strikingly in this regard were increased numbers of various T cell subsets observed by FC in patients with TCMR compared to patients without TCMR (p < 0.001 for FCR001-DR+ T cells and effector memory T cells) whereby CD8+ HLA-DR+ T cells were most distinctive (p = 5.1e-07, AUC = 0.866-0.967). Epigenetic analyses qualitatively confirmed T cell and TEC quantities as determined by FC. Furthermore, the ratio of absolute numbers of T cells and TECs determined by epigenetic analyses discriminated patients with TCMR from those with other specific biopsy proven diagnoses than rejection, but individual T cell populations showed a higher sensitivity and specificity in segregating both TCMR vs other: CD8+ T cells p=5.1e-05, AUC 0.87 (CI 95% 0.77-0.98), CD3+ T cells/TEC p=0.004, AUC 0.78 (CI 95% 0.65-0.92); ABMR vs other: CD8+ T cells p=0.0041, CD3+ T cells/TEC p=0.04).

**Conclusions:** Urinary T cell subsets reflect intrarenal inflammation in TCMR. TECs mirror intrarenal damage accompanied by rejection. Jointly, they yield high potential to monitor KT patients and detect rejection.

**Funding:** Government Support - Non-U.S.

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**Elevation of Serum IL-8 in Patients with Hematopoietic Stem Cell Transplantation-Associated Thrombotic Microangiopathy**

**Methods:** We measured the concentrations of several different cytokines and vasoactive peptides in the sera of 14 adult human HSCT recipients at the time of transplantation and again at 5-6 weeks following HSCT. Levels of IL-8, IL-6, IL-8, TNF-α, IFN-γ, VEGF-B, HGF were measured, using the highly sensitive ELISA single molecule array (Simoa) method.

**Results:** Statistical analysis of the change in each of the cytokines revealed that IL-8 was the sole marker that increased significantly over time in the TMA group. Next, we found that co-culture of irradiated peripheral blood mononuclear cells (PBMCs) with human umbilical vein endothelial cells (HUVECs) resulted in increased IL-8 expression by the PBMCs. Furthermore, in vitro treatment of HUVECs with IL-8 increased platelet adhesion and vWF expression. Treatment of platelets independently with IL-8 also increased their adhesion in vitro to HUVECs. Finally, treatment of HUVECs with IL-8 also induced senescence, and platelets were found to adhere more readily to senescent HUVECs in vitro. Moreover, exposure of these HUVECs to a senolytic agent abrogated the platelet adhesion.

**Conclusions:** These findings implicate IL-8 as a potentially important thrombogenic and pathogenic factor in TMA. In addition, these data highlight senescence of endothelial cells for the first time as a possible mechanism for the microvascular thromboses observed in TA-TMA patients, suggesting that modulation of IL-8 could be an effective therapeutic pathway for this severe disease.

**Funding:** NIDDK Support, Other NIH Support - NIAID
Results: One week following KT, median quantities of total ccfDNA were elevated ~2-fold over the reference value during the first month. At month 3, a 1.6-fold increase was observed, which normalized to the reference value over the first year post-KT. In contrast, the absolute quantity of dd-ccfDNA was initially elevated ~100-fold above the reference (1.06 RU/ml post-KT, which normalized over the first year). A time-dependent profile where it remained stable. The elevation in ccfDNA during the first week is likely due to trauma to the donor organ from surgery. Additionally, a significant elevation in both total and dd-ccfDNA was observed in patients who received a kidney from a deceased donor as compared to a living donor.

Conclusions: Total and dd-ccfDNA levels are highly dynamic in the first year post-KT but stabilized afterwards. Further investigation is needed to determine the causes of total-ccfDNA increases at months 3 and 4. Potential factors include inflammatory responses and NETosis, viral infection or transient interstitial fibrosis and tubular atrophy (IF/TA) in the kidney. The time dependent dynamics were statistically significant, but not on high coefficient of variance (CV>50%), which limits extrapolations to individual patients. Potential variability should be considered when interpreting dd-ccfDNA tests performed within the first week post-KT.

PO2046
p53 Is Activated in Cold Storage/Transplantation to Mediate Tubular Injury and Renal Graft Dysfunction
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Background: Kidney injury associated with cold storage/transplantation is a leading cause of delayed graft function and poor outcome of renal transplants. p53 has been implicated in both ischemic and nephrotoxic kidney injury, but its involvement in kidney cold storage/transplantation is not clear. This study aimed to investigate the role of p53 in cold storage/transplantation kidney injury and test the therapeutic effects of p53 inhibition.

Methods: Donor kidneys from C57BL/6 mice were preserved in ice-cold University of Wisconsin (UW) solution for 0.5, 2, 6 or 8.5h and transplanted into syngeneic recipients for 24h. Tubular injury, cell death and p53 activation were observed and their correlations were assessed. The acute response of kidneys from pifithrin-α and DMSO (the vehicle solution) treated mice was examined and compared, as well as response of kidneys from p53 conditional knock out (KO) mice and their wild type (WT) littermates.

To explore the therapeutic potential of p53 inhibition, pifithrin-α was also administered to test its effect on graft injury and function on day 6, when the graft became the sole life-supporting kidney after native kidney removal at day 5. Rat kidney proximal tubule cells (RPTCs) were incubated in UW solution at 4°C for cold storage, followed by full medium replacement at 37°C for rewarming. Pifithrin-α was added to UW solution or dominant negative p53 was transfected into RPTCs, for the purpose of evaluating their effect on RPTCs death in cold storage/rewarming.

Results: p55 was activated in kidney tubule cells during cold storage transplantation, which correlated with tubular injury and cell death. Pifithrin-α significantly reduced acute tubular injury, cell death and inflammation during cold storage/transplantation. Similar effects were shown by ablation of p53 specifically from kidney proximal tubule cells. p53 conditional knock out (KO) rats eliminated kidney injury and improved the function of transplanted kidneys as the life-supporting graft. In RPTCs, cold storage followed by rewarming induced cell death and p53 activation. Both pifithrin-α and dominant-negative p53 could attenuate RPTC cell death during cold storage/rewarming.

Conclusions: p53 plays a critical role in kidney injury and dysfunction during cold storage/transplantation. p53 inhibitors may provide therapeutic benefits for donor kidney preservation and transplantation.

Funding: NIDDK Support, Veterans Affairs Support

PO2047
Multi-Omics Analysis Reveals Regulatory Mechanisms in Chronic Cyclosporine A-Induced Nephrotoxicity Studied in a Rat Model

Background: Chronic calcineurin inhibitor (CNI) nephrotoxicity is a major drawback in current immunosuppressive regimens. In the chronic setting, arteriolar hyalinosis, decreased glomerular filtration rate, interstitial fibrosis and tubular dedifferentiation are the major adverse side effects. Regimens with cyclosporine A (CsA) and tacrolimus (Tac) have been compared before the background of potentially more harmful effects of CsA. Conversely, CsA is still widely used in transplant recipients and has been considered for replacement of Tac in posttransplant diabetes. To identify regulatory mechanisms in CNI nephrotoxicity we used quantitative transcriptomic, proteomic and phosphoproteomic methods. We tested the hypothesis that tubulointerstitial pathomechanisms play a significant role in chronic CNI nephropathy.

Methods: Whole transcriptome RNA-seq as well as global proteomic and phosphoproteomic methodologies were performed on kidney extracts from normal Wistar rats receiving CsA (25mg/kg b.w./day) or vehicle for 3 weeks. Differentially expressed genes were compared before the background of potentially more harmful effects of CsA. Conversely, CsA is still widely used in transplant recipients and has been considered for replacement of Tac in posttransplant diabetes. To identify regulatory mechanisms in CNI nephrotoxicity we used quantitative transcriptomic, proteomic and phosphoproteomic methods. We tested the hypothesis that tubulointerstitial pathomechanisms play a significant role in chronic CNI nephropathy.

Results: CsA treatment stimulated genome-wide alterations in rat kidney according to the RNA-seq data. We identified 342 transcripts upregulated which included Ribosome and Oxidative phosphorylation pathways, whereas 331 transcripts were downregulated, with enrichment in genes critical for amino acid metabolism. Data were controlled by the established upregulation of renin and downregulation of calbindin in global proteomics. KEGG pathway and GO analysis from proteomics largely corresponded to the RNA-seq results. Upregulated proteins were further related to ECM-receptor interaction and focal adhesion pathways (padj<0.05). Phosphoproteomics demonstrated functional phosphorylation of components from unfolded protein response pathways, indicating an activation of the integrated stress response upon CsA.

Conclusions: In sum, using integrated -omics analysis in CsA nephrotoxicity proves to be a powerful approach. Chronic CsA treatment is associated with enhanced energy metabolism and activation of the unfolded protein response pathways. A tubulointerstitial focus has been demonstrated. Potential biomarker candidates have further been obtained and are currently verified in the rat model.
Calcineurin Inhibitor Nephrotoxicity as Viewed by Comparative Analysis of the Effects of Cyclosporine A vs. Tacrolimus on Epithelial Pathology in Rodent Models

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Background: Calcineurin inhibitors (CNI) are widely in use for immunosuppression in transplant recipients. Although essentially beneficial, their nephrotoxicity may cause or aggravate renal disease. We have challenged the hypothesis that the safety of the commonly applied CNI, cyclosporine A (CsA), and tacrolimus (Tac), differs regarding tubulointerstitial pathology. Mechanisms of proteostasis, autophagy and lysosomal dysfunction are addressed.

Methods: We have compared the effects of CsA and Tac in rat and mouse models. A focus was set on epithelial alterations. Adult Wistar rats received CsA (25 mg/kg/d), Tac (2 to 6 mg/kg/d), or vehicle via subcutaneously implanted minipumps. A megalin-deficient mouse model was tested for the role of endocytosis. After 4 wk, kidneys were prepared for histopathology or biochemical analysis.

Results: In rats, CsA and Tac produced similar alterations in the tubulointerstitium (Fig. 1). Preferentially the initial proximal tubule (S1, and S2 segments) was affected, displaying dysmorphic lysosomes with peripheral LAMP1 signal, autophagic and mitophagic vacuoles. Dedifferentiation was focally strong, with loss of brush border, basement membrane thickening, and interstitial collagen accumulation. Alterations in unfolded protein response (UPR) and autophagy parameters included significant increases in p-eIF2α, pPERK, CHOP, BiP, and LC3B, and ATG5 products and enhanced epithelial TUNEL signal. Endocytosis was substantially impaired. Cultured NRK cells indicated sensitivity to chemical chaperones ameliorating proteostasis and revealed similar apoptosis rates upon CsA and Tac.

Conclusions: These results suggest that alterations in tubular epithelial proteostasis upon long term CsA- or Tac-induced nephrotoxicity are similar. Addressing restitution of epithelial proteostasis may have renoprotective potential for both drugs.

Cyclosporine A but Not Tacrolimus Promotes Pro-Apoptotic Endoplasmic Reticulum Stress in Cultured Kidney Cells


Background: Current immunosuppressive regimen in organ transplantation include calcineurin inhibitors (CNI), cyclosporine A (CsA) or tacrolimus (Tac), as the first-line therapy. Both CNI may produce renal side effects, which are typically stronger in patients receiving CsA. Sustained clinical demand for CsA requires improved understanding of mechanisms underlying its nephrotoxicity. CsA builds complexes with cyclophilins, whereas Tac recruits FKBP12 for calcineurin inhibition. We hypothesized that cytotoxic effects of CsA may be related with impaired chaperone function of cyclophilins resulting in endoplasmic reticulum (ER)-stress and pro-apoptotic unfolded protein response (UPR).

Methods: Effects of CsA vs. Tac (10 µM for 6 h) on the UPR signaling were compared in cultured native HEK293 cells, as well as in genetically modified cells lacking critical ER-stress sensors, PERK or ATF6. An established ER-stress inducer, thapsigargin (Tg) served as a positive control.

Results: CsA and Tg, but not Tac, induced ER-stress and UPR in native HEK293 cells, which was reflected by increased abundance of key UPR products (CHOP, spliced XBP1, and phosphorylated IRE1α). Furthermore, CsA but not Tac increased the abundance of caspase 3(cCasp3) suggesting stimulated apoptosis. Similar to CsA, knockdown of cyclophilin A or cyclophilin B using siRNA augmented CHOP and cCasp3 levels. Deletion of PERK or ATF6 blunted the CsA-induced UPR. Furthermore, the CsA-dependent ER-stress was significantly reduced by concomitant application of chemical chaperones, TUDCA or 4-PBA.

Conclusions: In summary, these results suggest that renal side effects of CsA are partially mediated by suppression of cyclophilins, ER-stress, and pro-apoptotic UPR. Pharmacological modulation of UPR bears potential to alleviate the CsA nephrotoxicity.

Funding: Government Support - Non-U.S.
Results: Unsupervised hierarchical clustering identified a subset of patients with increased pro-inflammatory cytokine levels (Figure a, cluster 2). This patient subset (N=20) was hallmark by high prevalence (75%) of donor-specific anti-human leukocyte antigen antibodies (HLA-DSA) (Figure b) and histological rejection (70%), and had worse graft survival compared to the group with low cytokine levels (N=172, HLA-DSA in 1.7% and rejection in 33.7%). Serum C-reactive protein and polymavirus and/or CMV viremia did not differ between the two clusters. Thirty percent of patients with high pro-inflammatory cytokine levels and HLA-DSA did not have histological rejection. Single-cell RNAseq analysis on public data from kidney transplant biopsy demonstrated expression of these cytokines in endothelial cells, monocytes, and natural killer cells. We confirmed the inflammatory cytokine profiles in in vitro models of HLA-DSA-mediated crosstalk between endothelial cells, NK cells, and monocytes.

Conclusions: This is the first study implicating autoantibodies anti-Ro/SS-A and anti-La/SS-B, these antibodies were significantly increased in AMR/mixed rejection compared to ACR. Significant increases in IgG anti-Ro/SS-A and IgM anti-La/SS-B antibodies in AMR/mixed rejection with shedding of lipoprotein clearance receptor syndecan-1 and unfavorable cholesterol HDLc/HDLc ratio associated with neointima score in the transplanted kidneys (r=0.65; p=0.05) and with glomerulosclerosis (r=0.53; p=0.021), whereas non-HDLc/HDLc ratio associated with creatinine clearance, (all p<0.05 compared to baseline), along with glomerulosclerosis and arterial neointima formation. Saline-treated recipients developed hypertension, proteinuria, and loss of kidney function. There were significant increases in serum syndecan-1, albumin, and IgG anti-SS-A which were significant in AMR/mixed rejection compared to ACR/ATN.

Conclusions: The expression of pro-inflammatory cytokines is increased in peripheral blood of kidney transplant patients with circulating HLA-DSA, even in the absence of histopathology of rejection. These results challenge the vision that kidney transplant histology is the gold standard for identification of ongoing allo-immune processes.

Results: Increased autoantibodies against Ro/SS-A and La/SS-B are associated with AMR and may have a role in the induction of acute rejection.

Conclusions: Antibody-mediated rejection (AMR) causes >50% of late kidney graft losses. In addition to anti-HLA donor-specific antibodies (DSA), antibodies against non-HLA antigens are also linked to AMR. Identifying key non-HLA antibodies will improve our understanding of AMR.

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Methods: We analyzed non-HLA antibodies in sera from 80 kidney transplant patients with AMR, mixed rejection, acute cellular rejection (ACR), or acute tubular necrosis (ATN). IgM and Igs antibodies against 134 non-HLA antigens were measured in serum samples collected pre-transplant or at the time of diagnosis.

Results: Fifteen non-HLA antibodies were significantly increased (p<0.05) in AMR and mixed rejection compared to ACR or ATN pre-transplant, and seven at diagnosis. AMR and mixed cases showed significantly increased pre-transplant levels of IgG anti-Ro/SS-A and anti-CENP-B, compared to ACR. Together with IgM anti-CENP-B and anti-La/SS-B, these antibodies were significantly increased in AMR/mixed rejection at diagnosis. Increased IgG anti-Ro/SS-A, IgG anti-CENP-B and IgM anti-La/SS-B were associated with the presence of microvascular lesions and class-II DSA (p<0.05). Significant increases in IgG anti-Ro/SS-A and IgM anti-CENP-B antibodies in AMR/mixed rejection compared to ACR were reproduced in an external cohort of 60 kidney transplant patients.

Conclusions: This is the first study implicating autoantibodies anti-Ro/SS-A and anti-La/SS-B in patients with kidney allograft rejection.

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Results: RBT-9 exhibited moderate antiviral activity against BK virus under both treatment conditions. The 50% effective concentration (EC₅₀) averaged 5.5 μM in 2 independently run standard qPCR assays and 5.4 μM in the neutralization assay. The EC₅₀ of RBT-9 in these assays is 11 times lower than the highest dose of RBT-9 tested in Phase 1 studies and considered to be well tolerated. The 50% cytocidal concentration (CC₅₀) in the in vitro studies averaged 8.9 μM, indicating RBT-9 did not adversely affect host cell viability at concentrations 16.5 times higher than its effective concentration.

Conclusions: Given the antiviral activity of RBT-9 against BK virus in vitro and the safety profile of RBT-9 in Phase 1 human studies, a clinical study assessing the efficacy of RBT-9 is warranted in patients who are at risk of developing BK virus-induced nephropathy.

Funding: Other NIH Support - National Institute of Allergy and Infectious Diseases, Commercial Support - Renibus Therapeutics, Inc.

PO2056

The Survival Benefit of Re-Kidney Transplantation in Older and Younger Patients with Graft Failure

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Background: The survival benefit of re-kidney transplantation (re-KT) has been demonstrated two decades ago in younger patients. The proportion of patients with graft failure is increasing, particularly among those aged≥65. We compared the survival benefit of re-KT by patient age.

Methods: Using data from the Scientific Registry of Transplant Recipients, we listed for re-KT between 1990-2019. We treated re-KT as a time-dependent variable and compared the survival benefit of retransplant by patient age (listing at age ≥65 years) using a Wald test.

Results: Overall, 42,366 patients were listed for re-KT and 47.5% underwent re-KT by 10/31/2020. The number of patients being listed for re-KT tripled between 1990 and 2019. The mortality rate was 6.6 per 100 person-years among patients being listed and 3.0 per 100 person-years among those retransplanted. Overall, the risk of mortality was lower after re-KT than during listing (adjusted hazard ratio [aHR] = 0.43). However, the association differed by age (Pinteraction=0.03), but the survival benefit of retransplant was observed among both younger (aHR = 0.42) and older patients (aHR = 0.49).

Conclusions: Our finding suggests that re-KT is associated with a significant survival benefit in younger and older patients. In addition, long-term outcomes in older re-KT recipients were comparable to those in older first KT recipients. Transplant centers should consider expanding re-KT to appropriate older adults.

Funding: NIDDK Support, Other NIH Support - NIAID, NIA

PO2057

Development and Determinants of Quality of Life After Kidney Transplantation in Elderly Recipients


Background: Kidney transplantation is regarded as the best treatment for end-stage kidney disease, with survival benefits also in elderly patients. However, little is known regarding (determinants of) health-related quality of life (HRQoL), and changes in HRQoL in elderly kidney transplant recipients (KTR).

Methods: We used data from KTR ≥65 years old at the time of kidney transplantation, enrolled in the ongoing prospective TransplantLines Biobank and Cohort Study. Data on HRQoL were assessed using SF-36 mental and physical component scores (MCS and PCS). Side effects of immunosuppressive drugs were assessed using MTSOSD-59R questionnaires. In a subgroup with available data on HRQoL before transplantation, we investigated HRQoL trajectories.

Results: We included 111 KTR (age 70±4 years, 39% pre-emptive and 45% living donors). At one year after transplantation, eGFR was 48±16 ml/min/1.73m, MCS was 51.8, and PCS was 52.7. MCS was lower in females (P<0.018), and in KTR that suffered from rejection in the first year (P<0.005). PCS was higher in KTR that were pre-emptively transplanted (P<0.010) and lower in those with post-transplantation diabetes mellitus (PTDM, P=0.008). Number of side-effects of immunosuppressive drugs was strongly associated with both MCS and PCS (both P<0.001). Age, eGFR, hemoglobin, pre-transplant comorbidities, hospitalizations and infections in the first year were not associated with HRQoL. In 43 KTR with available data both before and after transplantation, PCS increased significantly after transplantation (48 to 52; Ppoint trend=0.001, Figure 1), while MCS did not significantly improve (49 to 51; Ppoint trend=0.095).

Conclusions: Medication-related side-effects, transplant rejection, transplantation after start of dialysis and PTDM were associated with worse HRQoL among elderly KTR, whereas eGFR and age were not. Moreover, HRQoL improves after kidney transplantation in KTR ≥65 years old.

PO2058

Elderly Kidney Transplantation Donors After Circulatory Death: Is It Worth It?

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Background: Kidney transplantation (KT) remains the treatment of choice for end-stage renal disease, since it offers better outcomes and quality of life and is less costly in the long run compared with stay on dialysis. In order to expand the donor pool, donation after circulatory death (DCD) has become an increasingly popular strategy, and eligibility criteria for this procedure have widened in the last few years.

Methods: Single-center retrospective study in which we described the clinical characteristics and outcomes of all the patients who underwent Maasricht category-III controlled DCD (cDCD) KT from January 2006 to October 2019. IBM SPSS (v25.0) was used for all the statistical analysis. Two-sided p values of <0.05 were considered statistically significant.

Results: We performed 54 cDCD KT, median follow-up was 36 (0.5-155) months. Donors’ mean age was 50.2 years (range 19-81), 20.4% were ≥70 years, 64.8% male, 22.2% diabetics, 25.9% suffered hypertension. 24 (44.5%) patients Presented delayed graft function and 6 (11.1%) suffered primary nonfunction, with no differences depending on donor age (p >0.70). Primary nonfunction was the main cause of graft loss, which occurred in 8 patients (14.8%) and it was significantly higher in donors ≥70 years old (p=0.021). In the multivariant analysis only donor age ≥70 years was related to graft loss. Other factors examined such as cold ischemia time >14 hours, warm ischemia time >17 minutes and the presence of cardiovascular disease, didn’t show statistically significant differences. At one-year follow-up, renal function was significantly better in donors ≥70 years compared to donors ≥70 years, with mean serum creatinine 1.4 vs 2.1 mg/dl respectively (p=0.003), and estimated filtration rate 36.4 ± 19.95 vs 18.9 ± 8.9 ml/min per 1.73 m² (p=0.008). The mortality rate was higher among recipients from older donors (3 [23.7%] vs 2 [4.6%], p=0.021).
PO2059

Immunosuppression, Osteoporosis, and Fractures in Younger and Older Adults After Kidney Transplantation

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Background: Osteoporosis and fractures are important complications among kidney transplant recipients (KTx) that may be exacerbated by immunosuppression (ISx) and aging. We examined relationships of osteoporosis and fractures with ISx among older and younger adults in a national sample of Medicare beneficiaries.

Methods: We examined USRDS data (2005-2017) to explore associations of ISx regimens (within 6 mo) with osteoporosis and fracture diagnoses >6 mo-to-3 yr post-KTx among Medicare-insured younger (age <55) and older (aged ≥55) adults. We used multivariate Cox regression with inverse propensity weighting to compare cancer risk vs reference regimen of Thymoglobulin (TMG) or Alemtuzumab (ALEM) + Tacrolimus + antimetabolite + prednisone.

Results: Among 67,362 KTx Medicare-insured recipients, the 3-year composite risk of osteoporosis and fractures varied by age and ISx regimen. Among older adults, incidence ranged from 11% with TMG/ALEM no Pred, to 16% in those managed with CsA and mTORi-based regimens (Fig A). In adjusted models, TMG/ALEM + no Pred was associated with lower risk (aHR, 0.84; 95% CI 0.80-0.88) than TMG/ALEM + triple therapy (Fig B). Conversely, mTORi-based regimens (aHR, 1.23; 95% CI 1.19-1.27) and CsA-based regimens (aHR, 1.17; 95% CI 1.14-1.21) were associated with greater risk. Patterns were generally similar but relative impacts were amplified in younger patients, including greater benefits of steroid-avoidance (aHR, 0.55; 95% CI 0.53-0.57).

Conclusions: Among Medicare insured KTx recipients, steroid avoidance after TMG/ALEM inductions is associated with reduced risk of fractures and osteoporosis. Fracture risk is a consideration in tailoring ISx in older KTx recipients.

Funding: NIDDK Support

PO2060

Organ Procurement and Transplantation Network Effort to Increase Kidney Transplantation Through Kidney Accelerated Placement

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Background: In 2017 just over a quarter of kidneys deemed hard to place were transplanted while the rest were discarded. The Kidney Accelerated Placement (KAP) project aimed to increase the acceptance of these deceased donor kidneys, declined by a large proportion of programs, through the creation of a novel allocation system. Offering hard-to-place kidneys to transplant centers with a history of transplanting similar organs, utilization would increase by reducing time to find an acceptor and cold ischemia time (CIT) within the deceased organ allocation process. We hypothesized CIT mediated the effect of KAP on transplant center organ-level offer acceptance.

Methods: We used a pre/post design mediation analysis with OPTN database offers from kidney matches meeting criteria for KAP 7/18/18-7/15/19 (pre-KAP) and 7/19/18-7/15/20 (KAP). We employed logistic regression models of KAP and CIT on organ acceptance and a linear regression model of KAP on CIT, adjusting for additional risk factors (Fig 1).

Results: Transplant center organ-level offer acceptance rates were 0.37% (pre-KAP) and 0.23% (KAP). The total effect indicates that KAP increased odds of acceptance by 0.07. Decreases in CIT increased odds of acceptance by 0.02 (indirect effect) and the remaining portion of the total effect is attributable to other possible mechanisms (direct effect).

Conclusions: While KAP affected offer acceptance, the magnitude of the effect was small. Because the baseline level of offer acceptance was also small, our analysis indicates that KAP works conceptually to increase the use of these kidneys. At the same time, there is evidence that alternative approaches to KAP are needed to potentially decrease organ discard. Future iterations plan to consider complex risk adjustment including behaviors and the differential impact for donor types.

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PO2061

A Geospatial Method to Improve Sociodemographic Characterization of Transplant Referal Regions

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Background: Progress towards health equity in kidney transplant requires robust characterization of transplant center referral populations. Transplant referral regions (TRRs) define geographic catchment areas for transplant centers in the United States and have previously been linked to sociodemographic data using ZIP codes. We compared a spatial intersection method to a ZIP code crosswalk method of linking sociodemographic data to TRRs.

Methods: A spatial intersection method was used to assign census block groups to TRRs based on area of intersection. We compared the spatial congruence of the spatial intersection and ZIP code crosswalk methods by calculating the number of census block groups assigned to more than one TRR and calculating the total area assigned to the incorrect TRR.

Results: We defined 105 TRRs for 238 transplant centers (figure 1a). The ZIP code crosswalk method resulted in 4,627 census block groups being included in more than one TRR, while the spatial intersection method eliminated this problem. The spatial method resulted in a mean and median reduction in misassigned area of 65% and 83% across all TRRs, respectively, compared to the ZIP code crosswalk method (figure 1b).

Conclusions: Characterizing TRRs with census block groups increases spatial resolution, and provides more balanced population counts. Our spatial approach avoids errors due to duplicative assignments and allows more accurate characterization of referral population sociodemographics. This approach can enrich transplant center knowledge of local referral populations, assist researchers in understanding the influence of social determinants of health on access to transplant, and inform interventions to improve health equity.

Funding: Other NIH Support - Research reported in this publication was supported by the National Institute on Minority Health and Health Disparities under Award Number U54MD012530, Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO2062

Association of Medicaid Expansion with Medicaid Uptake and Uninsurance Among US Kidney Transplant Recipients

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Background: The differential uptake of Medicaid expansion among U.S. states following the Affordable Care Act created a natural experiment to investigate the association between Medicaid expansion and health insurance usage patterns among kidney transplant (KT) recipients. Adolescents and young adults (AYA) are at particular risk for insurance access disruption.

Methods: Using data from the Scientific Registry of Transplant Recipients, we constructed a multivariable difference-in-differences model to evaluate the association between living in a state with Medicaid expansion (vs. a state without) and two outcomes: primary insurance of Medicaid at the time of KT, and becoming uninsured 5 years following KT. We included U.S. recipients of kidney-alone transplantation between 1/1/2005 and 3/31/2020. We analyzed AYA (ages 15-26 years) and other nonelderly adults (ages 27-64 years) separately.

Results: The AYA group included 17,158 KT recipients, while the group of adults 27-64 years included 198,914 KT recipients. The effect of living in a Medicaid expansion state (vs. a nonexpansion state) on use of Medicaid as the primary insurance type at the time of KT was +1.9% (95% CI 0.4% to 4.3%) for the AYA group and +1.7% (95% CI -1.1% to +2.1%) for the non-AYA adult group. The effect of living in a Medicaid expansion state (vs. a nonexpansion state) on being uninsured 5 years after KT was +3.6% (95% CI -6.5% to -0.7%) for the AYA group and -0.9% (95% CI -1.3% to -0.4%) for the non-AYA adult group.

Conclusions: Living in a Medicaid expansion state was associated with greater use of Medicaid at the time of KT for adults ages 27-64, but not in the AYA group. In both age groups, living in a Medicaid expansion state was associated with a modest reduction in being uninsured 5 years following KT. Increased access to Medicaid may provide a protective effect against becoming uninsured after KT.

Funding: NIDDK Support

Results of difference-in-differences analysis examining the association of Medicaid expansion with insurance outcomes among U.S. KT recipients.*

*Adjusted for gender, race/ethnicity, cause of kidney failure, year of KT, and state fixed effects.

PO2063

Construct Validity of the Patient-Reported Outcomes Measurement Information System (PROMIS®) Profile Summary Scores in Patients with Kidney Failure

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Background: The PROMIS® profiles include a single pain intensity item and 7 multi-item scales (e.g., physical function, fatigue, depression, social participation, etc.). These domains can be summarized into physical (PHS) and mental health summary (MHS) scores. We examine correlations of the PHS and MHS with the SF-12 physical (PCS) and mental component score (MCS), the Patient Health Questionnaire (PHQ-9), EQ-5D-5L, KDQOL-36 symptom scores, and serum albumin.

Methods: Cross-sectional convenience sample of 606 adults. Higher PHS and MHS scores correspond to better health. We estimated correlations of the PHS and MHS with the SF-12 physical (PCS) and mental component score (MCS), the Patient Health Questionnaire (PHQ-9), EQ-5D-5L, KDQOL-36 symptom scores, and serum albumin. The PHS was hypothesized to be strongly associated with other measures of physical health, and the MHS with other measures of mental health.

Results: Correlations with the PROMIS PHS and MHS (Table) with legacy health-related quality of life measures were large. The patterns of correlations of the PHS and MHS were consistent with a-priori hypotheses. Patients on dialysis were older (mean[SD] age 64[14] vs 50[15] years), and less likely to be White (32% vs 68%); p<0.01 for all. Kidney transplant recipients reported better health than patients on dialysis: PHS (mean[SD] 47[10] vs 37[9], p<0.001) and MHS (50[9] vs 45[9], p<0.001) and this remained significant in multivariable adjusted (age, sex, ethnicity, marital status, comorbidity, serum albumin and hemoglobin) regression models (coefficient [95% CI] of difference between dialysis and transplant for PH-5.9 [3.8-7.9]; for MH: 3.2 [1.0-5.3]; both p<0.01).

Conclusions: These results support the construct validity of PROMIS PHS and MHS scores among patients treated with kidney replacement therapies. PHS and MHS was substantially better among kidney recipients compared to patients on dialysis.

Table

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*Linear test for trend among categories of SPPB p <0.01

**Footnote: * : higher PHS and MHS indicates better health; higher PHQ-9 score indicates more severe depressive symptoms; the correlation is negative**

PO2064

Association of Physical Performance with Death or Delisting in Patients Waitlisted for Kidney Transplantation

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Background: Patients awaiting kidney transplantation (KT) often report impairments in functional status, which are associated with higher risk of death or delisting. However, self-reported functional status is subjective and can differ from objective assessments of physical performance. We sought to determine whether objective metrics of physical performance were associated with death or delisting prior to KT and whether these metrics improve prediction of death or delisting compared with more routinely available clinical data.

Methods: We enrolled 443 patients from the UCSF KT clinic from 12/17-3/20 at an initial or re-evaluation for eligibility for a first KT. We administered the Short Physical Performance Battery (SPPB; including gait speed, balance, and sit-to-stand) and measured grip strength by dynamometer. We performed univariable and multivariable Cox models to examine the association between physical performance and death or delisting. We created models using combinations of metrics in addition to a “base” model for death or delisting (age, sex, diabetes, CAD, CVD, PVD, years on dialysis) and calculated Harrell’s concordance index for each model.

Results: Median age was 55 years, and 63% were male. Median SPPB score was 10 (8, 11), with 25.1% having grip speed <0.8 m/s. In multivariable analysis, lower SPPB and slower gait were associated with higher risk of death or delisting, and higher grip strength with lower risk (Table 1). Compared with the base model (C-index 0.70, p=0.03) and SPPB + grip strength (0.75, p=0.03) improved discrimination.

Conclusions: SPPB, grip strength, and slower gait were associated with death or delisting. SPPB and grip strength improved prediction of death or delisting. Transplant centers should consider routinely evaluating physical performance for waitlisted patients to help with clinical decision making.

Funding: NIDDK Support

Association of physical performance with death or delisting among 443 patients evaluated for primary KT

*SPPB: 10-12 [ref], 7-9, 4-6, <4
**Linear test for trend among categories of SPPB p <0.01

***Adjusted for covariates in “base” model

Footnote: * : higher PHS and MHS indicates better health; higher PHQ-9 score indicates more severe depressive symptoms; the correlation is negative
PO2065
Development of a Conceptual Model to Understand Disease Burden in Kidney Transplantation
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1DRG Abacus (Part of Clarivate), London, United Kingdom; 2Novartis AG, Basel, Switzerland.

Background: While kidney transplantation offers patients with end stage kidney disease significant health benefits compared to dialysis, the immunosuppressive therapies designed to improve graft survival result in complex treatment regimens and side effects for patients. The development of new therapies to reduce this patient burden and improve long-term patient outcomes is needed. To guide selection of patient-reported outcome (PRO) measures for clinical trials, it is important to understand how patients feel or function related to a health condition or its treatment. This study sought to develop a preliminary conceptual model in kidney transplantation to provide a visual representation of the concepts of importance to patients (signs, symptoms, and impacts).

Methods: A targeted review of published literature was conducted in Embase, Medline, and PsyCINFO databases to identify qualitative articles describing the patient experience following kidney transplantation and associated use of immunosuppressive treatment. Studies were selected based on number of concepts and direct patient quotations available for thematic analysis.

Results: From 61 eligible publications identified for full-text review, 20 were selected for data extraction. All studies involved qualitative interviews, focus groups, or analysis with kidney transplant recipients, and were conducted across various geographic locations (US, Europe and Australia). The most frequently reported concepts across studies included: ‘feeling anxious/worried’ (100%, n=20); ‘feeling distressed, overwhelmed’ (75%, n=15); ‘fatigue’ (60%, n=12); and ‘weight gain/loss’ (60%, n=12). The conceptual model identified nine domains to group the concepts as reported in the literature. These domains were delineated into the proximal effects of kidney transplantation (side effects and illnesses; physical/cosmetic changes; functional limitations; taxing medication regimen; and frequent medical appointments); and the more distal impacts (impacts on emotions, work, lifestyle, and relationships).

Conclusions: The conceptual model was based on a rich source of patient quotes and provides an important first step to understand the patient experience of kidney transplantation and inform the selection of PRO measures for use in clinical trials based on their conceptual coverage.

Funding: Commercial Support - Novartis

PO2066
Customizing PROMIS-Depression Computer Adaptive Testing Stopping Rules for Patients with Kidney Failure

Background: The Patient Reported Outcomes Measurement Information System Depression (PROMIS-D) computer adaptive testing (CAT) allows precise and tailored assessment of depressive symptoms. Due to the default stopping rules, many respondents without depression may need to answer 10-12 items. The maximum number of items required by the stopping rule can be reduced which could improve efficiency when the tool is used for screening. We assess the screening performance of customized CAT stopping rules in patients with kidney failure.

Methods: A cross-sectional convenience sample of adults with kidney failure treated with dialysis or kidney transplant completed PROMIS-D CAT as well as the Patient-Health Questionnaire-9 (PHQ-9). Moderate/severe depressive symptoms were defined as a PHQ-9 cut-off score ≥ 10. Sociodemographic and clinical characteristics were obtained from self-report and medical records. All patients completed CAT using the original stopping rule (CAT9) that requires a reliability of >90% or maximum 12 items. We compare this to three simulated CAT customizations with maximum 8, 6 and 4 items (CAT, CAT, and CAT, respectively). Reliable T score range (reliability is >90%), sensitivity and specificity of each version were assessed.

Results: Of the 336 patients, the mean SD age was 55(16), 63% were male, 49% were Caucasian and 32% were on dialysis. Based on PHQ-9, 16% reported moderate/severe depressive symptoms. Using a PHQ-9a10 as a reference for a moderate/severe depressive symptoms, sensitivity and specificity of a T score of 55 with CAT9 was 79% and 81% respectively. CAT9 presented no change in the reliable range (T-score 41 to 84), while CAT, and CAT, presented a small reduction in the reliable range (41-76 and 41-74 respectively) compared to CAT9. Sensitivity and specificity of the modified CAT versions remained essentially the same.

Conclusions: Customizing PROMIS-D CAT stopping rules have the potential to improve efficiency of screening for moderate/severe depressive symptoms. This reduces questionnaire burden without change in the discrimination of the T score. A PROMIS-D CAT with modified stopping rule (maximum 6 or even 4 items) could be used for screening for depressive symptoms among patients with kidney failure.

PO2067
Pre-Transplant Sarcopenia Does Not Predict Graft Function or Mortality in Kidney Transplantation
Taylor Norris, Neal Montgomery, Shelby Fishback, Diane M. Cibrik, Aditi Gupta. University of Kansas Medical Center, Kansas City, KS.

Background: Sarcopenia is common in end stage kidney disease (ESKD), and is associated with increased risk of cardiovascular events and mortality. The association between pre-transplant sarcopenia and post-transplant outcomes is unknown.

Methods: We conducted a single-center retrospective study to evaluate the association between pre-transplant psosas muscle cross-sectional area at level of L4 and post-transplant outcomes; change in graft function, length of hospitalization, rehospitalization at 30- and 90-days post-transplant, graft loss, and mortality.

Results: Of the 573 patients with pre-transplant CT images, 465 received kidney transplant (KT) alone, 71 received simultaneous liver-kidney transplantation (SLK), and 37 received simultaneous pancreas-kidney (SPK) transplantation. Pre-transplant psosas muscle cross sectional area was associated with longer hospitalization in KT alone and SPK transplants, but not with post-transplant graft function, rehospitalization rates or mortality (Table 1).

Conclusions: Unlike ESKD patients on dialysis, pre-transplant psosas muscle cross-sectional area is not associated with adverse post-transplant outcomes. Thus, sarcopenia should not be an exclusion criterion for transplant eligibility.

Cox proportional hazard models (adjusted for age, sex, race and diabetes) for normalized psosas cross sectional area and post-transplant outcomes.

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO2069
Transplant Clinician Opinions on Use of Race in the Estimation of Glomerular Filtration Rate: A National US Survey Study
Krista L. Lentine,1 Neeraj Singh,2 Benjamin E. Hippen,2 Kenneth J. Woodsie,3 Prince M. Anand,4 Matthew Cooper,5 Darshana M. Dadhania,6 Sruthi Ainapurupu,1 Mona D. Doshi,1 Saint Louis University School of Medicine, Saint Louis, MO; 2LSU Health New Orleans, New Orleans, LA; 3Geisinger Health, Danville, PA; 4Weill Cornell Medicine, New York, NY; 5University of Michigan Health System, Ann Arbor, MI; 6Metrolina Nephrology, Charlotte, NC; 7MedStar Health, Columbia, MD.

Background: Inclusion of race in eGFR equation has raised controversies based on concern that assigning a higher GFR to Black patients delays opportunity for preemptive kidney transplant listing.

Methods: We conducted a survey of adult kidney transplant center staff in U.S. (12/17/2020–2/28/2021) to assess opinions on use of race-based estimated GFR (eGFR) equations for waitlisting and living donor candidate evaluation, availability of serum cystatin-C testing and measured GFR, and related practices.

Results: Respondents represented 57% (124/218) of adult kidney transplant centers and 76.3% of recent practice volume. Nearly 95% of respondents felt that current race-based eGFR calculators need revision, primarily due to concerns around healthcare disparities and inaccuracies around reporting of race, particularly among multi-racial individuals. A majority of respondents (70.5%) believed that elimination of race would allow preemptive kidney transplant wait listing for Black patients, but a similar number (69%) also raised concern that removing race from GFR estimation could incur harms. One-third of responding programs lacked or were unsure of availability of cystatin C or mGFR at their institution. Nearly 15% of responding centers have removed race from GFR estimation and were either reporting eGFR for non-Black or ranges; 46% were planning to do so and 39.5% did not plan to change for now (Figure). There was no difference in GFR acceptance threshold for Black versus non-Black living donors.

Conclusions: This national survey highlights a broad consensus that extant approaches to eGFR calculations are unsatisfactory, but a range of opinion on what should replace the status quo. National consensus, guidelines, and infrastructure for laboratory testing are necessary to facilitate best practices to prevent further disparities in transplant care.

PO2070
Defining the Living Donor Transplant Evaluation Process for Optimization of a One-Day Evaluation Program
Ariana Noel,1,2 Greg A. Knoll,1,2 Ann Bugaj,1,2 1University of Ottawa, Ottawa, ON, Canada; 2Ottawa Hospital, Ottawa, ON, Canada.

Background: Living donor transplantation provides patients with end stage kidney disease increased longevity and quality of life compared with dialysis. The donor evaluation process can be inefficient and costly for patients and the healthcare system. There is a paucity of research on evaluation optimization in living kidney transplantation. We investigated our living donor evaluation process to develop a one-day program, improving program efficiency.

Methods: Living donor staff and patient partner from The Ottawa Hospital Living Kidney Donor program participated in individual, semi-structured interviews to develop a Lucidchart process map of the donor evaluation process and ascertain the time associated with each step. A one-day evaluation program model was developed based on our process map and interview participant feedback. Amount of time for each step of the process was collected for future cost assessment.

Results: Mean time to complete the evaluation process and reach donor approval is 9 months. The donor evaluation process can be divided into 3 phases: Initial Interview, Phase I, and Phase II. Phase I requires the most nursing and administrative time. The greatest barriers to process efficiency are 24-hour urine collections to estimate kidney function and coordinator time spent on correspondence with laboratories. A one-day evaluation will reduce the evaluation process and approval to approximately 4 weeks. Greatest barriers for patients included need for increased education and time off work. Next steps will include cost estimates of the current program with the goal of implementing a one-day evaluation program at The Ottawa Hospital.

Conclusions: A one-day evaluation program will increase the efficiency of the living donor process for donors, coordinators, and recipients. Phase I investigations are a barrier to program efficiency and can be streamlined with a one-day evaluation. The development of donor educational resources will improve the donation experience for patients.

PO2071
Comparison of CT Volumetry vs. Nuclear Renography to Predict Remaining Kidney Function After Living Kidney Donation
Sang Hun Pum, Hanbi Lee, Chul Woo Yang, Byung Ha Chung, Seoul Saint Mary’s Hospital, Seocho-gu, Seoul, Republic of Korea.

Background: Computed tomography(CT) and nuclear renography are performed to decide kidney procurement. The aim of this study was to compare single kidney(sk) function and single kidney(sk) volume in predicting post-donation kidney function. Further, we aimed to investigate which modality is better to decide which kidney is more appropriate in terms of kidney function recovery, especially when the results were contradictory.

Methods: CT volumetry and nuclear renography from 835 kidney donors were retrospectively included. We investigated correlation between sk-volume and sk-mGFR and the agreement of two modalities. Mismatch was defined as sk-volume higher and sk-mGFR smaller than the other kidney, or vice versa. We compared the predictive value for post-donation kidney function between two modalities in total group and in mismatched group. Based upon decision preference, we compared kidney function recovery between two modalities at 6 months after donation.

Results: Mean baseline estimated GFR was 100.01ml/min/1.73m². The mean right and left sk-volume were 171.18 and 179.71cm³ and mean right and left sk-mGFR were 53.72 and 53.44ml/min, respectively. 701(83.96%) donated left kidney. Sk-mGFR and sk-volume showed significant correlation(r=0.484, P<0.001) and the results showed significant agreement in Bland-Altman plot and Intraclass correlation coefficient was 0.647(P<0.001). In total group, CT volumetry was superior to nuclear renography in predicting kidney function after donation(1 month: βγ=0.402, P<0.001, βγintraclass=0.242, P<0.001; 6 months: βγ=0.448, P<0.001, βγintraclass=0.214, P<0.001) by multivariable linear regression analysis. In mismatched group(326 donors), CT volumetry still outweighed nuclear renography(1 month: βγ=0.453, P<0.001, βγintraclass=0.259, P<0.001; 6 months: βγ=0.480, P<0.001, βγintraclass=0.285, P<0.001). When mismatch occurred, 260(79.75%) procurements were decided by nuclear renography. Functional recovery was higher in CT volumetry preferred group, although it did not reach statistical significance(33.99% vs 30.09%, P=0.098).

Conclusions: CT volumetry was appropriate to assess single kidney function and it outperformed nuclear renography in predicting kidney function after donation. Therefore, when contradictory results between left and right kidney occur, CT volumetry can be preferred in procurement strategy.
PO2072
The Impact of New-Onset Diabetes After Transplantation on Survival and Major Cardiovascular Events in Korean Kidney Transplantation Recipients
Jangwook Lee,1 Donghyun Kang,2 Sehoon Park,3 Ji Eun Kim,3 Eunjeong Kang,2 Yaeirim Kim,4 Yong Chul Kim,3 Yun Su Kim,4 Yaeji Lim,5 Hajeong Lee,1 Dongmyung University Medical Center, Goyang, Gyeonggi, Republic of Korea; 1Keimyung University Dongsan Medical Center, Daegu, Republic of Korea; 2Seoul National University Hospital Department of Internal Medicine, Jongno-gu, Seoul, Republic of Korea; 3Chung-Ang University, Seoul, Republic of Korea; 4Armed Forces Capital Hospital, Seongnam, Gyeonggi-do, Republic of Korea; 5Korea University Guro Hospital, Seoul, Republic of Korea.

Background: New-onset diabetes after transplantation (NODAT) is a frequent complication in kidney transplant (KT) recipients with unfavorable outcomes, although a nationwide study on epidemiology and clinical outcome of NODAT in Korean KT recipients remain rare.

Methods: We identified KT recipients by using a Health Insurance Review and Assessment Service of South Korea from the year of 2008 to 2017. We excluded patients with preexisting diabetes, multi-organ transplantation, and being progressed to graft failure less than 1 year after KT. NODAT was defined as consecutive 30 days prescription history of antidiabetic medication after KT. We analyzed the impact of NODAT on death censored graft failure (DCGF), death without graft failure (DWF), and major adverse cardiovascular events (MACE) by time-dependent Cox analysis.

Results: Among a total of 16,719 KT recipients, 10,311 were included after exclusion. 19.8 percent of KT recipients were diagnosed with NODAT. The proportion of patients developing NODAT tended to increase with time, and 64% of NODAT was diagnosed within the first 6-months after KT. NODAT patients were older, more men, having longer pre-KT dialysis vintages, and being exposed more basiliximab induction and more rejection episodes requiring high-dose steroids treatment after KT. During follow-up, 520 DCGF, 180 DWF, and 213 MACE events were occurred. NODAT patients showed higher risks of DCGF (adjusted hazard ratio [aHR], 1.61; 95% confidence interval [CI], 1.27-2.04; p < 0.001), DWF (aHR 1.77;95% CI 1.28-2.43;p=0.001), and MACE (aHR 1.46;95% CI, 1.01-1.96;p=0.013) than patients without NODAT. Twenty-one percent of NODAT patients could be stopped their anti-diabetic medications after the diagnosis, although this did not affect the clinical outcomes.

Conclusions: About 20% of diabetes-naïve KT recipients were diagnosed with NODAT with a recently increasing pattern. NODAT in KT recipients affected worse graft and patients outcomes as well as MACE.

Funding: Government Support - Non-U.S.

PO2073
Association Between Early Post-Transplant Hypertension or Related Antihypertensive Use and Prognosis of Kidney Transplant Recipients: A Nationwide Observational Study
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Background: Additional research is warranted for the clinical significance of post-transplant hypertension and related antihypertensive medication usage in kidney transplant (KT) recipients.

Methods: This observational study included nationwide KT recipients who maintained functioning graft for at least 1 year after KT in South Korea during 2008 to 2017. The usage of antihypertensive medications between 6 months to 1 year was the main exposure, and those who had inconsistent/transient usage of antihypertensive drugs were also excluded. The primary outcome included death-censored graft failure (DCGF), death-with functioning graft (DWF), and major adverse cerebrocardiovascular events (MACCEs).

Results: We included 8014 patients without post-transplant hypertension and 6114 recipients who received treatments for hypertension in the post-transplant period. Those with post-transplant hypertension had significantly worse risk of DCGF than those without [adjusted hazard ratio (HR) 1.27 (1.09-1.48)]. Post-transplant hypertension patients who required multiple drugs showed significantly higher risk of DWF [HR 1.57 (1.17-2.10)] and MACCE [HR 1.35 (1.01-1.81)] than the controls. Among the single-agent users, those who received beta-blockers showed a significantly higher risk of DCGF, although the risks of DWF or MACCE were similar between the types of antihypertensive agents. Among the multiple agent users, the prognosis was similar regardless of the prescribed types of antihypertensive agents.

Conclusions: Post-transplant hypertension was associated with poor post-transplant prognosis, particularly when multiple types of medications were required for treatment. During initial prescription of antihypertensive medication, clinicians may consider that beta-blockers were associated with a higher risk of DCGF in the single-agent users.

The association between PTA and overall mortality
PO2075


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Background: Kidney transplantation recipients (KTR) with coronavirus disease 2019 (COVID-19) are at higher risk of death than general population. However, mortality risk factors in KTR are still not clearly identified. Our objective was to systematically analyze published evidence for risk factors associated with mortality in COVID-19 KTR.

Methods: Electronic databases were searched for eligible studies on 8 January 2021. All prospective and retrospective studies of COVID-19 in KTR were considered eligible without language restriction. Since data in case reports and series could potentially be subsets of larger studies, only studies with ≥50 patients were included. Random-effects model meta-analysis was used to calculate weighted mean difference (WMD) and pooled odds ratio (OR) of factors associated with mortality.

Results: From a total 564 articles retrieved, 10 were included in the meta-analysis comprising 1,778 KTR. Of these, 1,349 (76%) were survivors and 419 (24%) were non-survivors. Compared with survivors, non-survivors were significantly older (WMD 10.5 years, 95%-CI 9.0-12.0) and had shorter symptom onset before admission (WMD -1.3 days, 95%-CI -2.2 -0.3). KTR of deceased donor were at higher risk of death (OR 2.08, 95%-CI 1.03-4.20). Comorbidities including diabetes, cardiovascular disease, and cancer significantly increased mortality risk. KTR with dyspnea (OR 3.40, 95%-CI 2.51-4.60) and pneumonia (OR 3.61, 95%-CI 1.63-5.55) at presentation were at higher mortality risk. While diarrhea decreased the risk (OR 0.63, 95%-CI 0.39-0.92). Acute kidney injury was associated with mortality (OR 1.74, 95%-CI 1.10-2.98). Inflammatory markers were significantly higher in the non-survivors, including lactate dehydrogenase, C-reactive protein, D-dimer, pro-calcitonin, and interleukin-6.

Conclusions: A variety of COVID-19 mortality risk factors were identified from KTR patient characteristics, presenting symptoms, and laboratory investigations. KTR with these risk factors should receive more intensive monitoring and early therapeutic interventions to optimize health outcomes.

PO2076

Impact of Native Kidney Disease on Post-Transplant Cancer Development

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Background: Long-term risk of cancer development among patients with glomerulonephritis (GN) and congenital anomalies of the kidney and urinary tract (CAKUT) have been shown previously. However, the association between native kidney diseases and de novo cancers after kidney transplantation (KTx) need to be clarified.

Methods: We examined national Scientific Registry of Transplant Recipients (SRTR) data for patients underwent KTx (2000-2021) to investigate the association of native kidney disease with de novo cancer diagnoses after KTx. Patients with history of previous transplant and patients with history of cancer before KTx were excluded. We identified KTx recipients with hypertension (HTN) (n=68432), diabetes mellitus (DM) (n=79809), glomerulonephritis (GN) (n=54381), CAKUT (n=6508) and others (n=56048) as cause of native kidney disease.

Results: Compared with the reference HTN group, GN (aHR 1.39, 95%-CI 1.19-1.60) and CAKUT (aHR 1.37, 95%-CI 1.13-1.67) groups are significantly associated with higher risk of new onset cancers at 5 years post-KTx (Figure 1). GN (aHR 1.31, 95%-CI 1.13-1.50) and CAKUT (aHR 1.24, 95%-CI 1.04-1.49) groups are also associated with a higher risk of acute rejection within the 6 months post-KTx. Regarding graft failure, GN (aHR 0.92, 95%-CI 0.82-1.03) and others (aHR 0.80, 95%-CI 0.70-0.91) groups have significantly lower risk of 5 years all cause graft failure compared to reference group. However, the risk of death censored graft failure was significantly lower in DM (aHR 0.90, 95%-CI 0.73-1.11) and others (aHR 0.83, 95%-CI 0.68-1.01) groups.

Conclusions: Native kidney diseases, GN and CAKUT, have been associated with acute rejection and de novo cancers after KTx. Immunosuppressive treatment and cancer screening may need to be modified according to native kidney disease.

PO2077

Effect of Cold Ischemia Time on Death-Censored Graft Survival of Post-One-Year Survivor Deceased Donor Kidney Transplant Recipients in the United States

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Background: Prolonged cold ischemia has been associated with increased incidence of delayed graft function and poor short term graft survival among deceased donor allografts. However, the data on long term graft survival is less clear. Our aim was to evaluate long-term graft survival for deceased donor kidney recipients who survived one year after transplantation such that the immediate adverse outcomes do not cloud the long term outcomes.

Methods: We retrospectively analyzed data from the United Network for Organ Sharing (UNOS) from 1995 to 2017. Living donor transplants, multi-organ transplants, recipients <18 years age at transplantation, and those who died within 1 year of transplantation were excluded. Using multivariable Cox regression analysis, a total of 145,680 recipients were analyzed with death censoring to estimate graft survival with varying cold ischemia times.

Results: Compared with cold ischemic time of <5 hours, the graft failure probability steadily increased with increasing cold ischemia time such that the hazards of graft loss were 42% higher with ischemic time greater than 35 hours (Figure 1). Worse graft survival was also observed in males (HR 1.08), increasing donor age beyond 50 years, Blacks (HR 1.77), BMI >30 (HR 1.13), those who had dialysis prior to transplant (HR 1.41), diabetes (HR 1.12), and PRA >90% (HR 1.16). Recipients older than 40 years had lower graft loss compared to those between 18 and 40 years age.

Conclusions: Prolonged cold ischemia time adversely affects long-term graft survival among deceased donor kidney transplant recipients in the US. The hazards of graft loss appear to be proportional to the duration of cold ischemia time.

Funding: Clinical Revenue Support
PO2078
Polygenic Burden for Intracranial Aneurysm and Hypertension in Deceased Kidney Donors Who Died of Intracranial Haemorrhage
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Background: A polygenic risk score (PRS) estimates the cumulative effect of common genetic variants across the genome. It is calculated by summing up all the effect alleles present in the individual, weighted by the effect size, as measured in a GWAS. Intracranial haemorrhage is a common cause of death among kidney donors, but limited research has been done to investigate polygenic burden for intracranial aneurysm (IA) and hypertension in deceased transplant donors.

Methods: Our data consisted of 2,122 genotyped donor-recipient pairs from the United Kingdom and Ireland Renal Transplant Consortium (UKIRCT) and 5,519 controls from the 1958 British Birth Cohort and UK Blood Service. We created polygenic risk scores for IA and hypertension using published GWAS summary statistics from 7,495 cases and 71,934 controls for IA and 76,566 cases and 206,305 controls for hypertension. We investigated the difference in PRS between the UKIRCT donors who died of intracranial haemorrhage (1,303 individuals) and the controls while adjusting for covariates of sex and the first 4 principal components.

Results: We found that the IA PRS explained 4.1% of the variance between case and control status (p-value: 9.6 x 10^-10). The odds ratio on the phenotype for those in the lowest vs. highest decile of the IA PRS was 0.52 (95% CI: 0.34-0.82) compared to 2.8 (1.9-4.0) for those in the highest decile. Similarly, the PRS for hypertension explained 1% of the variance (p-value: 7.5 x 10^-4). The corresponding odds ratios were 0.68 (CI: 0.46-1.0) and 1.5 (1.1-2.3) for those in the lowest and highest deciles respectively.

Conclusions: PRSs for IA and hypertension based on these data appear to explain 4% and 1% respectively of the variance in case-control status between kidney donors who have died of intracranial haemorrhage and controls. These observations could have utility in testing relatives of donors who died of intracranial haemorrhage to determine if they share the same risk for intracranial haemorrhage and if so may be useful in advising screening or other precautions to minimize their risk of intracranial haemorrhage. These observations need to be confirmed in other cohorts. Further studies using similar approaches could investigate other causes of death among kidney donors.

Funding: Government Support - Non-U.S.

PO2079
Characteristics of Potential and Actual Living Kidney Donors: A Single-Center Experience
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Background: Living kidney donors contribute only 28% of all transplanted kidneys. Our study aimed to examine characteristics of potential compared to actual living kidney donors, in order to better understand barriers to successful donation.

Methods: We performed a retrospective analysis of 1,815 intake forms completed by kidney donor candidates from 2016-2018 at a single transplant center. We analyzed data from all potential donors who completed the intake until they became ineligible or withdrew, or, until donation was reached. Baseline characteristics were compared between potential and actual donor groups.

Results: The donation process was deconstructed into 5 steps. The percentage of potential donor drop out at each step and the most common reason for drop out are shown in Table 1. Of the 125 actual donors, 115 (94.5%) were white and 81 (64.8%) were female. A family member was more likely than an unrelated individual to complete the process. At the intake step 35.5% of potential donors identified as family of the potential recipient; at donation 72.7% were family, p <0.001. Many potential and actual donors considered prohibitive of fasting. Controls were potential LKD’s that have been approved for donation but were not favored by the recipient. In our study, 85 LKD’s & 27 controls were included. Donors were older (42.8 vs. 38.8 years) and had a higher baseline creatinine (103 vs. 72 umol/L). All other parameters were the same. The change between fasting and non-fasting creatinine was smaller in LKD’s than in controls (0.12 vs. 0.21% change P=0.04). Values of sodium, albumin & osmolality were not different between groups. Results: 85 LKD’s & 27 controls were included. Donors were older (42.8 vs. 38.8 years) and had a higher baseline creatinine (103 vs. 72 umol/L). All other parameters were the same. The change between fasting and non-fasting creatinine was smaller in LKD’s than in controls (0.12 vs. 0.21% change P=0.04). Values of sodium, albumin & osmolality were not different between groups.

Conclusions: LKD’s practicing a 24 hr fast show a different pattern from controls regarding the change in creatinine levels. This pattern cannot be considered hazardous for LKD’s. The emotional wellbeing of LKD’s is of utmost importance and this first report of the safety of a 24 hour fast in screening. These findings may be extended to other religious groups, e.g. the Muslim community who practice RAMADAN. Further follow-up is needed to explore the long term effects of a 25-26 fast in the LKD population.
PO2082
African American Kidney Donor Denial
Ivan E. Porter. Mayo Clinic’s Campus in Florida, Jacksonville, FL.
Background: Previous studies have demonstrated that the rate of living kidney donation is lower in African American (AA) compared to the Caucasian population but whether this low donation rate is related to higher denial rates in AA donors is unclear. Comorbidities play a major role in live donor evaluations, especially hypertension and DM, which could affect the pool of potential donors. The aim of our study is to report the rates and causes of living kidney donor denial in our facility and to further stratify the exclusion rate based on race.
Methods: A retrospective cohort study of 439 denied candidates (age ≥18) who underwent evaluation for living kidney donation at our facility in the period from 2006 to 2014 was performed. Donors underwent a 24 hour ambulatory blood pressure monitoring, isothalamate GFR, 24 hour urinalysis, and CT angiography as part of their donor evaluations. Reasons for denying donors were identified and grouped into 4 groups: 1) Low GFR, 2) Anatomical variation 3) Hypertension and 4) Other causes.
Results: The cohort consisted of 84 AA, 304 Caucasian and 32 Hispanic donors. Hispanic donors were excluded from further analysis. AA donors were younger (P=0.01) compared to Caucasians. Day time and night time systolic and diastolic arterial blood pressure were comparable between AA and Caucasian (P>0.3 for all) Table 1 summarizes the different reasons for donor denial by donor race. There was no difference between AA and Caucasians or Hispanics in the reason for denial for donation.
Conclusions: In this limited study the reasons for denial of kidney donation was not different between AA and Caucasians. Given that the disparity remains, other causes for the low donation in the AA population should be explored and mitigated.

Potential Donor Characteristics

<table>
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<tr>
<th>Donor Race</th>
<th>Low GFR</th>
<th>Anatomical Variation</th>
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<td>6/4</td>
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PO2083
“I Just Don’t Trust It”: Exploring the Role of Mistrust in Shaping Living Donor Kidney Transplant Pathways for African, Caribbean, and Black communities in Toronto, Canada
Lydia-Joi L. Marshall, University Health Network, Toronto, ON, Canada.
Background: In Canada, African, Caribbean, and Black [ACB] patients with kidney failure are 40-70% less likely to receive a LDKT compared to Whites. To date, research has focused on individual factors, neglecting the impact of systemic racism in shaping ACB community attitudes toward LDKT. Further absent is Canadian research using qualitative methodology.
Methods: We used an exploratory qualitative approach to understand perspectives and attitudes about LDKT in Canadian ACB communities. Using purposive and snowball sampling, we recruited 81 self-identified ACB community participants to take part in eight focus group discussions between January and November 2020. Participants were not identified as ACB for fear of stigmatization. We then applied a Critical Race analytical framework to analyze transcripts, focusing on the tenets of racial consciousness, social location, power dynamics, and counter narrativities.
Results: Of the 81 participants 63% was female, 46% were >50 years of age, 53% were immigrants to Canada. 36% self-identified as North American Black/African; 48% as Caribbean; 6% as North African; and 4% as Central/West African. Three key themes emerged from the data. First, that like in the U.S., participants expressed medical mistrust. Second, this medical mistrust was rooted in a combination of processes of racialization (medical racism), historical legacies of medical mistreatment, and lived negative experiences within the health care system. Lastly, medical mistrust informed health and illness related decision-making risk assessment, perspectives on LDKT, (lack) of engagement with traditional health care settings, and medical needs.
Conclusions: ACB community attitudes and decision-making processes about LDKT are complex, historically-rooted, and informed by broader medical mistrust. This suggests that broader systemic barriers to adequate health care outside of the LDKT pathway, may have far-reaching effects. Further research is needed to better understand how the broader medical experiences of ACB communities may be an underappreciated factor that shapes racial disparities in transplantation, and the kinds of interventions needed to facilitate broader use of LDKT.
Funding: Government Support - Non-U.S.

PO2084
Employment Status and Work Functioning in Kidney Transplant Recipients
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Background: Reliable employment figures of stable kidney transplant recipients (KTR) in Europe are lacking. Additionally, little is known about work functioning among employed KTR, and which clinical factors and (drug-related) side-effects are associated with work functioning.
Methods: We included 668 KTR of working age (59% male, age 51±11 years), at a median of 3 [IQR: 2 to 10] years after transplantation, enrolled in the ongoing TransplantLines Biobank and Cohort Study (NCT03272841, Groningen, The Netherlands). Work and work-related functioning were assessed using the work role functioning questionnaire (WRFQ). Self-reported work ability was assessed using an item of the Work Ability Index (WAI). Results were compared to 246 (43% male, age 53±9 years) potential kidney donors used as healthy controls (HC).
Results: Employment rates were significantly lower among KTR compared to HC (56% vs. 79%, respectively, P<0.001). Employed KTR reported lower work functioning compared to employed HC (median [IQR] WRFQ score: 94 [75 to 100] vs. 100 [83 to 100], P<0.026, Figure 1). Similarly, self-reported work ability was lower in KTR compared to HC (mean 7.8±1.9 vs. 8.6±1.5, P<0.001). Among KTR, fatigue was most strongly associated with working independently, potentially of potential confounders. Other parameters including anemia, blood albumin, use of beta-blockers, and neurological and mental drug-related side-effects were also independently associated with work functioning.
Conclusions: In our large representative population, only 56% of KTR in their working age were employed. In addition, employed KTR frequently experience impaired work functioning and have limited self-reported work ability. These results underline the individual and societal need to improve employment rates and work-related functioning among KTR. Fatigue, anemia, nutritional status, beta-blocker use, and drug-related side-effects may be potential targets, and should be further investigated.

PO2085
A2 to B Decedent Donor Renal Transplantation Outcome Analysis: A Single-Center Experience
Sandiya Bindroo, Mona D. Doshi. University of Michigan, Ann Arbor, MI.
Background: A2 to B renal transplantation has been underused and significant knowledge gaps are noted in areas of rejections, infection rate, and anti-A titers thresholds post-transplant. The purpose of our study is to assess antibody mediated rejection (AMR) rates in A2 to B DDKT and determine association with anti-A titer.
Methods: Retrospective chart review of 55 A2 to B DDKT performed at the University of Michigan from January 2015 to September 2020 was done. All patients received Thymoglobulin for induction and were maintained on triple immunosuppression. All patients underwent monitoring of anti-A2 titers and surveillance biopsy at 3, 6- and 12-months after transplant. Outcomes included graft function, rejection and infection rates at last follow-up.
Results: Our cohort consisted of 55 recipients with mean age of 54.8±13 years, 67 males and 29% African Americans. The median follow-up time was 2.5 [0.5-5] years. Ten developed acute rejection at 3 [1-6] months after transplant. One patient developed hyperacute rejection due to ABO incompatibility, five developed T cell mediated rejection, and four had AMR due to donor specific antibodies (DSA) against HLA. Anti-A titers remained undetectable or less (<1:4) in 98% patients in post-transplant period with no increase in titers at 3-6 month follow up. Anti-A titer increased to 1:128 in one patient with hyper acute rejection. Overall, 20% mortality was noted, unrelated to graft dysfunction at median follow-up of 1.8 [0.08-4] years. 20% post-transplant infections (bacterial, viral and fungal) accounted for 41% cases. BK viremia noted in 20% with BK nephropathy in six. The mean (SD) glomerular filtration rate, creatinine and urine protein creatinine ratio at three months, one year and at last follow up post-transplant was 49 (14.69), 1.40 (0.47), 0.32 (0.55), 54 (14.49), 1.3 (0.43), 0.17 (0.20) and 52.8 (14.69), 1.40 (0.59), 0.22 (0.27) respectively.
PO2086

A Successful Approach for A2 to B Cadaveric Renal Transplantation

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Background: Approximately 20% of blood group A individuals have reduced levels of A-antigen, termed A2, with less immunogenicity toward anti-A immunoglobulins. This allows the safe allograft of A2 kidneys into B or AB recipients. In 2014, the Kidney Allocation System was modified to encourage transplant centers to provide A2 kidneys for type B patients to reduce inequities in access. Studies have reported that rates of A2 to B transplants remain underestimated due to high rates of early acute rejection or thrombotic microangiopathy (TMA). We report on outcome metrics of A2 to B transplantation at the University of Texas Medical Branch (UTMB).

Methods: A retrospective, single center analysis of 29 patients who received A2 to B kidney transplants at UTMB between July 2015 and December 2020. We included stable (2 consecutive) patients. Anti-A titers ≤ 1:8 for A2 identified individuals. Anti-A titers were monitored quarterly in B waitlisted patients. All A2/A2 to B eligible recipients underwent pre-transplant volume exchange plasmapheresis, followed by 2 additional sessions on post-op days 1 and 3. Thymoglobulin was used for induction and steroids for maintenance immunosuppression.

Results: A major concern in A2 to B transplant is the development of TMA or graft rejection. The incidence of rejection within the first year of all types of renal transplants ranges from 7.9% to 21.4%. We instituted an aggressive plasmapheresis protocol to reduce levels of potential pre-formed IgM anti-A antibodies that may induce graft failure. We report a rate of 3.4% for rejection or TMA within the first year of graft life which is less than previously published reports. This is due to pre- and post-transplant plasmapheresis in combination with intravenous immunoglobulin therapy. We elected not to follow anti-A titers levels post-transplant which did not result in higher rates of graft loss.

Conclusions: Our A2 to B transplant patients had a low rate of rejection and TMA demonstrating the efficacy of our triple maintenance immunosuppression protocol. Anti-A titers need not be followed post-operatively.

RESULTS

Table 1

PO2087

Pneumocystis Jiroveci pneumonia in Renal Transplant Recipients: Experience at a Tertiary Care Center

Anukumar Subbiah, Sanjay K. Agarwal. All India Institute of Medical Sciences, New Delhi, India.

Background: Pneumocystis jirovecii pneumonia (PJP) is an important cause of morbidity and mortality in post renal transplant recipients. Data on PJP in renal transplant recipients from India is lacking and we have attempted to address these lacunae.

Methods: This single center retrospective study included all cases of PJP in renal transplant recipients diagnosed at our institute. Demographic, clinical, laboratory and therapeutic outcomes of all these patients were analyzed.

Results: Of the 1870 renal transplant recipient records analyzed, 37 (1.9%) recipients were diagnosed with PJP. The median age of the patients was 38 years (17-74) with 31 males (83.8%). Three (8.1%) patients had deceased donors while 34 (91.9%) had living donors. Infections: Prophylaxis for PJP was given to 3 patients (8.1%), clindamycin in 2 (5.4%), and trimethoprim-sulfamethoxazole in 11 (29.8%) and 21 patients (56.7%) received no induction. All patients received steroid based triple drug immunosuppression along with Tacrolimus in 27 (72%), Cyclosporine in 10 (27.1%), MMF in 34 (91.9%) and Azathioprine in 3 (8.1%). Septicemia was diagnosed in 23 patients (62.1%), sepsis in 11 (29.8%) and 21 patients (56.7%) received no induction. All patients received steroid based triple drug immunosuppression along with Tacrolimus in 27 (72%), Cyclosporine in 10 (27.1%), MMF in 34 (91.9%) and Azathioprine in 3 (8.1%). Septicemia was diagnosed in 23 patients (62.1%), sepsis in 11 (29.8%) and 21 patients (56.7%) received no induction. All patients received steroid based triple drug immunosuppression along with Tacrolimus in 27 (72%), Cyclosporine in 10 (27.1%), MMF in 34 (91.9%) and Azathioprine in 3 (8.1%). Septicemia was diagnosed in 23 patients (62.1%), sepsis in 11 (29.8%) and 21 patients (56.7%) received no induction.

Conclusions: Our A2 to B transplant patients had a low rate of rejection and TMA demonstrating the efficacy of our triple maintenance immunosuppression protocol. Anti-A titers need not be followed post-operatively.

PO2088

COVID-19 Infection in Kidney Transplant Patients: An Italian One-Year Single-Center Experience

Mariarosaria Campone,1 Carlo Alfieri,2 Donata C. Cresseri,1 Maria Teresa Gandolfi,1 Valentina Binda,1 Anna Regalia,1 Piergiorgio Messa,1,2 Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milan, Italy; 1Università degli Studi di Milano, Milano, Italy.

Background: COVID-19 is a life-threatening infection among elderly, comorbid patients, or transplanted patients. Lombardy (Region of Italy), accounts for 786,324 cases as of April 21st, 2021.

Methods: We retrospectively describe our single Centre experience in 82 adult kidney-transplant patients with COVID-19 infection during two pandemic outbreaks: 27 (first outbreak) and 65 (second). Results: Thirty-seven patients were hospitalized (HP) and 65 were home managed (HM). Infection presented with fever (80%), cough (51%) and dyspnea (33%). HP had more severe respiratory symptoms (dyspnea 62.1%, p<0.001 – cough 67% p<0.001), and a longer length of disease (30±28 vs 21±10, p<0.04). Incidence of acute kidney injury (AKI) was 29.7% (p<0.0001). Steroid dosage was increased in 66% of patients, p=0.0003 while Calcineurin Inhibitors were reduced up to one third in 43% of patients, p<0.0001. Eleven patients died (13%). HM patients recovered completely without sequelae. In the overall cohort, AKI development (p=0.006 OR 50.4 CI 95% 3.0-836) and age (p=0.04 OR 1.1 CI 95% 1.0-12.1) were the most important factors influencing the probability of death during the infection.

Conclusions: Although we report a relatively low incidence of infection (5.1%) incidence of death is almost four times higher than in general population.

Table 1: patients characteristics before COVID-19 infection.

PO2089

The Impact of COVID-19 on Deceased Donor Renal Transplant Program in a Federal State of South India

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Background: The Covid 19 pandemic has had an impact on all facets of health care system, including organ donation, procurement and transplantation in many countries. India is the country most affected with covid 19 and also the country with a huge waiting list for all solid organ transplants. SKSD is unique that different forms of RRT are available to sustain life. The risk - benefit ratio for delaying elective transplantation during the pandemic is not clear.

Methods: A descriptive cross sectional study. All the deceased donor solid organ transplantations that took place in the state of Telangana from Jan 2020 to May 2021 were included. Live transplants were excluded. Comparison of the number of transplants of different organs, before and during the pandemic was done. Unpaired t test was used to compare the outcomes between the waitlisted and transplanted group.

Results: The total number of solid organ transplants from deceased donors in the pandemic year of 2020 dropped down to 54% compared to the previous year. Comparison between different organs revealed the maximum decline in number for kidney transplantation (51%), compared to liver (42%), heart (18%) as opposed to 110% increase in lung transplantation. Infectivity rate of covid 19 in the waitlisted group (top 50 in each blood group) registered for deceased renal transplantation is 0.16%. The infectivity rate in the transplanted group (deceased donor renal transplant) during the pandemic in the post transplant period of 6 months is 0.19%. The mortality rate of covid 19 between the two groups is also similar (0.04 in the waitlisted group and 0.06% in the transplanted group). The unpaired t test showed no statistical difference between the two groups.
PO2090
The Impact of COVID-19 on Kidney Transplant Listing and Referral on the Mexican-American Border
Background: Laredo, Texas is a city on the Mexican-American border in South Texas that ranked as the most affected area in the United States relative to population in terms of COVID-19 in January 2021. The hospitalization rate, the area’s total resources devoted to treating coronavirus patients, reached 45.8% and it averaged 229.9 cases daily per 100,000 citizens. We reviewed data early in the COVID-19 pandemic in May 2020 and later in May 2021 to evaluate whether the pandemic affected rates of referral and/or waiting lists.
Methods: Data was gathered from three dialysis clinics in Laredo, TX. The number of patients waitlisted or scheduled for living donor transplantation was determined early in the COVID-19 pandemic in May 2020 and later in May 2021. The number of patients referred for transplantation but not yet waitlisted was also obtained as well as the number of patients not referred both early in the COVID-19 pandemic in May 2020 and in May 2021.
Results: In May 2020, a total of 285 patients were available for analysis. 52 patients (18.2%) were waitlisted or scheduled for living donor transplantation. An additional 91 patients (31.9%) were referred but not yet waitlisted nor scheduled for living donor transplantation. A total of 140 (49.1%) were not referred. In May 2021, a total of 244 patients were available for analysis. 36 patients (14.8%) were waitlisted or scheduled for living donor transplantation. An additional 71 patients (29%) were referred but not yet waitlisted nor scheduled for living donor transplantation. A total of 135 (55%) were not referred.
Conclusions: There was a smaller percentage of ESRD patients waitlisted or scheduled for living donor transplantation in May 2021 than early in the COVID-19 pandemic in May 2020. There was also a smaller percentage referred but not waitlisted and a larger percentage not referred. The 3.4% decrease in patients waitlisted or scheduled for living donor transplantation may be a result of the high COVID-19 burden in Laredo, TX and the wariness to travel approximately 150 miles to the nearest transplant center. It is not known whether this decrease will have lasting implications on access to transplantation.

PO2091
Coronavirus Disease 2019 and Kidney Transplantation in Saudi Arabia
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Background: Kidney transplant services all over the world were severely impacted by the coronavirus disease 2019 pandemic. The optimum management of kidney transplant recipients with coronavirus disease 2019 remains uncertain.
Methods: We conducted a multicenter cohort study of kidney transplant recipients with coronavirus disease 2019 infection in Saudi Arabia. Multivariable Cox regression analysis was used to study predictors of graft and patient outcomes at 28 days after coronavirus disease 2019 diagnosis.
Results: We included 130 kidney transplant recipients, with a mean age of 48.7 ( ± 14.4) years. Fifty-nine patients were managed at home with daily follow-up utilizing a dedicated clinic, while 71 (54.6%) required hospital admission. Acute kidney injury occurred in 35 (26.9%) patients. Secondary infections occurred in 38 (29.2%) patients. SARS-CoV-2 antibodies testing was carried out in 84 patients, of whom 70 tested positive for IgG and/or IgM. Fourteen patients died (10.8%). A multivariable Cox regression analysis showed that age, creatinine at presentation, acute kidney injury, and use of azithromycin were significantly associated with worse patient survival. Graft loss was associated with requiring renal replacement therapy and development of secondary infections.
Conclusions: Despite kidney transplant recipients with coronavirus disease 2019 infection having higher rate of hospitalization and mortality compared to the general population, a significant number of them can be managed using a telemedicine clinic. Most kidney transplant patients seem to mount an antibody response following coronavirus disease 2019 infection, and it remains to be seen if they will have a similar response to the incoming vaccines.

PO2092
Vitamin D Status and SARS-CoV-2 Infection in a Cohort of Renal Transplanted Patients
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Background: Immunomodulatory and anti-inflammatory properties have been hypothesized for native vitamin D (nVD). Very little is reported about nVD and risk of Sars-CoV-2 infection (COV) in renal transplant (RTx). In a cohort of renal transplanted patients (RTxp) we retrospectively evaluated: a) nVD status in patients with (COV+) and without (COV−) COV infection; b) the impact of nVD status on severity of COV.
Methods: The study includes 61 COV+ in whom nVD status was available in the year before the infection, and 122 COV- matched 1:2 for age (53±46±4) years, gender (M=60.7%); RTx vintage (72±15±5) years, presence of diabetes (18%), arterial hypertension (85%) and cardiac symptomatic disease (3%). Renal function, 24-h proteinuria, mineral metabolism (MM) parameters were evaluated at 1, 6 and 12 months before COV whereas nVD status was considered as the mean 25-OH-VD levels at the same timepoints. Severity of COV was based on the need for hospitalization (HOSP+: 27/61, 44.3%) and death (D1: ±6/61, 9.8%).
Results: a) nVD levels were significantly lower in COV+ than in COV- (19 [12-26] ng/ml and 23[16-30] ng/ml, respectively, p=0.01). No differences in the other biochemical parameters were found. The COV discriminative power of nVD status was evaluated by ROC curve (AUC 0.61, 95% CI 0.54-0.68, p<0.01), with a value of 25- OHV D 23.9 ng/ml showing the best discriminative power (sensibility 72%, specificity 47%); b) nVD levels showed a trend towards lower values in HOSP+ COV+ than HOSP- COV+ (17 [9-25] ng/ml vs 20[14-26] ng/ml) and in D+COV+ than D-COV+ (13 [6-23] ng/ml vs 20[13-36] ng/ml), although these differences did not reach the statistical significance (p=0.1 and p=0.2, respectively).
Conclusions: With the limitations of the retrospective nature of the study and the small sample size, our data report that: a) COV+ showed lower nVD levels in the year preceding the infection compared to controls with similar main demographic features and comorbid conditions; b) No differences were found in renal function, proteinuria, and other MM parameters between the two groups; c) No association was found between nVD levels in the year preceding the infection and COV severity.

PO2093
Treatment with Monoclonal Antibodies Minimize Severity of COVID-19 Illness Among Kidney Transplant Recipients
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Background: The mortality rate of kidney transplant recipients with COVID-19 is significantly higher than the general population, indicating a need for effective treatment to minimize potential severe symptoms in this population. We sought to evaluate the efficacy of monoclonal antibody therapy in decreasing the severity of COVID-19 symptoms among our kidney transplant recipients.
Methods: We reviewed 17 kidney transplant recipients who were infected with SARS-CoV2 and received treatment with monoclonal antibody therapy. All patients were on standard immunosuppression with Tacrolimus and Prednisone, and 88% were on Mycophenolate prior to COVID diagnosis, which was subsequently reduced or held for at least 2 weeks.
Results: Of the 17 patients reviewed, median age was 61 years (range 42 to 77 years), 47% were male, 59% were Hispanic, and 29% were African American. Additionally 94% had history of hypertension, 47% diabetes mellitus, 18% coronary artery disease, and median BMI was 28.8 (range 23.4 to 41.9). Eighteen percent were transplant<1 year, 29% between 1-5 years, 24% 6-10 years, and the remaining >10 years. All patients had mild symptoms without evidence of hypoxia, and 94% received monoclonal antibody therapy within 7 days of diagnosis. Bamlanivimab 700mg was the most commonly administered agent at 59%, while 18% received Bamlanivimab 700mg and Etesevimab 1400mg. Casirivimab 1200 mg and imevatimab 1200 mg was used in 24%. Only 2 out of the 17 patients (11.8%) required hospitalization, and both were non-COVID-19 related reasons. Five out of 17 patients (29.4%) were evaluated in the Emergency Department but not admitted. All 17 patients (100%) recovered from their COVID-19 illness. There were no episodes of graft failure.
Conclusions: Our experience suggests that monoclonal antibody therapies may be beneficial in preventing severe COVID-19 in renal transplant recipients and possibly reduce the need for COVID-19 related hospitalization in this high risk population. However, larger studies are needed to confirm these findings.
PO2094

Antibody Response to SARS-CoV-2 mRNA Vaccines in Pediatric Kidney Transplant Recipients

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Background: In the general population, mRNA SARS-CoV-2 vaccines are highly efficacious and patients form an antibody to S1 subunit of the SARS-CoV-2 spike protein. Early reports suggest a decreased antibody response in immunosuppressed adult solid organ transplant (SOT) patients. However, the serologic response in adolescent SOT patients has not yet been characterized.

Methods: Kidney transplant recipients (KTR) at our center who received both doses of an mRNA SARS-CoV-2 vaccine had SARS-CoV-2 spike protein antibody presence evaluated 4-8 weeks after their second dose of the vaccine as part of routine clinical care. We utilized the Abbott chemiluminescent microparticle immunoassay or Siemens Atellica IM SARS-CoV-2 IgG. Patients were characterized as vaccine responders or non-responders.

Results: Of 47 vaccine-eligible KTR in our program, 34 received both doses of a SARS-CoV-2 mRNA vaccine. Twenty-three patients had spike antibody titers obtained. The median age was 21.5 years and all except one were transplanted over 3 years ago. Twenty-two received Pfizer-Biontech vaccine and one received Moderna. Twelve patients (52%) had a positive spike antibody. Of those who responded, eight patients’ immunosuppression regimens included mycophenolate (mean dose 719 mg/m2/day), three were treated with azathioprine and one was not taking an antimetabolite due to EBV viremia. All non-responders were treated with mycophenolate (average dose 755 mg/m2/day). Three patients had prior COVID-19 infection, and all had a positive antibody response.

Conclusions: Our results suggest vaccine response in adolescent KTR is suboptimal and lower than the general population. However, 52% response rate is similar to that previously described in adult SOT patients. While our study is limited by small sample size and lack of standardized timing for measuring antibodies, it provides further evidence of lower immunogenicity to SARS-CoV-2 vaccination in SOT. Those who did not respond tended to have a higher average dose of mycophenolate and this supports further study of alternative antimetabolite dosing strategies around the time of vaccination or the potential utility of a third vaccine dose in SOT patients. At our center, efforts to continue characterizing antibody response of pediatric KTR are ongoing and we anticipate additional data in the coming months as vaccine eligibility expands to younger patients.

PO2095

A Tale of Survival: COVID-19, Disseminated Cryptococcus, and Cytomegalovirus Disease in an ABO-Incompatible Kidney Transplant Recipient

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Introduction: We present a rare case of Collapsing Focal Segmental Glomerulosclerosis (FSGS) in Covid-19 (COVAN), disseminated Cryptococcus and CMV infection in a kidney transplant recipient with dialysis dependent acute kidney injury and successful renal and critical illness recovery.

Case Description: 63yo black male with an ABO incompatible kidney transplant 8yrs ago, baseline creatinine (Cr) of 1.4 mg/dl with acute Covid-19 infection with presenting Cr of 5.5 mg/dl and nephrotic range proteinuria (5.9 gm/24h). Started hemodialysis on day 21 of the acute illness. Normal imaging, stable anti-ABO titers and transplant kidney biopsy with collapsing FSGS and ATN. Blood cultures ordered for persistent fevers were positive for Cryptococcus neoformans. Biopsy of right flank revealed variably sized yeast forms within the dermis consistent with cutaneous cryptococcosis. Treated with amphotericin B/fluconazole followed by fluconazole with clearance of fungemia, resolution of fever and improvement of skin lesions. Immunosuppression was continued with reduced dose of tacrolimus and prednisone 10mg/day. Antimetabolite was discontinued. Persistent weakness and diaphoresis lead to testing for CMV with PCR at 51,000copies/ml, treated with IV ganciclovir with complete resolution of symptoms. Discharged home on maintenance dialysis with valganciclovir and fluconazole prophylaxis. He returned on day 70 of illness with a Cr of 1.2 mg/dl, a 24hour urine collection with a creatinine clearance of 28 ml/min and 2gms of proteinuria. Dialysis was discontinued due to renal recovery. At last clinic follow up, day 100 from diagnoses, Cr remains stable at 1.7 mg/dl off dialysis.

Discussion: Immune dysregulation in the setting of acute Covid-19 infection coupled with long term immunosuppression may have contributed to multiple opportunistic infections. Optimal approach for immunosuppression in KTRs with acute Covid-19 infection is still evolving. Our patient was successfully treated without stopping all immunosuppression. Our case underscores importance of having low threshold to test for various opportunistic infections even in the setting of active Covid-19 infection. While data on COVAN in KTRs is limited, our case shows potential for renal recovery even in a high immunologic risk kidney transplant recipient.

PO2096

Cytomegalovirus Infection in Renal Transplant Recipients: Incidence, Clinical Profile and Outcome

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Background: Cytomegalovirus (CMV) is one of the commonly encountered opportunistic infection following renal transplantation, usually seen in the first 6 months of transplant. CMV diseases, untreated has a mortality rate of about 90% however has good response with prompt detection and antiviral therapy. With the changing immunosuppressive regimen, variation in pattern and occurrence of CMV infection can be seen. We studied the incidence, clinical profile and outcomes of CMV infection in renal transplant recipients at our center.

Methods: 291 renal transplant recipients between 2014 and 2020 were reviewed, 27 patients who had CMV infection, diagnosed by CMV DNA detection with polymerase chain reaction were included in the study and their demographic details, clinical profile and outcome were noted and analyzed.

Results: Among the 291 renal allograft recipients, 27 patients had 34 episodes of CMV infection with an incidence of 9.27% with a mean follow up of 52.6 months. 37.1% received deceased donor renal transplant and 62.9% received live renal transplant. Mean age at transplant was 33.8yrs, 81.4% were males. 18.6% were females. rATG as induction was given in 11.1%, Basiliximab in 37.1% and 51.8% received no induction therapy, all of them received triple immunosuppression with steroid, tacrolimus and MMF as maintenance immunosuppression. PTDM was present in 33.4%. Valganciclovir prophylaxis post-transplant was given in 77.8% where as 22.2% did not receive prophylaxis. 12.5% infections were detected in < 3months, 28.5% between 3-6 months, 11.8% between 6-12 months and 41.2% in >12month post-transplant. Symptomatic disease with fever, malaise and leucopenia was the most common presentation in 73.5% of patients and 26.4% had asymptomatic infection with leucopenia and transaminitis. All patients received IV Ganciclovir for 14-21 days followed by oral valganciclovir for 90 days as treatment of infection episode. Patient survival and graft survival rate was 85.2% and 77.7% at our center.

Conclusions: Changing immunosuppressive regimen with early withdrawal of steroid post transplant use of valganciclovir prophylaxis has been associated with lower incidence and milder form of CMV disease in our population. There seems to be a change in the traditional risk factors for CMV infection which needs to be further studied.

PO2097

Resistant Cytomegalovirus After Kidney Transplant: Reduced Immunosuppression, High-Dose Valganciclovir, and Letermovir Prophylaxis Guided by T Cell Immunity Assessment


Introduction: CMV infections resistant to available antivirals are associated with increased morbidity and mortality after kidney transplant.

Case Description: A 58 yo male with ADPKD underwent pre-emptive LURTx. Is included Thymoglobulin, followed by tacrolimus, mycophenolate (MMF), and prednisone. Ten days after completing 6 mos. of valganciclovir (VGCV) prophylaxis (ppx) for CMV D+/R- serostatus he developed malaise and fever; CMV PCR was 197,033 IU/ml. VGCV 900 mg BID was started and MMF reduced. CMV PCR declined to 1399 IU/ml after 6 weeks, but then plateaued. CMV resistance testing (VGCV treatment day 62) found wild-type and mutated virus (UL54 T931I mutation and UL97 H520Q mutation) with predicted resistance to ganciclovir and cidofovir, but susceptibility to foscarnet. MMF was stopped and VGCV was increased to 1350 mg BID (150% dose for GFR). Foscarnet was avoided due to risk of nephrotoxicity, lack of disease, and time from transplant. There was no significant leukopenia on VGCV. Over the next 2 months, CMV PCR decreased to several hundred IU/ml to Below the Limit of Quantification. Letermovir ppx was started (VGCV 1 day 85) and VGCV stopped 8 days later. CMV PCR remained negative to BLQ on letermovir. Low dose MMF was restarted. T cell immunity panel (Viracor) showed good CD8 (5.04%), but low CD4 (0.15%) response, suggesting CMV infection would recur without prophylaxis. The patient remains on letermovir ppx. Letermovir is a CYP3A inhibitor, and tacrolimus required 25% dose reduction. DSA is negative at 1 yr post-transplant; creatinine remains around 1.1 mg/dl. Letermovir is a new CMV selective antiviral with novel mechanism of action inhibiting the viral terminase complex in late stages of replication. It is approved for prophylaxis in HCT, active against resistant strains, and not associated with myelo or nephrotoxicity.

Discussion: Resistant CMV infection is a clinical challenge. While susceptibility to foscarnet was predicted in this case, it was avoided (nephrotoxicity). Instead, immunosuppression was cautiously reduced and higher-dose VGCV was tolerated well. Once CMV viral load was negligible, a newer agent with novel mechanism of action, letermovir, was used for prophylaxis. Letermovir has been continued based on a low level of anti-CMV CD4 response, predicting high-risk for CMV recurrence.
PO2098

Rare Oral Lesions from Cytomegalovirus in Kidney Transplant
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Introduction: Cytomegalovirus (CMV) infection occurs frequently with kidney transplant recipients and it can affect any segment of gastrointestinal tract, but intra-oral localization is exceedingly rare. We present an interesting rare oral lesion from CMV infection in kidney transplant recipient.

Case Description: A 49-year-old male with a history of kidney transplant admitted with odynophagia, pancytopenia, neutropenic fever and new tongue lesion for two weeks. Examination showed a 3X3 cm elevated, adherent plaque. He has a history of resistant CMV viremia with failed therapy to low-dose valganciclovir, ganciclovir, and letomovir. He attained an undetectable CMV viral load with Foscarnet but it was complicated with acute renal injury, and he was transitioned to a high dose valganciclovir. His CMV PCR was < 50 on admission and biopsy of the tongue lesion revealed a positive immunohistochemical stain for CMV. We held his Valcyte on admission and his pancytopenia improved with filgrastim. Repeat CMV PCR increased to 17,000 IU/mL. He refused Foscarnet and was restarted on oral valganciclovir (1350 mg twice daily) and topical cidofovir. Even with undetectable CMV at presentation, he was noted to have disseminated infection. Mycotic and Gengraf were held and discharged on prednisone alone. At 2-week follow-up, the lesion and its associated symptoms had resolved.

Discussion: The presentation of oral CMV infection is highly variable with mucosal erythema, painful deep ulcers, erosions, but elevated tongue lesion have rarely been reported in literature to our knowledge. Treatment options includes ganciclovir, valganciclovir, foscarnet, letomovir and cidofovir. Early diagnosis is important because CMV increases other opportunistic infection and allograft rejection. Saliva and valganciclovir, foscarnet, letomovir and cidofovir. Early diagnosis is important because CMV increases other opportunistic infection and allograft rejection. Saliva and peridontal packets serve as reservoirs for CMV infection and frequent monitoring of periodontal health is needed post-transplant.

3X3 cm elevated, adherent tongue lesions

PO2099

Use of Epstein-Barr Virus (EBV) Cytotoxic T Lymphocyte Therapy in a Kidney Transplant Recipient with EBV-Associated Smooth Muscle Tumors
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Introduction: Epstein-Barr virus (EBV) is commonly associated with malignancies in transplant recipients, the most frequent being Post-transplant lymphoproliferative disorder. A rare, yet distinct, oncological entity are the EBV-associated smooth muscle tumors (EBV-SMTs). We present the case of multiple, malignant EBV-SMTs in a 34-year-old kidney transplant recipient, and the use of Tabelecleucel (EBV cytotoxic T lymphocyte therapy) as a targeted therapy for these tumors.

Case Description: A 34-year-old female kidney transplant recipient presented with fatigue, anorexia, and nighttime chills. Subsequent lab analysis revealed lymphopenia, elevated creatinine, hypercalcemia and high EBV viral load. PET scan revealed intensely avid FDG liver, splenic and lytic lesions of the left femoral head (Fig.1). Diagnosis of EBV-SMTs was confirmed by immunohistochemistry positive for smooth muscle actin, supporting smooth muscle differentiation (Fig.2), and confirmatory in situ hybridization for EBV-encoded RNA. Patient’s immunosuppression was switched from tacrolimus to sirolimus, and treatment was initiated with Tabelecleucel. At the time of the writing of this report, the patient has completed the first cycle of treatment with Tabelecleucel and preparing for a second cycle of treatment. The patient’s symptoms have improved significantly and creatinine, calcium and white cell counts have returned to baseline, EBV viral load fell from 4120 to 133 and PET scan showed stabilization of disease. We will continue to report on the patient’s progress.

Discussed: EBV-SMTs are rare tumors which can present in a variety of ways and are easily missed. They are typically aggressive, with a poor response to radiation and chemotherapy. Tabelecleucel is an EBV cytotoxic T lymphocyte therapy, primarily used in immunosuppressed and stem cell transplant recipients. Use in kidney transplant recipients is promising but requires further investigation to better understand optimal HLA matching of cell lines with recipients and allografts.


Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
**PO2101**

**When Is a Second Kidney Transplant Lifesaving? Effect of Waiting Time on Mortality in a Retrospective Cohort Study Using Target Trial Emulation**

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**Background:** The median kidney transplant half-life is 10 to 15 years, and because of the scarcity of donor organs and immunological sensitization of candidates for retransplantation, there is a need for quantitative information if, and when a second transplantation is no longer associated with a reduced risk of mortality compared to waitlisted patients treated by dialysis. Therefore we investigated the association of time on waitlist with patient survival in patients who received a second transplantation versus remaining on waitlist with continued dialysis treatment.

**Methods:** In this retrospective study we used data of 2346 patients from the Austrian dialysis and transplant registry merged with data from Eurotransplant who were waitlisted for second kidney transplantation during the years 1980 to 2019. The analysis was based on target trial emulation via a sequential Cox approach, in which each observed transplant allocation started a virtual trial mimicking a randomized trial via inverse probability weighting. The analysis was adjusted for recipient age and sex, year and duration of first transplantation, duration of dialysis, and time between first graft loss and initial joining date of the waiting list for the second transplantation.

**Results:** Second kidney transplantation showed an increased restricted mean survival time (RMST) at 10 years of follow-up compared to remaining on the waiting list (5.8 life-months gained, 95% CI 6.9 to 11.1). However, this survival benefit was diminished in patients with longer waiting time after first graft loss: RMST differences at 10 years of follow-up were 8.0 (95% CI 1.9 to 14.0) and 0.1 life-months gained (95% CI -14.3 to 15.2) for patients waiting a time after first graft loss of less than one year, and eight years, respectively.

**Conclusions:** Based on these data we conclude that a second kidney transplant leads to prolonged patient survival compared to remaining waitlisted by treatment by dialysis, but that the survival benefit diminishes with longer waiting time. Nevertheless, the higher quality of life after transplantation could be an argument to favour retransplantation if a suitable donor organ is available.

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**PO2102**

**Correlation Between CT Volumetric and Nuclear Renal Scans in Donors with Renal Asymmetry**

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**Background:** The Organ Procurement and Transplant Network (OPTN) lists renal asymmetry as a relative contraindication to donation. Clinicians resort to nuclear medicine scans to address discrepancies in kidney size observed by computed tomography (CT) volumetric. Our study looked at the correlation between CT volumetrics and nuclear medicine scan in addressing renal asymmetry.

**Methods:** At a large US transplant center, 62 potential donors with discrepancies in kidney size underwent both CT volumetric and nuclear medicine renal scans. The concordance correlation between the CT scan and nuclear medicine scan results of was determined separately for the right and left kidney.

**Results:** The donors were 52.2% years of age (median IQR: 38.5, 61.7), 29.0% male, and 59.7% white. By CT, the right kidney was 45.5% and left kidney was 54.5% of the overall volume. On nuclear medicine scans, right kidney was 46.8% and left kidney was 53.3% (Table 1). The Pearson correlation coefficient was 0.59 for the right kidney and was 0.58 for the left kidney (Figure 1, 2).

**Conclusions:** Nuclear medicine seems to offer no advantage over CT volumetrics and it adds to the overall time (30-60 minutes) and cost (~$1,587) of the donor evaluation process.

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[Correlation between CT scan and nuclear medicine scan for left kidney]

**PO2103**

**The Effect of Race Coefficients on Preemptive Listing for Kidney Transplantation**


**Background:** Race coefficients of glomerular filtration rate estimation (eGFR) formulas may be partially responsible for racial inequality in preemptive listing for kidney transplantation. The objective was to determine whether differences in racial distribution of preemptively listed candidates are reduced by calculating eGFR irrespective of race.

**Methods:** The Scientific Registry of Transplant Recipients database was used to evaluate differences in racial distribution of preemptive listing before and after application of the MDRD and CKD-EPI race coefficients to all preemptively listed non-Black kidney transplant candidates (eGFR modulation). Non-Black patients who had a recalculated eGFR > 20 were removed from the preemptive group. Odds ratios of preemptive listing were calculated by race with Black as the reference before and after eGFR modulation. Variables known to influence preemptive listing were included in the multivariable model.

**Results:** Among 385,087 kidney-alone transplant candidates from January 1, 2010 to December 2, 2020, 118,329 (30.7%) were identified as preemptively listed (median eGFR 20ml/min were removed. Compared to Black candidates, the adjusted odds of preemptive listing for White candidates decreased from 2.01 (CI 1.78-2.26; p<0.001) before eGFR modulation to 1.18 (CI 1.0-1.39; p=0.046) with the MDRD and 1.37 (CI 1.18-1.58; p=0.001) with the CKD-EPI equations after adjusting for race coefficients.

**Conclusions:** The racial distribution of preemptively listed candidates closely mirrored the distribution on the wait list when all races were subject to the Black race coefficients. Removing race coefficients in GFR estimation formulas may result in more equitable racial distribution of preemptively listed candidates.
PO2104

Increasing Frequency of Kidneys Allocated Out of Sequence by Organ Procurement Organizations
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Background: Allocation of deceased donor kidneys follows a ranked match-run list of potential recipients. Organ procurement organizations (OPOs) deviate from the mandated match-run in exceptional circumstances with unknown frequency.

Methods: Using SRTR data on all deceased donor kidney transplants (Ktx) in the US from 2015-2019, we identified cases where an OPO-initiated allocation exception occurred (Operational-OPO, Donor Medical Urgency, Expedited Placement). We examined the frequency of Ktx from these exceptions over time and characteristics of donors with kidneys placed out-of-sequence.

Results: From 2015-2019, 981 kidneys from 673 donors were transplanted via OPO-initiated allocation exception. These transplants (median KDPI 67, age 47 yrs) nearly doubled from 2015-2019: 153 kidneys in 2015 (1.5% of all Ktx) to 291 in 2019 (2.1%). 52 of 58 OPOs used this process at least once (median <1 per year, but 2 outlier OPOs accounted for 54% of the exceptions over 5 years [426 (43%) and 110 (11%), Figure 1]. Only 56% of transplant centers received any allocation-exception Ktx, with 2 centers receiving 26% (129 (13%) and 132 (13%)). Donor kidneys placed via allocation exception had less favorable characteristics, but only 25% had KDPI<85% (Table 1). Allocation exception Ktx went to recipients with 2 fewer priority points (median score: 4.3 vs. 6.3 in-sequence), equivalent to 2 less years of waiting time.

Conclusions: Two OPOs and a few Ktx centers are driving an increase in OPO-initiated exceptions in kidney allocation. Although kidneys placed out-of-sequence were lower quality, the majority did not meet the traditional threshold for marginal kidneys. Without monitoring, increasing pressure to improve organ utilization risks increasing out-of-sequence allocation potentially exacerbating disparities in access to transplantation.

PO2105

Survival Time Gained by Kidney Transplantation Compared to Remaining Waitlisted on Dialysis: A National Registry Study Using Target Trial Emulation
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Background: It is widely taken for granted that kidney transplantation improves survival compared to remaining on dialysis. However, the previous evidence based on cohort studies is at high risk of bias and randomized controlled trials are not feasible. We aimed to investigate survival of kidney transplantation compared to remaining waitlisted on dialysis across different transplant candidate ages as well as depending on waiting time applying causal inference methodology.

Methods: We included all dialysis patients recorded in the Austrian Dialysis and Transplant Registry who were waitlisted for their first kidney transplant between 2000 and 2018 and utilized repeated updates on waitlisting status and relevant covariates. To estimate causal effects of kidney transplantation across ages, we specified a target trial protocol mimicking a series of controlled clinical trials initiated at the ordered times of transplantation relative to waitlisting. At each trial in the series patients were classified as either treated (transplanted) or control (remained on waitlist). We estimated restricted mean time gained by transplantation using sequential Cox regression adjusted for confounding and adherence to the treatment strategy by inverse probability weights for treatment and censoring, and stratified our analysis by pre-transplant waiting time (up to 1 year, 1 to 2 years, more than 2 years).

Results: 4445 patients were included, 33% were women, mean age was 50 years. 3621 patients (81%) were transplanted, 1392 patients died. Transplanted patients had longer survival. 10-year restricted mean survival times compared to patients remaining waitlisted across all ages. E.g. a patient aged 70 at transplantation gained 0.85 years within 5 years posttransplant. Stratified analyses showed a gain of 0.61 years condition on having been waitlisted up to 1 year and 0.82 and 1.35 years condition on having been waitlisted for 1 to 2 years or more than 2 years respectively.

Conclusions: Our study provides evidence that state-of-the-art causal inference methodology for moderately increased survival after kidney transplantation in the elderly and irrespective of time on waiting list.
Late Presentation of JC Virus-Associated Nephropathy in a Renal Transplant Recipient

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Introduction: JC virus (JCV) is a Polyomaviridae family member. JC virus-associated nephropathy (JCVAN) is more common in renal transplant recipients in comparison to other organ recipients. We report a case of JCVAN presenting after fourteen years post-renal transplantation.

Case Description: A 65-year-old female with primary kidney disease attributed to chronic hypertension, who received a preemptive renal transplant in 2006. Postoperatively, her hospital course was uneventful, with a baseline creatinine of 1.1 mg/dL at discharge. Induction immunotherapy consisted of anti-thymocyte globulin, maintenance immunosuppression and antiproliferative agents. Tacrolimus was titrated to achieve a trough level of 3-5 ng/dL. JC Viremia responded to lowering IS and became negative. The allograft function declined with creatinine increasing from 1.55 mg/dL to 2.43 mg/dL. The patient underwent a renal biopsy, which revealed positive staining for SV40 in multiple tubular nuclei suggestive of a persistent polyomavirus in the renal tubules. The patient's renal function deteriorated with creatinine increasing from 1.55 mg/dL to 2.43 mg/dL. The patient underwent a renal biopsy, which revealed positive staining for SV40 in multiple tubular nuclei suggestive of a persistent polyomavirus in the renal tubules (Fig 1). Plasma levels of BK virus were negative. Plasma JC virus titers were 61,400 copies/mL. Mycophenolate was stopped, and tacrolimus was reduced to trough level 3-5 ng/dL. JC Viremia responded to lowering IS and became negative. The allograft function declined and the patient returned to dialysis in less than a year.

Discussion: JCVAN is unusual in renal transplant recipients. Risk factors include previous acute rejection episodes and male gender. Notably, this female patient had no proven previous episodes of acute rejection. JCVAN usually occurs within the first year post-renal transplant. However, the reported case was an older female diagnosed with JCVAN fourteen years following the living donor kidney transplant. The diagnosis of JCVAN is confirmed histologically by obtaining a kidney biopsy and the mainstay of management is reducing the degree of immunosuppression.

A Case of Unexplained Encephalopathy in a Kidney Transplant Recipient

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Introduction: Progressive multifocal leukoencephalopathy is a fatal demyelinating disease caused by the JC virus. Kidney transplant patients who are immunosuppressed are at higher risk of this infection.

Case Description: A 42 year old woman with CKD5 from FSGS who underwent a living donor kidney transplant 5 months ago, on immunosuppression with tacrolimus, mycophenolate and prednisone, presented with acute confusion, expressive aphasia and gait disturbance. Differentials included structural, infectious, metabolic and nutritional causes. A lumbar puncture and MRI brain were unremarkable. She was treated for suspected thiamine deficiency with intravenous thiamine. She developed myoclonus and hyperreflexia. Benzodiazepines and cyproheptadine were started with concern for serotonin syndrome. Tacrolimus dose was reduced with concern for calcineurin inhibitor toxicity. Within hours she developed cardiac arrest and was successfully resuscitated. CT head post arrest demonstrated diffuse cerebral edema and tonsillar herniation indicating devastating neurological injury. She was declared brain dead on hospital day 17. The CSF metagenomic testing panel later returned positive for JC virus. The diagnosis of JCVAN was confirmed histologically by obtaining a kidney biopsy and the mainstay of management is reducing the degree of immunosuppression.

BORON EXPOSURE AND DECREASED RISK OF MORTALITY IN KIDNEY TRANSPLANT RECIPIENTS

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Background: In a search for potential modifiable factors to improve long-term outcome among kidney transplant recipients (KTR), we studied dietary patterns in the Blue Zones, and hypothesized that boron exposure is associated with improved long-term outcome in KTR.

Methods: We determined 24h urinary boron excretion using inductively coupled plasma mass spectrometry in 693 stable KTR (57% male, mean age 53y), enrolled in the TransplantLines F&N Biobank and Cohort Study. Dietary intake was assessed using validated food-frequency questionnaires.

Results: Linear regression analyses showed that dietary intake of fruit, wine and nuts were key determinants of boron intake in KTR. In contrast, boron excretion was negatively associated with homocysteine and inflammation parameters. In total, 73 (32%), 47 (20%) and 30 (13%) patients died among the lowest, middle and highest tertiles of boron, respectively.
**Etiology for CKD**

HIV-Associated Lupus-Like Nephropathy in a Transplanted Kidney: An Associations of urinary boron excretion with risk of all-cause mortality, based on a trials are warranted to confirm the potential of dietary boron supplementation in KTR and other patient populations.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
H&E stain shows Necrotizing interstitial nephritis with prominent tubular necrosis and destruction associated with poorly formed necrotizing granulomas and neutrophils.

IF shows diffuse C4d staining in peritubular capillaries

PO2114
Medial Arterial Calcification and Transplant Outcomes
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Background: Medial arterial calcification, a disorder distinct from atherosclerosis, is common in ESRD and associated with poor outcomes. Since this lesion does not regress after renal transplantation, it may be associated with poor outcomes in these patients as well. This was tested in a retrospective cohort of females undergoing renal transplantation using breast arterial calcification (BAC) as a specific marker of medial arterial calcification.

Methods: We identified all females with renal transplantation (Tx) through 2017 with digital mammograms performed at this institution. Mammograms were examined for arterial calcification, which was quantified by summing the lengths of calcified arterial segments. BAC was considered present at Tx if present any time prior to Tx or within 1.5 years after Tx. BAC was considered absent if absent within one year before Tx and any time after Tx. Medical records were reviewed for graft loss, cardiovascular disease (CVD: myocardial infarction, amputation, stroke, or any revascularization), and risk factors.

Results: 132 patients were identified with qualifying mammograms, which were performed a median of 0.50 years from Tx date. Clinical follow-up ranged from 3-13 years after Tx. BAC was considered absent if absent within one year before Tx and any time after Tx. Medical records were reviewed for graft loss, cardiovascular disease (CVD: myocardial infarction, amputation, stroke, or any revascularization), and risk factors.

Conclusions: Medial arterial calcification was an independent predictor of renal allograft failure. It also predicted post-Tx CVD events but this was largely accounted for by adjustment of multiple confounding factors, compared to reference levels. There were no differences in the rate of DGF, re-hospitalization within 30 days across the groups. The moderate group was associated with a lower need for re-operation (HR: 0.39; 95% CI: 0.17 to 0.89; p=0.025).

PO2116
Peripheral Arterial Disease and Risk of Infection-Related Complications After Kidney Transplantation

Background: Infection-related hospitalizations after kidney transplantation are a common complication associated with significant morbidity and increased healthcare costs. Peripheral arterial disease (PAD) is a common comorbidity associated with poor wound healing and frailty, and may be an unrecognized risk factor for serious infections.

Methods: We included adults who received a kidney transplant in the US between 2006 and 2016. We used Fine-Gray models to assess the relationship between PAD and the composite outcome of infection-related hospitalization or infection-related death within the first year after transplant, while accounting for the competing risks of non-infection-related death or graft failure. We evaluated for presence of interactions between PAD and specific factors including age≥60, diabetes, and donor type (living vs. deceased) for this outcome.

Results: Out of 108,133 kidney transplant recipients (KTRs), 22,442 experienced the composite outcome in the first year after transplantation. In adjusted models, PAD was associated with a 38% higher hazard of the primary outcome (95% CI 1.34-1.43) [Figure]. Statistically significant interactions were present between PAD and donor type and age category. In subgroup analyses, PAD was associated with a higher risk for the composite outcome in living donor KTRs and with slightly higher risk in younger vs. older KTRs.

Conclusions: PAD was associated with an increased risk of infection-related hospitalization or death in the first year after transplantation, especially in subgroups who traditionally may not be evaluated for PAD prior to transplant, such as living donor KTRs and younger populations. Better screening for PAD even in young populations may improve our ability to reduce the risk of complications post-transplant.

PO2117
Pegloticase for Uncontrolled Gout in Kidney Transplant Recipients: Provisional Data Report of a Multicenter, Open-Label, Efficacy and Safety Study
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Background: Kidney transplant (KT) recipients have a high prevalence and severity of gout. Pegloticase (pegylated recombinant uricase) rapidly metabolizes urate and efficacy is not impacted by CKD stage. Immunomodulator co-therapy with pegloticase has improved treatment response rates over phase 3 monotherapy trials by attenuating anti-drug antibodies (ADAs). This ongoing Phase 4 trial (PROTECT NCT04087720) examines safety and efficacy of pegloticase in KT patients with uncontrolled gout (UCG).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: KT recipients with UCG (serum urate [SU]>7 mg/dL, intolerance/inefficacy to urate lowering therapy, and ≥1 of the following: tophi, chronic gouty arthritis, a2 flares in past yr) and functioning KT graft (eGFR>15 ml/min/1.73m2) on stable immunosuppressive (IMS) therapy are included (KT>1 y earlier). Pegloticase (8mg q2w for 24wks) safety and efficacy are examined. Primary endpoint was SU response during Month 6 (SU <6 mg/dL for ≥80% of time). Health Assessment Questionnaire (HAQ) pain (most severe: 100) and Disability Index (HAQ-DI) scores (max: 3) were evaluated.

Results: 20 patients enrolled (meansSD; age: 53.9±10.9 y, time since KT: 14.7±6.9 y, SU: 9.1±1.5 mg/dL, gout duration: 8.4±1.6 y; all on ≥2 IMS). At the time of analysis, 10 patients completed treatment, 3 discontinued treatment, 2 met SU monitoring rules (pre-dose SU>6 mg/dL at 2 consecutive visits) and discontinued pegloticase, and 5 were ongoing. All patients experienced initial substantial reductions in SU, which was maintained in the majority: 2 patients met monitoring rules. At week 24, no notable eGFR changes were observed. In patients that completed treatment, HAQ-pain and HAQ-DI scores improved by 26.7±30.3 (baseline: 35.9±30.2) and 0.2±0.5 (baseline: 1.0±1.0), respectively, at Week 24 (n=10). 7 SAEs (2 cellulitis, duodenal ulcer, sepsis, a-fib, diverticulitis, and localized infection) deemed unrelated to pegloticase, were reported in 5 patients. No anaphylaxis or IR events have occurred.

Conclusions: Preliminary results from the PROTECT trial, with Fall 2021 completion, demonstrate substantial and sustained SU decrease in the majority of KT recipients with uncontrolled gout. These findings are consistent with other reports on the effect of immunomodulation use with pegloticase.

Funding: Commercial Support - Horizon Therapeutics plc
PO2121
Hyophosphatemia in the Context of Hematopoietic Stem Cell Transplantation: An Underappreciated Complication
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Background: Hyophosphatemia (and hypokalemia) occur frequently in the context of hematopoietic allogeneic stem cell transplantation (allo-SCT) and during autologous SCT (auto-SCT) and have been attributed to uptake of these electrolytes by the reconstituting bone marrow. Similar metabolic complications can also occur after chemotherapy and during stem cell mobilization prior to auto SCT. These metabolic abnormalities have not been well described in the nephrology literature and in current textbooks of oncopharmacology. Aim of the research was to describe the clinical course of patients with these electrolyte abnormalities in the context of SCT, chemotherapy and after bone marrow stimulation prior to SCT harvesting.

Methods: Chart review of patients undergoing SCT, after chemotherapy and SCT for harvesting.

Results: We identified 42 patients with 67 episodes of hyophosphatemia and hypokalemia. The clinical features and course are provided in the table.

Conclusions: Besides uptake of phosphorous and potassium by the reconstituting bone marrow under the stimulation of granulocyte colony a stimulation factor, other factors contributing to these metabolic abnormalities include poor oral intake, the use of phosphate binders, diuretics and losses during renal replacement therapy.

Figure 1. Cumulative frequency of complications

PO2122
Kidney Graft Ultrasound (US) After Elective JJ Stent Removal (EJJR)
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Background: Improving kidney transplant (KTx) outcomes remains a primary challenge and KTx ureter JJ stenting has been used to prevent urological complications. There is no consensus about EJJR timing, and literature regarding routine US imaging after EJJR is lacking.

Methods: We retrospectively analysed all routine KTx US done in our Unit from 2016-2020 by an experienced interventional nephrologist. US post EJJR findings were compared with previous US. KTx characteristics, treatment outcomes and outcomes were recorded. We aimed to define incidence of urological complications diagnosed, US utility and best time interval to perform it.

Results: 345 KTx were done: 62.9% were male receptors, 81.7% had a first KTx and 91.5% of the organs were from a deceased donor. No routine US post EJJR was

Funding: Private Foundation Support
PO2124

SGLT-2 Inhibitor Treatment in Renal Transplant Recipients: A Single-Center Experience
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Background: Dapagliflozin, a sodium glucose transport protein 2 inhibitor (SGLT2-i), was recently approved for use in chronic kidney disease patients regardless of the presence of diabetes, after studies demonstrated improved renal and cardiovascular outcomes even in the absence of diabetes. The use of SGLT2-i in transplant recipients have been limited due to concerns for acute kidney injury (AKI) resulting from volume depletion or urinary tract infections (UTI) or other genital infections due to their glucosuric effect.

Methods: Retrospective review of all adult renal transplant recipients transplanted at our center between January 2013 and June 2020.

Results: 22 adult renal transplant patients at our center received treatment with an SGLT2-i during the study period. The patient’s ethnicity was representative of our patient’s population with 45% being Hispanic and 40% black. 68% of the patients were men and the median age was 64 years old. The vast majority of patients, 77%, had diabetes mellitus as the etiology of ESRD. 73% received a deceased donor kidney transplant and were started on SGLT2-i at a median time of 38 months post-transplant. 13 patients were treated with empagliflozin with a starting dose of 10mg daily, 7 with canagliflozin at 100mg daily, 1 dapagliflozin at 5mg daily, and 1 ertugliflozin at 2.5mg daily. The median creatinine at the start of treatment was 1.1mg/dl, urine protein creatinine ratio was 206 mg/g, and A1C 8.6%. SGLT2-inhibitors were well tolerated without significant adverse events. 4 patients developed hypoglycemia. Two patients developed a UTI and only 1 patient developed AKI requiring discontinuation of the drug. The median creatinine one-year post treatment initiation was stable at 1.1mg/dl, UPCR was 448.4 mg/g, and A1C was 7.7.

Conclusions: There was no significant interaction with the immunosuppression medications. The tacrolimus level remained stable and the patients did not require dose modifications post therapy initiation.

PO2125

Immunosuppression and Incident Cancer Risk in Older Kidney Transplant Recipients
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Background: Cancer is a serious complication after kidney transplant (KTx), especially among older adults. The relationship of immunosuppression (ISx) to cancer in older KTx recipients is not well described.

Methods: We examined USRDS data (2005-2017) to explore associations of ISx regimens (within 6 mo) with new-onset cancer diagnoses >6 mo to 5 yr post-KTx among Medicare-insured aged (age 65) adults. We used multivariate Cox regression with inverse propensity weighting to compare cancer risk vs. reference regimen of Thymoglobulin (TMG) or Alemtuzumab (ALEM) + Tacrolimus + antimetabolite + prednisone. Cancer diagnoses were also examined as time-dependent mortality predictors.

Results: Among 12567 older recipients, skin cancer incidence was higher with Tac+anti-metabolite avoidance (10.3%) and CsA-based ISx (8.9%) compared to TMG/ALEM+triple ISx (6.4%; P=0.03 and P=0.002), while non-viral driven/non-skin cancer was less common with CsA-based ISx (10.9% vs. 14.7%; P=0.03) (Fig. A). In adjusted models, IL-2Rab+triple ISx was associated with lower skin cancer risk (aHR 0.76 aHR 95% CI 0.61, 0.96); IL-2Rab+steroid avoidance was associated with increased non-viral driven/non-skin cancer (aHR 1.34, CI 1.04, 1.72), while CsA-based ISx predicted lower risk (aHR 0.72 aHR 95% CI 0.57, 0.91) (Fig. B). However, adjusted for time-averaging impact of viral-driven (aHR 2.27 aHR 95% CI 1.69, 3.03) and non-viral driven/non-skin cancers (aHR 2.27 aHR 95% CI 1.69, 3.03), CsA use (aHR 1.24 aHR 95% CI 1.14, 1.36) predicted increased mortality in older recipients.

Conclusions: Although CsA-based ISx appears beneficial for non-skin cancer risk in older KTx recipients, this regimen is associated with increased mortality. Cancer risk is a consideration in tailoring ISx in older KTx recipients.

Funding: NIDDK Support

PO2126

Belatacept Conversion in Proteinuric Kidney Transplant Recipients: Data from a Retrospective Cohort and a Prospective Trial
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Background: Proteinuria is a strong predictor of graft loss in kidney transplant (KT) patients. Treatment options for proteinuria are limited to ACEis/ARBs. Belatacept targets B7-1 which is also expressed on podocytes and has been linked to proteinuria by inducing podocyte migration. We examined the utility of belatacept conversion in proteinuric KT recipients.

Methods: In the phase I multicenter trial, we recruited EBV IgG+ adult KT recipients >6 months post-KT with an eGFR >30ml/min/1.73m2, proteinuria >1g/day on CNI-based immunosuppression. Patients were converted from CNI to belatacept. The primary outcome was 25% reduction in proteinuria in 12 months. In the retrospective cohort, we included patients who were converted to belatacept in 2015-2019.

Results: In the retrospective cohort, 12 of 77 belatacept conversion patients had pre-conversion proteinuria >0.4 g/g and follow up values. Baseline proteinuria decreased from 1.0±0.9 g/g to 0.68±0.9 g/g at >12 months (p=0.070). Mean eGFR increased from 37±12 to 49±15 ml/min/1.73m2 at 12 months. In the prospective cohort, 15 KT recipients were recruited. At 12 months post-conversion, mean (±SD) eGFR remained stable at 43.7±12.9 ml/min/1.73m2 and proteinuria improved from 2.5±1.9 to 1.7±1.8 g/g (p=0.068). Primary outcome was reached in 53% of the patients. None of the patients had graft rejection in the first year. One patient had worsening of proteinuria and discontinued belatacept. At 24 months, eGFR remained stable and proteinuria was 1.4±1.2 g/g. Figure 1 summarizes eGFR and proteinuria course from both cohorts.

Conclusions: Belatacept conversion in proteinuric KT recipients was associated with stable allograft function and reduction in proteinuria at 1 year and beyond.

Funding: Commercial Support - Bristol Myers Squibb
Outcomes of Thymoglobulin vs. Basiliximab Induction Therapies in 2DR Mismatch Living-Donor Renal Transplant Recipients


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Background: 2DR HLA mismatch indicates a high immunological risk of renal transplant. Induction therapy with Thymoglobulin and Basiliximab result in a marked reduction of acute allograft rejection rate and improve graft survival. However, the outcomes in 2DR HLA mismatched renal transplant recipients (RTRs) in the tacrolimus era remain understudied.

Methods: Using data from UNOS, all 2 DR mismatched RTRs who were maintained on tacrolimus and mycophenolate mofetil immunotherapy between September 2017 and September 2019 were included. Follow-up data was until September 2020. Patients who received transplants from living donors were included in the study. Collected data included recipient (age, sex, ethnicity, diabetes, body mass index), transplant (delayed graft function, cold ischemia time, number of previous transplants, panel reactive antibodies, HLA-mismatches, induction therapies, maintenance immunotherapy, and donor factors (donor type, donor age). RTRs were divided based on induction therapy into r-ATG and IL-2RA. Instrumental variable regression models were used to assess the effect of induction therapy on acute rejection episodes at 12 months post-transplant, serum creatinine levels at 12 months post-transplant, and graft survival. Type of induction therapy was instrumented for the transplant center to reduce the center effect on the choice of the induction therapy. The regression models were adjusted for the collected recipient, donor, and transplant factors.

Results: 788 patients received Basiliximab while 1727 patients received Thymoglobulin induction. There were no significant differences between Basiliximab versus Thymoglobulin induction in acute rejection episodes at one-year post-transplant (coefficient=-0.229, P value=0.106, 95% Confidence interval:-0.508 to 0.049), serum creatinine levels at one-year post-transplant (coefficient=-0.024, P value=0.128, 95% Confidence interval:-0.055 to 0.006) or overall graft survival (coefficient=0.008, P value=0.801, 95% CI:0.001 - 0.001).

Conclusions: The study showed no significant difference in acute rejection episodes or graft survival when using Thymoglobulin or Basiliximab in 2DR HLA mismatched living donor renal transplant recipients in the current tacrolimus-based maintenance immunosuppression era. Therefore, Basiliximab is a safe induction therapy in this group of patients.

PO2128
Outcomes of Early and Late Calcium Oxalate Deposition Following Kidney Transplantation


Background: Calcium oxalate deposition (CaOx) can result in progressive native kidney disease. The pathophysiology of hyperoxaluria in kidney transplant (KT) differs, especially early after surgery where the allograft encounters high levels. It is not clear whether CaOx in a kidney allograft portends worse outcomes. Determining its clinical relevance will influence the need for aggressive dietary or medication-based interventions.

Methods: All KT recipients at our center with CaOx on kidney allograft biopsy were categorized into two cohorts: delayed graft function (DGF; n=13) and late graft dysfunction (n=25). Up to 5 controls were selected per DGF case through event density sampling matched for organ type (kidney vs. simultaneous pancreas-kidney), prior transplants, and history of prolonged DGF prompting a biopsy (n=46). Controls for ‘late’ cases were matched for organ type, prior transplants, and living vs. deceased donor (n=125). Variables found to be statistically significantly associated with case status in bivariate analysis (p<0.10) were included in multivariate Cox regression analyses of allograft outcomes.

Results: DGF cases were more likely to have had gastric bypass surgery (7.7% vs. 0%, p=0.06) and less likely to have a history of rejection (7.7% vs. 37.0%, p=0.06) than controls. CaOx during DGF was not associated with increased risk of graft failure after adjustment (HR 1.1, p=0.87; Figure 1). ‘Late’ CaOx cases diagnosed median of 56.7 months (IQR: 9.8-108.9 months) after transplant were older at time of transplant (53.9 vs. 48.4 years, p=0.04) and less likely to be male (36% vs 61%, p=0.03) than controls. ‘Late’ CaOx was associated with a higher risk of allograft failure after adjustment (HR 3.2, p<0.001; Figure 2).

Conclusions: CaOx in kidney allograft during DGF may be a consequence of high circulating oxalate levels and was not associated with worse KToOutcomes. ‘Late’ CaOx, likely related to increased intestinal oxalate absorption, a phenotype similar to secondary hyperoxaluria in native kidneys, was associated with increased risk of allograft failure.

PO2129
HLA Antibody Elevation Following Red Blood Cell Transfusions in CKD: Results from the START-CKD Trial

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Background: Red blood cell (RBC) transfusion avoidance wherever possible is recommended in kidney transplant candidates in order to prevent the risk of allo sensitization. We have previously reported allosensitization following RBC transfusions in dialysis patients with anemia and advanced CKD, but no study has addressed allosensitization in patients with CKD not on dialysis. The START-CKD trial evaluated an ESA treatment on the incidence of RBC transfusions in anemic CKD subjects. This study prospectively collected transfusion data along with antibody (Ab) samples. We hypothesized that RBC transfusions would be associated with: a) development of de novo Abs, b) increase in relative strength of existing HLA Abs, and c) increase in calculated panel reactive Ab (cPRA).

Methods: We used two different cohort designs: matched cohort containing subjects with RBC transfusion in between 2 HLA Ab samples, versus subjects with 2 HLA Ab samples without intervening RBC transfusion event. Each transfused subject was matched with up to 2 non-transfused subjects with 4 variables. The second identified cohort consisted of cross-over subjects with longitudinal pre- and post-transfusion Ab samples allowing the subject to serve as their own control. In total, 476 samples from 211 subjects were tested for Ab reactivity to HLA by LabScreen single antigen (One Lambda).

Results: We identified 72 transfused and 124 non-transfused patients, and 54 crossover transfused patients. A greater proportion of patients experienced changes in MFI a ≥25% for class I and a ≥30% for class II antigens in the transfused compared with non-transfused patients in both matched (any change, 25% vs 7%; significant change, 24% vs 3%) and cross-over cohorts (any change, 19% vs 9%; significant change, 17% vs 2%). In the matched and cross-over cohorts, positive cPRA change occurred in 19% and 11% of transfused subjects, respectively, vs 5% and 6% of non-transfused subjects respectively.

Conclusions: RBC transfusion in patients with anemia and advanced CKD not on dialysis was associated with new HLA antibody development, increased risk of relative strength of antibodies and higher cPRA. These findings establish an important causal relationship between RBC transfusions and clinically relevant HLA Ab development for the first time in this population.

Funding: Commercial Support - AMGEN
PO2130
Chronic Active Antibody-Mediated Rejection: Response Rates to Treatment and Predictors of Graft Survival
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Background: There is limited information on response rates to Rx and predictors of graft survival following chronic active antibody mediated rejection (CABMR).

Methods: We reviewed changes in kidney function, DSA, and histology in 3-month surveillance biopsies after initial therapy with pulse steroids/IVIG or rituximab in kidney transplant recipients with CABMR between 01/2017 and 08/2020. Rx response was defined as ≥3 M eGFR within 10% of baseline, proteinuria (UPC) decline by > 15%, DSA decline by > 50%, and MVI (p) g score = 0.

Results: The study included 82 patients. 50% received rituximab. Mean time from Tx to cABMR was 10 years. Mean ptc, g, and eGFR at index biopsy were 1.1, 2.1, 0.2, and 2, respectively. 47 patients (57%) had measurable circulating DSA; Mean eGFR, and UPC were 38 mL/min and 1.6 g/dL. Thirty (37%) patients lost their allograft during the mean follow-up of 2.4 years. At 3M, Rx with pulse steroids/IVIG was associated with eGFR, UPC, DSA, and MVI response in 27%, 49%, 7%, and 19% of patients. The addition of rituximab improved response to 66%, 61%, 20%, and 69%, respectively. On univariate analysis, rituximab use (HR=0.13, p=0.001, 95%CI 0.05 to 0.34) and a response in eGFR (HR=0.11, 95% CI 0.02 to 0.49) were associated with improved death-censored graft survival. Multivariate analysis only retained eGFR response (HR=0.12, p=0.01, 95%CI 0.02 to 0.64).

Conclusions: Our study suggests that a return to baseline eGFR at 3M after initial biopsy is the best predictor of graft survival in patients with CABMR. Short-term histological and immunological response to treatment were not independently associated with graft survival.

Response Rate at Surveillance Biopsy

Table 1

<table>
<thead>
<tr>
<th>Response</th>
<th>Steroid/IVIG</th>
<th>Steroid/IVIG/Rituximab</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR</td>
<td>(14.0±17.7)</td>
<td>(27.2±18.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>UPC</td>
<td>25.1±49.9</td>
<td>25.6±49.5</td>
<td>0.65</td>
</tr>
<tr>
<td>DSA</td>
<td>0.4±0.9 (p&lt;0.01)</td>
<td>0.4±0.9 (p&lt;0.01)</td>
<td>0.997</td>
</tr>
</tbody>
</table>

PO2131
Outcomes of Acute and Chronic Antibody-Mediated Allograft Rejection in Kidney Transplant Recipients
Ayman Al Jundi, Laura Goldfarb Cyrino, Marie-Camille Lafargue, Leonardo V. Riella, Riella Lab, 1Massachusetts General Hospital, Boston, MA; 2Brigham and Women’s Hospital, Boston, MA; 3Universite de Paris, Paris, France.

Background: The optimal treatment regimen for antibody-mediated rejection (AMR) in kidney transplant recipients (KTRs) has yet to be established. The purpose of the study was to evaluate the outcomes of KTRs with acute and chronic AMR managed with different treatment regimens.

Methods: We conducted a retrospective cohort study of all KTRs with biopsy-proven acute or chronic AMR between January 2017 and September 2020 at a single center. The primary outcome was allograft loss at last follow up. Secondary outcomes included differences in allograft survival between treatment regimens, and changes in estimated glomerular filtration rate (eGFR) and urine protein-creatinine ratio (UPCR) at last follow up.

Results: 53 KTRs with AMR were included in the study. Mean age was 51 years, 50% were female and the most common cause of end-stage kidney disease was glomerular disease. 37% received living donor transplants, median number of human leukocyte antigen ABDR mismatches was 4, and 38% had pre-transplant donor-specific antibodies. For induction immunosuppression, 61% received anti-thymocyte globulin, 35% received basiliximab and 4% received alemtuzumab. 35% had acute AMR and 65% had chronic-active AMR. The time to biopsy, median (IQR) eGFR was 32 (22-42) mL/min/1.73 m² and UPCR was 1.1 (0.4-2.5) g/dL. For treatment, 72% received pulse steroids, 64% received intravenous immunoglobulin, 51% received plasma exchange (PLEX) and 43% received bortezomib. At a median follow up of 23 months, patient survival was 94% and death-censored allograft survival was 74%. Median (IQR) eGFR was 27 (11-43) mL/min/1.73m² and UPCR was 0.48 (0.17-0.97) g/dL. There was no difference in the risk of allograft loss in patients who received PLEX compared to those who did not (RR=0.97, 95% CI: 0.4-2.4) and in those who received bortezomib compared to those who did not (RR=0.8, 95% CI: 0.3-2.0). The risk of allograft loss was higher in KTRs with UPCR>3 g/dL at AMR diagnosis compared to those with <3 g/dL (RR 4.3, 95% CI: 1.6-11.6).

Conclusions: Higher proteinuria at AMR diagnosis is associated with a higher risk of allograft loss. Use of PLEX or bortezomib was not associated with lower risk of allograft failure in KTRs with AMR. Novel treatment regimens are needed to improve the outcomes of KTRs with acute and chronic AMR.
PO2133

Monoclonal Gammapathy in Kidney Transplanted Patients: Novel Insights into Long-Term Outcomes

Marie-Sophie Meuleman,1 Juliette Gueguen,2 Stephanie Vicca,1 Olivier Aubert,3 Bertrand Arnulf,1 Dany Anglicheau,4 Frank Bridoux,2 Camille Cohen,5 Hôpital universitaire Necker-Enfants malades, Paris, France; 6 Centre Hospitalier Universitaire de Poitiers, Poitiers, France; 7 Hôpital Saint-Louis, Paris, France.

Background: Monoclonal gammapathy (MG) is a frequent condition affecting 0.05 to 6% of general population. Little is known about the prevalence of MG and its consequences on long-term outcomes in the setting of kidney transplantation (KT).

Methods: We conducted a monocentric retrospective cohort study based on 2272 patients who underwent a KT from January 2007 to June 2019 at Necker Hospital Paris, France. A systematic extraction of serum protein electrophoresis (SPE) results performed during this period was used to distinguish patients with MG at the time of KT (MGKT) and patients who developed de novo MG (DVMG) after KT. Serum free light chain (SFLC) were retrospectively measured on stored frozen sera from MGKT patients, taken at the day of KT.

Results: We identified 66 patients with MGKT and 79 with DVMG. Patient’s characteristics are summarized in Table 1. Eleven (6%) patients developed a hematological disorder, i.e. post transplantation lymphoid disorder (n=6) and multiple myeloma (n=5), without difference between groups. Infectious complications were similarly frequent, regarding viral (n=68, 47%), bacterial (n=96, 66%) and fungal infections (n=12, 14%). Strikingly, median overall survival was significantly lower in MGKT patients compared to DVMG patients (78 months vs not reached, respectively, p=0.005). The five MGKT patients with an abnormal SFLC ratio (<0.3 or >3.3) at the time of KT tended to have lower OS compared to those with normal SFLC ratio (p=0.07), suggesting that abnormal FLC ratio might represent a risk factor for early death in KT recipients. Death censored graft survival was not different between groups.

Conclusions: By analyzing the most important cohort of KT patients with MG reported to date, we found that MGKT affects overall survival and that SFLC measurement at the time of KT may refine risk stratification. Measurement of SFLC and SPE should be incorporated to the pre-transplant evaluation workup.

Funding: Government Support - Non-U.S.

Table 1: Annual change in eGFR

<table>
<thead>
<tr>
<th>Ratio Measurement</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline to First Year</td>
<td>0.001</td>
</tr>
<tr>
<td>First Year to Second Year</td>
<td>0.001</td>
</tr>
<tr>
<td>Second Year to Third Year</td>
<td>0.001</td>
</tr>
<tr>
<td>Third Year to Fourth Year</td>
<td>0.001</td>
</tr>
<tr>
<td>Fourth Year to Fifth Year</td>
<td>0.001</td>
</tr>
<tr>
<td>Fifth Year to Sixth Year</td>
<td>0.001</td>
</tr>
<tr>
<td>Sixth Year to Seventh Year</td>
<td>0.001</td>
</tr>
<tr>
<td>Seventh Year to Eighth Year</td>
<td>0.001</td>
</tr>
<tr>
<td>Eighth Year to Ninth Year</td>
<td>0.001</td>
</tr>
<tr>
<td>Ninth Year to Tenth Year</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 2: Outcomes by induction therapy between 2009-2019

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. Patients</th>
<th>Rejection</th>
<th>Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATG/ALG</td>
<td>934 (39.1%)</td>
<td>53 (5.7%)</td>
<td>15 (1.6%)</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>92 (3.9%)</td>
<td>8 (0.9%)</td>
<td>2 (0.2%)</td>
</tr>
<tr>
<td>IL2</td>
<td>73 (3.1%)</td>
<td>10 (1.3%)</td>
<td>3 (0.3%)</td>
</tr>
</tbody>
</table>

PO2134

Renal Outcome and Infectious Complications Associated with Induction Regimens for Kidney Transplantation Among Children: A NAPRTCS and PHIS Collaborative Study

Daniella Levy-Frez,1,2 Helen Pizzo,4 Nancy M. Rodig,3 Troy Richardson,3 Michael J. Somers,1 The Children’s Hospital of Philadelphia, Philadelphia, PA; 4 Schneider Children’s Medical Center of Israel, Pethau Tikva, Israel; 5 Boston Children’s Hospital, Boston, MA; 6 Cedars-Sinai Medical Center, Los Angeles, CA; 7 Children’s Hospital Association, Overland Park, KS.

Background: Few studies compare induction agents in pediatric kidney transplants (KTs), and induction is often guided by local practice more so than specific outcome data. We evaluated how different agents affected outcomes in children enrolled in both the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) registry and the Pediatric Health Information System (PHIS).

Methods: Retrospective study of merged data from NAPRTCS and PHIS between 1997-2017. Participants grouped by induction agent: no induction, IL2 RB only, rATG/ALG, alantuzumab. Estimated GFR (eGFR) was calculated with adjustments for age, diagnosis, repeat KT status, delayed graft function, and rejection. Subgroup analysis evaluated rejection rates and infectious complications between 2009-2019. Outcomes were compared using chi-square or Kruskal-Wallis tests.

Results: 2410 KT recipients with data in both datasets were identified. 340 subjects (14.1%) received no induction, 960 (39.9%) IL2 RB only, 934 (39.1%) ATG/ALG, and 176 (7.3%) alantuzumab. Table 1 highlights eGFR decline, using ratios obtained by dividing any year’s eGFR by the preceding year. Annual decline in eGFR was slower in the ATG/ALG group vs IL2RB or alemtuzumab and higher among children transplanted between any year’s eGFR by the preceding year. Annual decline in eGFR was slower in the ATG/ALG group vs IL2RB or alemtuzumab and higher among children transplanted between any year’s eGFR by the preceding year. Annual decline in eGFR was slower in the ATG/ALG group vs IL2RB or alemtuzumab and higher among children transplanted between any year’s eGFR by the preceding year.

Conclusions: Long-term decline in eGFR was similar across all induction agents, though decline with ATG/ALG was lowest. Although rejection and BK viremia was lowest with alemtuzumab, there was no difference with EBV or CMV infection or post-KTx malignancy.

Funding: Private Foundation Support

Table 2: Comparison of rejection and infectious complications

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
<th>Rejection</th>
<th>Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>No induction</td>
<td>960 (39.9%)</td>
<td>54 (5.6%)</td>
<td>18 (1.9%)</td>
</tr>
<tr>
<td>IL2 RB only</td>
<td>934 (39.1%)</td>
<td>50 (5.4%)</td>
<td>15 (1.6%)</td>
</tr>
<tr>
<td>rATG/ALG</td>
<td>176 (7.3%)</td>
<td>16 (1.7%)</td>
<td>4 (0.4%)</td>
</tr>
</tbody>
</table>

PO2135

Bacteremia in Kidney Transplant Recipients with Septic Arthritis Is Perilous

James D. Alstott,1 Margaret R. Jorgenson, Christopher Saddler, Sandesh Parajuli, Nirovika Garg, Maha A. Mohamed, Didier A. Mandelbrot, Arjang Djamali, Fahad Aziz. University of Wisconsin-Madison, Madison, WI.

Background: Features and clinical sequelae of septic arthritis in the general population have been described, however, the epidemiology and outcomes of septic arthritis in kidney transplant recipients (KTRs) is limited, and the potential impact on graft function has not been reported.

Methods: A single-center, retrospective, observational cohort study including patients with a history of kidney transplant and subsequent septic arthritis between 1/1997/12/2017 was performed.

Results: During the 20-year study period 6,184 patients received kidney and kidney-pancreas transplants, of these 65 (1%) patients had documented diagnosis of septic arthritis. 51 patients had kidney alone transplants and 14 had simultaneous kidney and pancreas transplants. The mean age at the time of transplant was 50 ± 10.4 years. The mean time from the transplant to the septic arthritis diagnosis was 6.6 ± 6.6 years. The most commonly affected joint was the knee (38%), followed by the shoulder (11%) and hip (7%). Joint with hardware accounted for 14 (21.5%) cases. Staphylococcus species were the most commonly isolated bacteria (52%) followed by gram-negative rods (14%). Only two patients had fungus isolated from joint aspiration (one histoplasma and one aspergillus). Antimicrobials were used in all of the patients. The majority of patients were treated with either joint aspiration (39%) or I&D (39%). The need for curative amputation was uncommon (4%). When evaluating subsequent graft function, the mean eGFR declined 12 ± 8 ml/min/1.73 m2 at one year after diagnosis. The presence of bacteremia at time of diagnosis was associated with significant worse joint (HR 5.37, p=0.01, 95%CI 1.57 to 18.41) and graft outcomes (HR 5.37, p=0.004, 95%CI 1.53 to 9.35). By last follow-up, 21 patients lost their allografts and 28 patients died with functional kidney graft.

Conclusions: Septic arthritis is an uncommon complication in KTRs. When seen, it typically occurs >1 year after transplant with similar pathogens and management as in the general population. However, it appears to be associated with negative graft effects. A high index of suspicion, timely diagnosis, and appropriate management are needed to ensure optimal outcomes for septic arthritis in KTRs.
Methods: A total of 995 KTRs were enrolled in KoreaN cohort study for Outcome in patients With Kidney Transplantation (KNOW-KT) between July 2012 and August 2016. KTRs were categorized into 3 groups: nondiabetic, preexisting DM and PTDM. Vitamin D status at KT was defined to deficiency (<10 ng/ml), insufficiency (10-30 ng/ml) and normal (≥30 ng/ml). This study aims to investigate clinical significance of vitamin D based on diabetic status in KTRs.

Results: Nondiabetic group was 643 (64.6%), preexisting DM group, 267 (26.8%), and PTDM group, 85 (8.5%). In all groups, vitamin D levels gradually increased after KT, then showed equilibrium at 2 years, and decreased after 4 years, but there was no significant difference of vitamin D levels. The proportion of vitamin D deficiency at KT was the highest in preexisting DM group compared with other groups, but there was no significant difference of that since 1 year after KT. There were no significant differences of immunologic findings among them. The rate of cardiovascular event was significantly higher in preexisting DM group compared with other groups (P=0.001). Death-censored graft survival rate was significantly lower in preexisting DM group compared with other groups (P<0.049), but there was no significant difference according to vitamin D status. Death-censored graft survival rate in KTRs with preexisting DM and vitamin D deficiency was the lowest, and it showed the significant synergistic effect on the allograft outcome (P=0.022). In the multivariate analysis, older age was an independent risk factors for allograft failure (HR 1.045, 95% C.I. 1.005-1.087, P=0.026). Patient survival rate was significantly lower in preexisting DM group compared with other groups (P=0.008).

Conclusions: The prognostic of KTRs with preexisting DM and vitamin D deficiency was the worst comparing nondiabetic and PTDM groups. Therefore, careful monitoring after KT of candidates with pre-transplant DM and vitamin D deficiency is required.

PO2138
Network Science and Hemodialysis Patients’ Kidney Transplant Attitudes
Avrum Gillespie,1 Rafael Aljurbua,2 Zoran Obradovic,2 1Levis Katz School of Medicine at Temple University, Philadelphia, PA; 2Temple University, Philadelphia, PA.

Background: Hemodialysis patients’ attitudes towards kidney transplantation may depend on their local (egocentric) and overall characteristics of their clinic social network. We determine whether these local and overall social network characteristics improve machine learning (ML) logistic regression and neural network models of the patient’s transplant attitudes.

Methods: We surveyed hemodialysis patients’ social networks and transplant attitudes in two hemodialysis clinics. We evaluated which ML model (logistic regression vs. neural network) best classified a patient’s transplant attitude using survey and egocentric network data. Then, we tested whether multidimensional overall network information represented as a vector (node2vec) improved the model. Models were evaluated for accuracy, precision, recall, and F1-score using Python (version 6.1.4) and Gephi (0.9.2).

Results: The mean age of the 116 surveyed participants was 60 ± 13 years. Half (55%) identified as male, and 75% identified as Black. Figure 1 shows the 83 participants (circles) who were in a clinic social network. The 33 network isolates are not shown. Network members with positive attitudes (57%) are the red circles. Green circles are those with negative attitudes. Adding egocentric network data improved the accuracy of the ML logistic regression model of transplant attitudes from 58% to 68% and the F1 score from 65% to 74%. The ML logistic regression model outperformed the neural network model in F1 score (73% vs. 66%) when including isolated participants. Addition of the overall network data (node2vec) further improved the F1-score of the ML logistic regression model to 77%.

Conclusions: The participant’s social network characteristics improved ML classification of the participant’s attitude towards kidney transplantation. The ML logistic regression model outperformed the neural network model, testing the limits of ML models on smaller data. Future research will examine how patient social networks disseminate information and affect attitudes and behaviors towards kidney transplantation.

Funding: NIDDK Support

PO2137
Preeclampsia and Kidney Transplant: Offspring and Mother Outcomes in a Single-Center Cohort in the West of Mexico

Background: Pregnancy in a kidney transplant recipient (KTR) is possible and safe after a 1-2 year post transplantation, stable serum creatinine (<1.5 mg/dl), controlled or no hypertension, proteinuria in 24 hours ≤500 mg and stable immunosuppressive levels. Preeclampsia is a common complication in KTR pregnant women associated to worse maternal and offspring outcomes, there is scarce available information this topic in a KTR in Latin America.

Methods: Retrospective cohort study from October 2018 to April 2021 included 18 pregnant patients (≥18 years who got pregnant after KT). Serum creatinine (SCr), proteinuria before, during pregnancy and after delivery, the presence of hypertension before pregnancy, episodes of kidney graft rejections, immunosuppressant therapy, and preeclampsia were recorded from medical chart, and compared it to the offspring’s gestational age, weight, APGAR score, NICU requirement and NICU stay.

Results: The frequency of preeclampsia was 33%, none of them were diagnosed with hypertension before pregnancy. Three women died after delivering (no obstetric associated), 1 lost graft function (in PD), SCr was higher during pregnancy and after delivery, offspring’s gestational age was lower, offspring’s weight was considerably lower, as well as APGAR score in women with preeclampsia, all NICU requirement were in children whose mother had preeclampsia and they had a NICU media stay of 19 days. In a logistic regression analysis, preeclampsia is a risk factor to a lower APGAR SCORE (p=0.001), requirement of NICU (p=0.001) and NICU stay. Other results are shown in the table.

Conclusions: Age, time between KT and pregnancy, gestational age, hypertension, serum creatinine, cesarean delivery was not different among preeclampsia, compared to the control group. Children from preeclamptic women tend to have lower weight and had lower apgar score and higher NICU requirement.

Funding: Government Support - Non-U.S.

PO2139
Assessing Social Difficulties in Patients Treated with Kidney Replacement Therapy (Dialysis or Kidney Transplant)
Aljurbua,1, Mengxi Sun,1 Mengxi Yang,1 Hiba Alhabbal,1 Karma S. Gaytso,1 Ghazaleh Ahmadzadeh,1 Aysha Afzal,1 Madeline Li,2 Doris Howell,1 Istvan Mucs1.1 University Health Network, Toronto, ON, Canada; 2Princess Margaret Hospital Cancer Centre Department of Supportive Care, Toronto, ON, Canada; 3Princess Margaret Cancer Centre, Faculty of Nursing, University of Toronto, Toronto, ON, Canada.

Background: The Social Difficulties Inventory (SDI) is used in the clinical management of patients with cancer in the UK. We examine the construct validity of the SDI in patients with kidney replacement therapy (KRT: dialysis or kidney transplant [KT]).

Methods: This is a secondary analysis of data collected in multicenter, cross-sectional studies. Adults receiving KRT completed the SDI and other patient reported outcome measures. Clinical and sociodemographic characteristics were also collected. For SDI, the degree of difficulty is rated: no difficulty, a little, quite a bit or very much. 16 items form the SD16 and three subscales: “Everyday Living”, “Money Matters” and “Self and Others.” We used Cronbach’s alpha to assess reliability. We assessed the correlation of SD16 and its subscales with variables that measure similar constructs. Further, we compared scores between groups that are expected to have different degree of difficulties.

Results: 788 participants (mean[SD] age 57[15] years) completed the SDI. 61% of them were male and 58% were on dialysis. Internal consistency was good for all scales: α=0.87, 0.82, 0.75, 0.88, for “Everyday Living”, “Money Matters”, “Self and Others” subscales and the SD16, respectively. The “Everyday Living” subscale was moderately
correlated depression (Rho=0.61, p<0.001) and physical functioning (Rho=0.72, p<0.001). The “Self and Other” subscale was moderately correlated with depression (Rho=0.56, p<0.001). SD16 scores were higher for patients on dialysis vs KT (median [interquartile range – IQR] 7 [3,13] vs 3 [1,8], p<0.001). “Everyday Living” scores were higher in patients with Charlson Comorbidity Index of ≥2 (3 [0.6,5] vs 1 [0.3,5], p<0.001). “Mystery Matters” scores were higher in individuals facing high vs low material deprivation (6 [0.4] vs 8 [0.3], p<0.008). “Self and Other” scores were higher in participants that are uncomfortable or reluctant in relationships vs those that find it easy (3 [1,7] vs 1 [0,3], p<0.002).

Conclusions: These results suggest that the SD-16 and its subscales have good reliability and structural validity. Further research is required to explore the potential clinical benefits of using the SD16 in patients with kidney failure.

PO2140
Symptom Management Preferences of Kidney Transplant Recipients and Caregivers

Background: Kidney transplant (KT) recipients frequently experience physical, emotional, and social challenges. These are often understudied and can lead to impaired quality of life. Better understanding of the perspectives of KT recipients and their caregivers about their symptom experiences and management needs will improve post-transplant care for KT recipients.

Methods: As part of a larger study aimed at developing a patient-centered electronic assessment toolkit, adult (a18 years) KT recipients and caregivers of KT recipients were recruited for this study via flyers. Patients not fluent in English or cognitively impaired were excluded. Qualitative description was used to explore and understand participants’ post-transplant experiences and preferences. A semi-structured interview guide with open-ended questions was used to facilitate in-depth, individual interviews. Interviews were audio recorded and transcribed verbatim. Transcripts were analyzed via content analysis using deductive and inductive coding strategies. Codes and categories were developed and refined by the research team.

Results: Seven KT recipients and one caregiver (age: 52-76 years, 8-20 years post-transplant, 5/8 male) participated. Participants identified significant challenges in physical (e.g. fatigue, sleep disturbances, weight or mobility issues); emotional (e.g. depression, anxiety); and social (e.g. financial challenges, self-care, social roles) domains. Participants considered fatigue as the most troublesome symptom. Furthermore, patients described the clustering of their post-transplant symptoms across domains. For example, fatigue overlapped with depression and the inability to perform self-care activities and maintain relationships. Participants also expressed that their post-transplant care centered on physical symptoms with little exploration and support of psychological and social issues. Finally, participants emphasized that a care plan integrating all aspects of health is needed to adequately support their needs.

Conclusions: This analysis identified a range of patient-valued, physical, emotional, and social concerns, with fatigue being the most troublesome symptom. These findings will inform the development of future interventions to improve patient-centered post-transplant care.

PO2141
Airflow Limitation, Fatigue, and Health-Related Quality of Life in Kidney Transplant Recipients
Tim J. Knobbe,1,2 Daniel Kremer,1,2 Tji Gai,1,2 Cathy Annema,1,2 Stefan P. Berger,1,2 Stephan J. Balcker,1,2 Rijksuniversiteit Groningen, Groningen, Netherlands; 1Universitair Medisch Centrum Groningen, Groningen, Netherlands.

Background: Many kidney transplant recipients (KTR) suffer from fatigue and poor health-related quality of life (HRQoL). Airflow limitation may be an underappreciated comorbidity among KTR, which could contribute to fatigue and poor HRQoL in this population. In this study, we compared the prevalence of airflow limitation between KTR and healthy controls (HC), and investigated associations of airflow limitation with fatigue and HRQoL in KTR.

Methods: Data from the ongoing TransplantLines Biobank and Cohort Study (NCT03282841) were used. Airflow limitation was defined as forced expired volume in one second (FEV1) <5th percentile of the general population. Fatigue and HRQoL were assessed using CIS20R and SF-36 questionnaires.

Results: A total of 539 KTR (58% male, mean age 56±13 years) and 244 HC (45% male, mean age 57±10 years) were included. Prevalence of airflow limitation was higher in KTR than in HC (133 vs 25%, p<0.001). Airflow limitation was independently associated with higher risk of severe fatigue (OR 2.53, 95%CI 1.41 to 4.55, p<0.002) and poor HRQoL (physical component score (PCS): st β -0.10, 95%CI -0.19 to -0.01, p=0.034) in KTR. Fatigue mediated the association of airflow limitation with PCS and MCS for 76.2% and 99.6%, respectively (Figure 1).

Conclusions: Airflow limitation is common among KTR. Its occurrence more than doubles the risk of severe fatigue, and is associated with poor HRQoL. Mediation analyses show that airflow limitation causes fatigue, which in turn decreases HRQoL.

Since airflow limitation can be improved by treatment and training, it may be a promising therapeutic target to reduce fatigue, and consequently to improve HRQoL among KTR.

PO2142
Outcomes of Liver Transplant Recipients Who Developed AKI Before Liver Transplant
Pyavadee Homkrailas,1,2 Suphamai Bunnyapradit.1 1University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA; 2Bhumibol Adulyadej Hospital, Bangkok, Thailand.

Background: Multiple factors including level of kidney function, patient comorbidities and functional status may influence the decision whether to simultaneous liver-kidney (SLK) transplant or waiting for kidney function recovery in end stage liver disease. Consequence of waiting for subsequent kidney transplant (KT) those without kidney recovery is unknown.

Methods: The Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) data of patients who were initially listed for liver transplant (LT) alone who also developed acute kidney injury (AKI) requiring dialysis within 60 days before LT and subsequently listed for KT during year 2000 – 2018 were included. Kidney function recovery defined as discontinuing dialysis >1 year. Our cohort therefore included 1) SLK; 2) listed for subsequent KT within one-year after LT and 3) listed for subsequent KT after recovery.

Results: A total of 7,853 liver recipients received dialysis within 60 days before LT. There were 110 patients receiving SLK and 445 patients listing for subsequent KT within one-year. Seven thousand two hundred and ninety-eight patients had kidney function recovery and 301 (3.8%) patients were listed for subsequent KT after dialysis free >1 year. One-year patient survival rates were 78.1% (95%CI 69.2 – 84.8) and 86.0% (82.4 – 88.9) among receiving SLK and listing for subsequent KT within one-year group, respectively. Ten-year patient survival rates were 45.5% (35.2 – 55.0) and 49.2% (42.8 – 55.3), respectively. Patients who survive and had dialysis-free more than one year had the best ten-year survival which were 62.9% (55.8 – 69.1).

Conclusions: Only 7.1% of liver recipients who developed AKI requiring dialysis within 60 days before LT did not have kidney recovery and remain on dialysis. These patients who received SLK had lower one-year patient survival but comparable ten-year patient survival compared to patients who listed for subsequent KT within one-year after LT.

PO2143
Clinical Outcome After Combined Liver and Kidney Transplantation in Children in Europe: A CERTAIN Registry Analysis
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Background: Combined liver and kidney transplantation (CLKT) in children is still a challenging procedure and therefore performed only in specialized centers. Outcome of these patients is mostly published as single center reports. To gain more insights in outcome and specific challenges of this rare disease group we aimed for an European registry analysis.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Methods: We conducted a multi-center, retrospective, cohort study using data of the Collaborative European Pediatric Renal Transplant Registry (CERTAIN) and 50 pediatric renal transplant centers in Europe. For this specific study we established an additional dataset for liver allograft recipients which includes essential liver transplantation-related data. The survival curves were assessed with the Kaplan-Meier method and compared with the log-rank test. The statistical analyses were performed with SPSS, Version 27.

Results: In the study, 159 patients from 13 transplantation centers. The primary indication for transplantation was primary hyperoxaluria type 1 (PH1) in 64 patients, in 70 patients autosomal recessive polycystic kidney disease (ARPKD), and in 25 patients various other diagnoses. The median follow-up time was 3.9 years (range, 5 days-17 years). Patient survival was good with 9 deaths reported. This led to an overall patient survival of 94% with no difference between PH1 and ARPKD. The kidney and liver graft survival rates were 92.5% and 91.1%, respectively. Long-term cefTR calculations showed stable renal function until 9 years of follow-up. Thereafter, kidney function slowly deteriorates. Liver function tests were stable over the whole study period.

Conclusions: CERTAIN registry data showed that CLKT lead to an excellent patient and survival without a difference between PH1 and ARPKD patients. In addition, patient survival after CLKT is comparable to isolated liver or kidney transplantation. The retrospective study design may have led to a reporting bias.

PO2146
Gender-Based Disparities in Access and Survival Outcomes of Simultaneous Liver-Kidney Transplantation Among Liver Transplant Candidates with Renal Dysfunction in the United States
Giselle Peschard, 1 Mei Wang, 1 Yazen Al-Hosni, 1 Krista L. Lentine, 2 Su-Hsin Chang, 1 Tarek Alhamad. 1

Background: Post-liver transplant (LT) renal insufficiency is an established predictor of morbidity and mortality for liver transplant recipients. Current reports on renal outcomes in liver transplant candidates have exclusively focused on patients from the MELD era. There is little information on the progression of kidney disease since the implementation of the MELDNa scoring system. We sought to characterize the prevalence of kidney disease after LT and its risk factors during the MELDNa era.

Methods: This is a retrospective cohort study of 107 adult, single-organ, primary liver transplants performed at the University of Maryland Medical Center between January 2016 and January 2017, after implementation of the MELDNa scoring system. We determined the pre-transplant chronic kidney disease (CKD) status (defined as eGFR <60mL/min/1.73m² or dependence on renal replacement therapy) by using the CKD-EPI Creatinine equation, available lab values, and the renal replacement therapy (RRT) status within the 90 days prior to transplant. The primary outcome was persistent CKD or mortality at 12 months. Recipients of MELDNa exception scores as well as Status 1 liver transplants were excluded.

Results: The mean patient age was 54.2 ± 11.7 years, 74 male, 85 Caucasian, 30 with diabetes, 55 were hypertensive, and 27 had HCV. 32 patients had pre-LT renal insufficiency and 25 patients were on RRT at the time of LT. The overall 1-year mortality rate post-LT was 11.2%. 36 patients had CKD at 12 months. Among the patients with pre-LT renal insufficiency, 13 demonstrated improved renal function, 13 remained with CKD, 2 ended up on long-term RRT, and 4 died by 12 months. Renal insufficiency equivalent to CKD stage 4 or more or dependence on renal replacement therapy were associated with increased risk of recipient death or CKD at 12 months. Other variables including age, sex, HCV, DM, HTN, CKD Stage 3 MELDNa score, BMI, and organ rejection were not predictive of the outcome.

Conclusions: Our study in the MELDNa era patients suggests that 40% of the patients with pre-transplant renal dysfunction pre-LT recovered renal function by 12 months post-LT. RRT at the time of LT, and moderate to severe renal impairment prior to LT are risk factors for recipient mortality or persistent CKD at 1 year post-LT.

PO2145
Gender Disparities in Access to Simultaneous Liver-Kidney Transplantation in the Pre- vs. Post- Allocation Policy Eras
Giselle Peschard, 1 Mei Wang, 1 Yazen Al-Hosni, 1 Krista L. Lentine, 2 Su-Hsin Chang, 1 Tarek Alhamad. 1

Background: Gender differences in access to simultaneous liver-kidney transplant (SLKT) is not well-understood. We recently found that women are disadvantaged in access to SLKT, especially women not initially listed for SLKT. No studies have examined these disparities in SLKT access after the implementation of the SLKT allocation policy in 2017, intended to facilitate equity and utility organ allocation.

Methods: Using retrospective data from the Organ Procurement and Transplantation Network (OPTN) database, we identified two cohorts of patients on the liver transplant (LTX) and kidney transplant (KTX) waiting list with renal dysfunction (RD) from February 28, 2002 to August 9, 2017 (pre-SLK allocation policy) and from August 10, 2017 to March 31, 2020 (post-SLK allocation policy). Multilevel time-to-competing-events regression adjustment for center effect was used to examine the likelihood of receiving SLKT in both cohorts.

Results: A total of 3,389 candidates with RD were included and 5,823 candidates with RD listed for SLKT in the pre-SLKT allocation policy era. 9,668 candidates with RD listed for SLKT in the post-SLKT allocation policy era. Pre-SLK allocation policy era, females with RD listed only for LT had a 55% lower likelihood of receiving SLKT (aHR 0.45, 95% CI 0.39-0.51), compared to males (Figure 1). Post-SLK allocation policy era, females still had a 22% lower likelihood of receiving SLKT (aHR 0.78, 95% CI 0.70-0.88), compared to males (Figure 1).

Conclusions: Prior to the implementation of the SLKT allocation policy, women had a lower likelihood of receiving SLKT compared to male candidates regardless whether they were listed for SLKT. After the policy implementation, these disparities are reduced but persist. This calls for further work on developing new policies that address gender disparities in access to organ transplantation.
Development Following Paediatric Kidney Transplantation

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Background: This study aims to assess quality of life, mental health, motor development, executive functioning and medication adherence in paediatric patients following kidney transplantation.

Methods: In a cross-sectional study we used standardised tools (FABEL, KINDL, PedsQL, CBCL, M-ABC, WISC-V, BAASIS) to assess the relevant parameters and analyse them against the background of selected medical data.

Results: We included 53 kidney transplanted children aged 0-18 (732 (21)). Parents reported increased financial burden and fear of the future. Half of the patients showed some symptoms of mental distress. 34 of 32.5%) patients fulfilled DSM-criteria for mental health problems. Most frequent symptoms linked to depression and anxiety. Participants who started renal replacement therapy in their first three years of life mainly expressed symptoms of the externalising spectrum. Motor-development could be assessed in 47 patients. Developmental deficits could mainly be observed in the field of fine motor skills and dexterity as well as body-balance. In total 14/47 (23.4%) patients had fine-motor skills below the 2nd percentile. 24 (48.9%) had deficits in body-balance scoring below the 2nd percentile. Processing speed was assessed in a subgroup of 36 patients without cognitive developmental delay. Mean score was 84 (45-112; sd 16.0). 5/36 (13.9%) patients had results below the 2nd percentile.

Conclusions: Even after successful transplantation chronic kidney disease seems to impact on the overall health and development of the affected child. While nowadays allograft survival is considered to be acceptable, it is time to shift focus on quality of survival and non-renal consequences of a renal disease. Besides further research clinical programs are needed to offer tailored assessments and support.

Long-Term Outcomes of Kidney Transplantation in a Disadvantaged Population in Mexico

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Background: Access to kidney transplantation in Mexico was limited to patients with social security. Since 2010 at the Dr. Eduardo Liceaga General Hospital of Mexico, a kidney transplant program was established for patients with terminal chronic kidney disease living in extreme poverty or without social security. We aim to analyzed patient survival, graft survival, post-kidney transplant complications, and modification of work status before and after transplantation were analyzed.

Methods: Case-control study nested in a cohort. Kidney transplant recipients who were in disadvantaged conditions from 2010 to 2020 were analyzed.

Results: During the study period, 345 transplants were performed. The median age was 31.5 ± 11.58 years, 58.6% were men and 74% of the transplants were from living donors. Ninety patients (26%) with social security (With SS) and 255 patients (74%) were in disadvantaged conditions from 2010 to 2020 were analyzed. We included 53 kidney transplanted children aged 0-18 (732 (21)). Parents reported increased financial burden and fear of the future. Half of the patients showed some symptoms of mental distress. 34 of 32.5%) patients fulfilled DSM-criteria for mental health problems. Most frequent symptoms linked to depression and anxiety. Participants who started renal replacement therapy in their first three years of life mainly expressed symptoms of the externalising spectrum. Motor-development could be assessed in 47 patients. Developmental deficits could mainly be observed in the field of fine motor skills and dexterity as well as body-balance. In total 14/47 (23.4%) patients had fine-motor skills below the 2nd percentile. 24 (48.9%) had deficits in body-balance scoring below the 2nd percentile. Processing speed was assessed in a subgroup of 36 patients without cognitive developmental delay. Mean score was 84 (45-112; sd 16.0). 5/36 (13.9%) patients had results below the 2nd percentile.

Conclusions: Even after successful transplantation chronic kidney disease seems to impact on the overall health and development of the affected child. While nowadays allograft survival is considered to be acceptable, it is time to shift focus on quality of survival and non-renal consequences of a renal disease. Besides further research clinical programs are needed to offer tailored assessments and support.

Renal Transplant Biopsy Outcomes: A Nephrology and Radiology Standpoint in an Academic Center

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Background: Renal transplant biopsies are the gold standard for evaluating allograft dysfunction. Studies comparing biopsy safety outcomes between transplant nephrologist and interventional radiologist are lacking. We describe our academic center experience and outline their risk factors.

Methods: This is a retrospective study of patients who underwent percutaneous ultrasound-guided renal transplant biopsy (US-RTB) at a single center between January 2013 to August 2016. This cohort was stratified into two groups according to the team that performed the biopsy: interventional radiology(IR,n=447) and transplant nephrology(TN,n=231). The predictors of post-biopsy complications were assessed by multivariate logistic regression.

Results: A total of 678 US-RTB were performed in 573 patients. There was no significant difference in the rate of total complications, blood transfusion, or perinephric hematoma between the IR and TN groups. The regression analysis showed that the team that performed the biopsy was a significant predictor for total complications, blood transfusion or perinephric hematoma. The predictors of total complications were uncontrolled blood pressure and anticoagulation therapy. The predictors of blood transfusion were female sex, antiplalet therapy, anticoagulation therapy, and blood urea nitrogen. The predictors of perinephric hematoma were female sex, black race, uncontrolled blood pressure, and anticoagulation therapy(Figure).

Conclusions: Kidney transplant biopsies are safe when performed by transplant nephrologists and interventional radiologists in an academic center. Blood pressure control and management of anticoagulation are fundamental to decrease the risk of complications. Studies need to be done to understand why sex and race were predictors for blood transfusion and perinephric hematoma.
PO2151
Outcomes of Kidney Referrals from Donors with High Infection Risk in the Most Populous Donor-Specific Antibody
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**Background:** Overdose-death donors (ODD) increased from 1.1% of donors in 2000 to 13.4% in 2017. Kidneys from ODDs were discarded at a higher rate than trauma-death donors. US Public Health Service defines organs from individuals with opioid abuse as being at increased risk of infection with HIV, HepB and HepC. CAOP is the most populous DSA in the country and improving utilization of organs within the DSA is of great importance. We aimed to study the utilization of kidneys from High-Infectious Risk Donors in this DSA.

**Methods:** We obtained data from UNOS and the Organ Procurement Organization (OPO), OneLegacy between January 2015 and September 2020. We calculated the organ decline rate, organ referral rate and rate of organs refused under the UNOS organ referral code Donor age quality and Donor Social History. We also compare these results to the trauma-death donors.

**Results:** Out of 2686 kidneys that were considered for recovery, 382 kidneys were from ODDs between September 2017 and September 2020. 109 ODD kidneys (22.6%) were shared and successfully transplanted. 51 ODD kidneys were discarded locally in the DSA (22.2%), 47.5% were refused by centers due to Donor Age, Quality and Social History before being either transplanted or being discarded. 103 kidneys of the ODDs were not recovered or offered for transplant. 82 kidneys were recovered from Hepatitis C positive donors, out of which 52 (66.7%) were shared and transplanted outside the DSA and 15 were discarded locally.

**Conclusions:** Higher infectious risk increased risk donors were being shared and discarded at a high rate. Given we have more evidence that these higher infectious risk kidneys are transplantable efforts to improve their utilization are needed.

**Funding:** Private Foundation Support

PO2152
Lack of Insurance Predicts with Follow-up Deficiencies After Living Kidney Donation
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**Background:** Follow-up after living kidney donation in the United States has improved with recent policy mandates. We hypothesized that lack of insurance at donation may be a barrier to postdonation follow-up.

**Methods:** We examined Scientific Registry of Transplant Recipients (SRTR) data for 90,460 living kidney donors (LKD) in 2004-2018 to examine associations (adjusted odds ratio, aOR) of insurance status and other baseline factors with clinical and laboratory follow-up after donation.

**Results:** Follow-up increased over time, and was especially high in older LKD. Follow-up was lower in uninsured compared to insured LKD over time, including in the era of the Affordable Care Act (Fig A). In 2018, for uninsured vs insured LKD, respectively, clinical follow-up was 87.5% vs 90.4% at 6-months, and 76% vs 86.7% at 12-months, while 12-month lab follow-up was 55.4% vs 68.4%. In multivariate regression including adjustment for donation year and other baseline factors, uninsured status was associated with 7% lower odds of 6-month clinical follow-up (aOR, 0.93) and 14% lower odds of lab follow-up (aOR, 0.86). Follow-up was also significantly (P<0.05) lower for LKD who were African American (aOR 0.85) or Hispanic (aOR 0.91), unrelated to their recipient (aOR 0.85), not working (aOR 0.81) and with less than college education (Fig B).

**Conclusions:** While follow-up after living kidney donation is improving, uninsured LKD and those who are non-white, unemployed, and with lower education are less likely to receive follow-up. Novel initiatives are needed to provide access to follow-up care for at-risk LKD, including the uninsured and under-insured, to minimize the risk of socioeconomic disparities in long-term postdonation outcomes.

**Funding:** Other U.S. Government Support

PO2153
Visualizing Waitlist Outcomes for Kidney Transplant Candidates Whose Centers Have Declined Deceased Donor Offers
Cory Schaffhausen,1,3 Jon Miller,2 Arthur J. Matas,4 Ajay K. Israni,1,5 Andrew Wey,2 Allyson Hart,2 1Hennepin Healthcare Research Institute, Minneapolis, MN; 2Hennepin Healthcare Research Institute, Minneapolis, MN; 3Scientific Registry of Transplant Recipients, Minneapolis, MN; 4Chronic Disease Research Group, Minneapolis, MN; 5University of Minnesota Department of Surgery, Minneapolis, MN; 6University of Minnesota Department of Medicine, Minneapolis, MN.

**Background:** While transplant centers closely monitor posttransplant outcomes for each transplant recipient, centers currently lack data to monitor waitlist outcomes of individual candidates. Waiting candidates may receive multiple deceased donor organ offers. Centers may decline offers on behalf of the candidate in order to wait for a better offer. These decisions may impact waitlist outcomes because a better offer may not arrive, and dialysis-related morbidity may worsen. We sought to develop waitlist outcome reports to facilitate monitoring of candidates receiving donor offers.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Mark Andrew Elizabeth Aleksandra

Transplantation: Clinical - Underrecognized Risk Factors, Traditional Considerations, and Outcomes

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2 years (p=0.8; (4.8), and total body weight loss was 4.4 (8.2) kg (3.6% (6.5). BMI has not improved at of 43.1 (4.4) who had bariatric surgery by 1 year post consultation. Options were discussed. A comparator group (n= 15) included patients with the mean BMI for 1-year post weight loss consultations, where the surgical and non-surgical weight loss BMI. The best approach to weight loss to facilitate active listing is unknown. Additional research is warranted to evaluate additional relevant candidate and donor data impact of offer decisions made on behalf of waitlist candidates. Additional research is warranted to evaluate additional relevant candidate and donor data between May 7, 2019 and May 6, 2020. For each candidate, offers were identified from candidates who died after waiting offers, additional time on dialysis, and changes to quality and frequency of donor offers over time. Figure 1A depicts multiple patients on a waitlist. Each horizontal row represents one candidate, and each colored cell represents the highest-quality donor offer for each month, indicated by Kidney Donor Profile Index (KDPI). The report visually identifies several outcomes: candidates who died after awaiting offers, additional time on dialysis, and changes to quality and frequency of donor offers over time. Figure 1A depicts multiple patients on a waitlist. Each horizontal row represents one candidate, and each colored cell represents the highest-quality donor offer for each month, indicated by Kidney Donor Profile Index (KDPI). The best approach to weight loss to facilitate active listing is unknown. Additional research is warranted to evaluate additional relevant candidate and donor data impact of offer decisions made on behalf of waitlist candidates. Additional research is warranted to evaluate additional relevant candidate and donor data impact of offer decisions made on behalf of waitlist candidates.

Methods: A report mockup used patient-level data from the Scientific Registry of Transplant Recipients (SRTR). Data included a deidentified random sample of 200 kidney waitlist candidates from across the United States who had received at least one offer between May 7, 2019 and May 6, 2020. For each candidate, offers were identified from match runs from January 1, 2014 to May 6, 2020. Match run data included any offer that was ultimately accepted somewhere and resulted in a transplant. Offers in the match run after the last accepted offer and multi-listed candidates were excluded.

Results: The report visually identifies several outcomes: candidates who died after receiving offers, additional time on dialysis, and changes to quality and frequency of donor offers over time. Figure 1A depicts multiple patients on a waitlist. Each horizontal row represents one candidate, and each colored cell represents the highest-quality donor offer for each month, indicated by Kidney Donor Profile Index (KDPI). The best approach to weight loss to facilitate active listing is unknown. Additional research is warranted to evaluate additional relevant candidate and donor data impact of offer decisions made on behalf of waitlist candidates. Additional research is warranted to evaluate additional relevant candidate and donor data impact of offer decisions made on behalf of waitlist candidates.

Conclusions: The waitlist reports are a potential method for centers to self-monitor candidates and may supplement posttransplant outcome monitoring and existing decision support tools such as statistical outcomes calculators. The reports illustrate how offer frequency and KDPI change while candidates wait, as well as candidates’ dialysis burden. Additional research is warranted to evaluate additional relevant candidate and donor data impact of offer decisions made on behalf of waitlist candidates.
Results: The sample included 95 SOT recipients (Table), 68 of whom were not receiving RRT within 50 hours of ZS-9 administration. After adjusting for differences in follow-up time (34±11 hours), serum K* decreased by 0.88±0.81 mmol/L (p<0.002). The fully longitudinal downward trajectory of K* through up to 49 hours (p<0.001) is depicted (Figure). Adverse events were infrequent and mild as shown in the Table.

Conclusions: ZS-9 for treatment of acute hyperkalemia in hospitalized SOT recipients was efficacious and safe in this single center study. These findings are important in understanding the utility of ZS-9 broadly in SOT recipients.

Funding: Other NIH Support - REDCap use funded by UL1 TR000445 from NCATS/NIH

Table 1

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (n)</td>
<td>11 (6.25%)</td>
<td>28 (17.3%)</td>
</tr>
<tr>
<td>Recurrence of K+</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Age at diagnosis (y)</td>
<td>35 (22-82)</td>
<td>54 (19-72)</td>
</tr>
<tr>
<td>Age at administration (y)</td>
<td>35.5 (6-86)</td>
<td>65 (18-77)</td>
</tr>
<tr>
<td>&lt;5 yr (n)</td>
<td>7 (63.6%)</td>
<td>2 (25.0%)</td>
</tr>
<tr>
<td>BMI</td>
<td>28.1 (16-31)</td>
<td>22.9 (17-24)</td>
</tr>
<tr>
<td>African-American</td>
<td>30 (28.9%)</td>
<td>8 (26.6%)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>4 (3.8%)</td>
<td>4 (12.5%)</td>
</tr>
<tr>
<td>Time of diagnosis to ZS9 Administration hours</td>
<td>45 (0-144)</td>
<td>45 (0-228)</td>
</tr>
</tbody>
</table>

Unless noted, table entries are frequency (%) or mean ±/-%. SD.

PO2158
Glomerulonephritis After Kidney Transplantation: Prevalence, Clinical Characteristics, and Outcomes
Belen Martinez-Vázquez, Octavio R. Garcia-Flores, Cesar Flores Gama.
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Background: The Glomerulonephritis after kidney transplantation (GNKT) is an unknown disease, being the third cause of kidney allograft loss. It is defined as the development of glomerulonephritis (GN) in the allograft and is classified in: recurrent, novo and with unknown primary disease. The prevalence varies to 2-12%, the majority report figures to 6-8%. Recurrent GN have a higher risk of kidney allograft failure (KAF), the most frequent reported are IgAN (9.7%), FSGS (12.7%), MPGN (14.4%) and MN (12.5%).

Methods: We conducted a single-center, retrospective cohort study during 10 years in a tertiary hospital in Mexico City. We included 50 patients with biopsy-proven GN in the kidney allograft. We examined the relationship between clinical, biochemical and histologic parameters to predict the KAF in GNKT. We used age and sex adjusted Cox proportional hazards models.

Results: 50 patients were included, median age 39 years, 50% were female, mean creatinine and proteinuria at biopsy were 2.6±3.0 mg/dl and 2.8±2.9 g/day respectively. The main biopsy indications was allograft dysfunction in 46%. The main follow-up was 41.7±31.1 months. KAF occurred in 18 patients (36%). Of the total cases 7 corresponded to recurrent GN and 5 cases to de novo GN. The main etiologies were IgAN (24%), MN (10%), DDK 9 (18%) and PGN 5 (10%). 12 patients had acute rejection and was not associated with kidney allograft loss (p= 0.06).

Conclusions: In the present study we found that the incidence of GNKT is similar to that reported in other series, with primary GN being the ones with the highest incidence, in our series IgAN was the most frequent. There were 7 cases of recurrent GN and only 5 cases of the novo GN, the rest GNKT with unknown primary disease. It is noteworthy that in our series we identified 5 cases of ANCA-associated vasculitis. The KAF was 36%, similar to that reported in the literature and MN was the main etiology.

PO2157
Clinical Characteristics and Outcomes of FSGS in Kidney Transplant Recipients: A Single-Center Experience
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Background: Focal segmental glomerular sclerosis (FSGS) is a common etiology of chronic kidney disease in adults. Many progress to end stage renal disease requiring dialysis initiation and/or renal transplantation. It is also known to recur in transplantation, however there is limited literature addressing treatment options and outcomes in these patients. The purpose of this study is to evaluate clinical characteristics and post-transplant outcomes in kidney transplant recipients (KTRs) with primary and secondary FSGS.

Methods: This is a single-center retrospective study where data was collected from November of 2014 to December of 2020 on all KTRs with the diagnosis of FSGS within the Henry Ford Health System in Detroit, MI.

Results: A total of 39 KTRs were studied. 28% had primary FSGS and 71% had secondary. Baseline characteristics of KTRs can be found in table 1. 5 had recurrent and all had primary disease. Recurrence was suggested by worsening proteinuria (>3.5 g/day), and/or albumin <3.5 g/dl, and confirmed by renal biopsy. Median time of recurrence was 24 months post-transplant. Median proteinuria at time of diagnosis was 5.6 g. 3 that recurred were African American, 1 was Caucasian and 1 was Indian. A total of 4 out of 5 were treated with plasmapheresis. 2 had complete remission which was defined by reduction in proteinuria to <300 mg/day. One who did not achieve remission continues to have stable allograft function with ongoing proteinuria and the other had allograft loss at 96 months. None experienced adverse effects from treatment.

Conclusions: Recurrence of FSGS is more prevalent in patients with primary disease. Response to treatment is associated with significantly better outcomes and complete remission was achieved in 50% of cases.
Outcomes of Renal Transplantation in Patients with AL Amyloidosis: An International Collaboration Through the International Kidney and Monoclonal Gammapathy (IKMG) Research Group

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Background: New systemic therapies that successfully suppress toxic light chain production have led to an increase in the number of patients with AL amyloidosis who survive longer albeit with end stage renal disease. There is a critical need to identify patients in this specific population who can have good outcomes with renal transplantation.

Methods: We evaluated renal transplant outcomes in 237 patients from 5 countries with AL amyloidosis who underwent renal transplantation between 1987 and 2020. Cox regression analysis and Kaplan–Meier method were used.

Results: The majority of the patients (62%) underwent high dose melphalan and autologous stem cell transplantation (HD SCT). Overall survival (OS) from renal transplantation was 8.6 years with a median follow-up of 8.5 years. One-, three- and five-year OS from renal transplantation was 95%, 83% and 73%, respectively. The median time of graft survival was 7.8 years. Death censored graft survival at one-, three- and five-year was 79%, 69% and 69%, respectively. Survival outcomes were analyzed based on degree of hematologic response to therapy at the time of renal transplantation. Overall and graft survival were better in patients with complete hematologic response and very good partial response (CR+VGPR) compared to partial response, no response or treatment naive patients (TN). Survival was lower (16% vs 37%, p=0.01) and the time to amylodosis recurrence was significantly longer in the CR+VGPR group (median time not achieved vs 10 years, p=0.001). Comparing CR vs VGPR there was no difference in OS and graft survival. A total of 69 patients (29%) experienced hematologic relapse requiring treatment after renal transplantation. Graft survival for those who had a hematologic relapse was not statistically different from that of patients without relapse. Successful hematologic treatment prevented graft loss in 87% of patients who had amyloid recurrence in the graft.

Conclusions: Our results show that selected patients with AL amyloidosis undergoing kidney transplantation have good outcomes.

Primary Hyperoxaluria Type 2: Is Combined Liver Kidney Transplantation Necessary? Ayesha Mallick1, Emanuela Zauda,2 Fasika M. Tedla,1,2 1Icahn School of Medicine at Mount Sinai, New York, NY; 2Recanati/Miller Transplantation Institute at Mount Sinai, New York, NY.

Introduction: Primary Hyperoxaluria (PH) is a group of rare inborn errors of glyoxylate metabolism characterized by overproduction of oxalate. Oxalate is poorly soluble and is deposited as calcium oxalate in various organs, with the kidneys being the prime target leading to ESRD.

Case Description: 60-year-old female with a history of diabetes, hypertension and PH type-2 was seen due to tertiary hyperparathyroidism in an early post-renal transplant patient, which was managed and improved with parathyroidectomy.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
**PO2164**

**Association Between Recipient-Donor HLA Genotypes and Recurrent Membranous Nephropathy After Kidney Transplantation**

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**Background:** Recurrent membranous nephropathy (MN) occurs in up to 40% of kidney transplant recipients (KTRs) and is a major cause of graft loss. Recipient alleles at the HLA-D loci were found to have an increased risk of disease recurrence in KTRs with primary MN. However, the association between recipient-donor HLA characteristics and disease recurrence has not been explored.

**Methods:** We integrated data from two registries: United Network for Organ Sharing, and Australian and New Zealand Dialysis and Transplant registries between 1963 and 2020. Least Absolute Shrinkage and Selection Operator (LASSO) regression was used for variable selection. The penalization parameter was chosen by cross-validation and the covariates with non-zero coefficients were included in a logistic regression, together with class, and fitted using maximum likelihood. The model performance was evaluated using C-statistics.

**Results:** 8058 KTRs with primary MN were included and 232 had recurrent MN. Of the 266 variables, group LASSO selected 59 variables considered as variables of importance and were included in the adjusted logistic regression model. Recipient HLA genotype at DR11 (odds ratio, 95% confidence interval) (1.81, 1.30-2.51, p<0.001), B38 (1.93, 1.00-3.43, p<0.04), and B46 (6.75, 1.55-26.30, p=0.007) and donor-recipient HLA-B65 match (3.38, 1.07-8.35, p=0.02) were associated with an increased risk of recurrent MN, adjusted for recipient sex, ethnicity, comorbidities (diabetes, hepatitis C and cancer), immunosuppression regime (T cell depletion induction therapy, B cell depletion induction therapy, tacrolimus, corticosteroid, or other maintenance therapy), donor type, biopsy-proven rejection, and country of origin. The overall performance of the model was good (C-statistic 82%).

**Conclusions:** Recipient HLA-DR11, B38, B46 and donor-recipient HLA-B65 match were associated with an increased risk of recurrent MN in KTRs.

![Figure 1. Recipient-donor HLA characteristics associated with recurrent membranous nephropathy in kidney transplant recipients](image)

**PO2165**

**The Cumulative Dose-Dependent Benefit of Metformin in Kidney Transplantation Recipients**

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**Background:** The status of metformin as a primary choice is concrete, moreover it has recently been recommended for advanced chronic kidney disease. Although, the evidence of metformin usage in kidney transplant recipient (KTRs) is lacking. We investigated the effect of metformin in KTRs.

**Methods:** The primary outcomes were all-cause mortality and death censored graft survival (DCGS) and secondary outcome was biopsy proven acute rejection (BPAR). Cox analysis and propensity score matching were used. Time-varying and marginal structural cox was conducted for HbA1c. A defined daily dose (DDD) of WHO and a penalized spline curve were used to evaluate cumulative effect of metformin.

**Results:** In 2,048 diabetic KTRs, 1,199 patients were metformin user and 849 patients were non-metformin user. Pro-existing DM patients before transplantation were majority (78.7%) and tend to be less prescribed metformin than NODAT (DM 56.0%; NODAT 68.0%; P<0.001). The metformin user had a lower risk of all-cause mortality, DCGS and BPAR. Even after time varying adjustment of HbA1c, metformin usage was associated with significant reduction in all outcomes. (Table 1) Also, the more cumulative metformin exposure was correlated to the less risk of whole outcomes. (Figure 1)

**Conclusions:** In conclusion, metformin can be also considered as first-line anti-diabetic treatment in KTRs, not only from the benefit of lower mortality, graft survival and acute rejection, but also cumulative dose dependent protective effect.

![Figure 1](image)
Successful En Bloc Liver Kidney Transplant in a Morbidly Obese Patient
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Introduction: En bloc liver and kidney transplant is a variant for the traditional simultaneous liver kidney transplant (SLKT) technique that, with simultaneous reperfusion of both grafts through a common vascular anastomosis, can decrease operative time, cold ischemia time and risk of surgical site infections.

Case Description: A 50-year-old morbidly obese (BMI >50) male with history of ESRD due to hypertension, on hemodialysis for 4 years, decompensated NASH cirrhosis, ischemia time and risk of surgical site infections.

Discussion: KDPI is a valuable tool for adult donors but takes an oversimplified approach to the pediatric donor population. KDPI calculation includes donor age, weight, and height does not lead to a proportional scaling of the hazard in pediatric donors. It leads to misclassification and underestimation of a sizable number of kidneys from small pediatric donors. In addition, although it was found en bloc to be a significant factor and shown EBK versus SKT as an important predictor for graft performance, it was decided not to include this criterion in KDPI. Pediatric EBKs had the lowest acute rejection and delayed graft function rates in comparison with SKT. Furthermore, the cGFR for pediatric EBKs improves due to the continuous growth of pediatric grafts over time. In summary, modified KDPI tailored to the pediatric donors is warranted to accurately represent pediatric donor kidney survival, attract recipients and surgeons to address the problem of organ shortage.

PO2167
Little Goes a Long Way: Is Kidney Donor Profile Index (KDPI) a Good Predictor for Pediatric Kidney Donors Less Than 10 kg?
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Introduction: Pediatric deceased donor kidneys (DDK) constitute 10-12% of the DDK supply and are allocated using the same criteria as adult kidneys. Kidney Donor Profile Index (KDPI) is designed to predict kidney graft performance in adult recipients based on 10 donor characteristics. A KDPI scale goes from 1 (best) to 100 (worst). Most child donor kidneys classified as KDPI-C (≥85% but ≤85%) and KDPI-D (>85%) which makes them less desirable. In addition, few programs use kidneys from donors less than 1 year.

Case Description: We report a case of pediatric en bloc kidney (EBK) transplantation procured from a 7-month-old female donor, with a bodyweight of 7.7 kg. KDPI is 87%. The recipient is a 39-year-old female with a bodyweight of 54 kg and a diagnosis of ESRD secondary to biopsy-proven FSGS. The recipient had been on PD for 37 months, baseline sCr of 12-15 mg/dL and was oliguric. Cold ischemic time of the kidneys was 8 h 33 mins, warm ischemic time - 24 mins, estimated blood loss - 200 mL. Intraoperative challenges included tedious organ preparation and extremely small vessels requiring complex reconstruction along with the creation of 2 ureteral anastomoses. A postoperative complication included delayed graft function required 2 hemodialysis sessions. Thereafter graft function improved and sCr trended from 15.48 mg/dL to 1.46 mg/dL at 4 weeks follow-up.

Discussion: KDPI is a valuable tool for adult donors but takes an oversimplified approach to the pediatric donor population. KDPI calculation includes donor age, weight, and height does not lead to a proportional scaling of the hazard in pediatric donors. It leads to misclassification and underestimation of a sizable number of kidneys from small pediatric donors. In addition, although it was found en bloc to be a significant factor and shown EBK versus SKT as an important predictor for graft performance, it was decided not to include this criterion in KDPI. Pediatric EBKs had the lowest acute rejection and delayed graft function rates in comparison with SKT. Furthermore, the cGFR for pediatric EBKs improves due to the continuous growth of pediatric grafts over time. In summary, modified KDPI tailored to the pediatric donors is warranted to accurately represent pediatric donor kidney survival, attract recipients and surgeons to address the problem of organ shortage.

PO2168
Pickering Syndrome in a Kidney Transplant Recipient
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Introduction: Pickering syndrome (PS) refers to hypertensive urgency with recurrent flash pulmonary edema (FPE) due to bilateral renal artery stenosis (RAS) or unilateral RAS in patients with a solitary kidney or kidney allograft. We report a case of PS in a kidney transplant recipient.

Case Description: A 68-year-old gentleman with a history of end-stage kidney disease secondary to diabetic nephropathy treated with deceased donor kidney transplantation (on Belatacept, Mycophenolate Mofetil, and Prednisone) and a history of recurrent admissions for FPE presented 3-months post kidney transplantation with recurrent admissions for FPE. He was discharged home on POD 6 and the ureteral stent was removed on POD 48. At 3 months follow-up, the portal vein and renal artery remain normal. On backtable, the donor right renal artery and splenic artery were anastomosed to leave these arterial systems in continuity and perfused from the celiac trunk. Reperfusion occurred simultaneously in all organ systems after venous inflow followed by the venous inflow (Fig. 1B). Direct flow assessments by doppler was excellent. The ureter was anastomosed to the recipient’s ureter via a side-to-side cavocavostomy. Reperfusion occurred simultaneously in both arterial systems from the arterial orifice and distal IVC (Fig. 1A). The liver transplant was done with a piggyback technique with a side-to-side cavocavostomy. Reperfusion occurred simultaneously in both arterial systems from the arterial orifice and distal IVC (Fig. 1A). The liver transplant was done with a piggyback technique with a side-to-side cavocavostomy. Reperfusion occurred simultaneously in both arterial systems from the arterial orifice and distal IVC (Fig. 1A). The liver transplant was done with a piggyback technique with a side-to-side cavocavostomy. Reperfusion occurred simultaneously in both arterial systems from the arterial orifice and distal IVC (Fig. 1A).

Discussion: This case illustrates that liver kidney transplant is a variant for the traditional En bloc.

PO2169
Predictor for Pediatric Kidneys from Donors Less Than 10 kg?
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Introduction: Pediatric renal vein thrombosis (bRVT) is a critical complication after renal transplant with reported prevalence of 0.1% to 4.2% leading mostly to graft loss. Thrombolytic therapy and surgical thrombectomy has been described previously to treat bRVT. EOS is a modern and innovative ultrasound-facilitated catheter directed thrombolytic technique that proved superior for treatment of pulmonary embolism, deep vein thrombosis and arterial occlusion. It requires ultrasound core wire and infusion catheter for delivery of fibrinolytic agent such as Tissue plasminogen activator (tPA).
The ultrasound core wire or transducer generates ultrasound waves that help accelerate fibrinolysis, decrease the treatment time and decrease the risk of bleeding. The use of EKOS for iRT has not been reported in pediatric literature and we describe one such case. 

Case Description: We describe a 17-year-old boy with history of congenital nephrotic syndrome who has been on dialysis for 18 years. In 2005, his non transplant course was complicated by multiple episodes of deep venous thrombosis in right lower extremity, chronic right inguinal venous thrombosis with collaterals in lower extremities, maintained on anticoagulant therapy. He presented with serum creatinine elevation of 3.7 mg/dL (baseline of 1.4 mg/dL) and ankle edema. On renal US Doppler, the transplant renal vein was not seen and there was concern of lack of flow/RVT. CT venogram performed showed acute lumen occluding thrombus in left lower extremity venous system extending from left popliteal and femoral vein all the way to the left transplant renal vein in the left iliac fossa. He was started on IPa as per hematology without any improvement. Active discussions between hematology, nephrology and vascular surgery led to a trial of EKOS device to salvage the allograft. The patient then underwent thrombolysis using EKOS catheter with peripheral access to the left transplant renal vein, without any complications. The repeat renal US Doppler showed patent left renal transplant vein, with continued occlusion in the left external iliac vein. The serum creatinine returned to baseline 1.4-1.5 mg/dL one week after procedure.

Discussion: We describe a novel report of successful treatment of transplant renal vein thrombosis using EKOS catheter. Further studies are needed to provide more insight in this therapy.

PO2170

Reversal of Prolonged Delayed Graft Function Following Kidney Transplantation with a Belatacept-Based Regimen
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Introduction: Delayed graft function (DGF) following kidney transplantation is associated with adverse graft and patient outcomes. Many factors contribute to the development of DGF including ischemia-reperfusion injury. There is concern that calcineurin inhibitors such as tacrolimus can perpetuate DGF through tubular injury and vasoconstriction. The non-nephrotoxic co-stimulation blocker belatacept could potentially be beneficial in improving allograft function in such scenarios. We present a patient who experienced prolonged DGF following kidney transplantation that reversed following switching immunosuppression from a tacrolimus-based to belatacept-based regimen.

Case Description: A 73-year-old non-sensitized female with a history of coronary artery disease, hypertension, and type 2 diabetes mellitus on maintenance hemodialysis underwent kidney transplantation from a 63-year-old brain-dead donor with acceptable procurement kidney biopsy and kidney donor profile index (KDPI) of 88%. Cold ischemia time was 27 hours. She received induction with Thymoglobulin followed by tacrolimus/mycophenolic acid maintenance with early steroid withdrawal. In the peri-operative period, she experienced hemodynamic instability from cardiogenic shock requiring prolonged ICU stay. She developed DGF requiring dialysis support. Despite clinical improvement, she remained dialysis-dependent. Allograft biopsies at 2 weeks and 2.5 months post-transplant showed acute tubular injury and no rejection. Four months from transplant, immunosuppression was changed from tacrolimus-based to belatacept-based regimen. One week after this change, the urine output started improving and 10 days later the patient came off dialysis. Her serum creatinine continues to improve with a most recent value of 2.4 mg/dL and excellent urine output 3 weeks since stopping dialysis.

Discussion: The patient experienced very prolonged DGF after receiving a high KDPI kidney. We believe that replacing tacrolimus with belatacept facilitated the reversal of prolonged DGF and freedom from dialysis in this patient. Conversion of tacrolimus to belatacept in kidney transplant recipients experiencing prolonged DGF and utilization of de novo belatacept-based maintenance regimens in patients at high risk for developing DGF should be considered in order to improve graft and possibly patient outcomes.

PO2171

Disease-Specific Tissue RNAs as Diagnostic Tool for Kidney Transplant Pathology
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Background: MicroRNAs (miRNAs) play an important role in the development of renal diseases as epigenetic regulators of gene expression. However, there are limited data on miRNA tissue expression in transplantation-related kidney disease.

Methods: Study enrolled fifty-six transplant kidney patients with surveillance biopsy. Indication kidney transplant biopsy including pretransplantation biopsies, which were performed due to an increase in serum creatinine and nonspecific chronic changes in patohistological analysis were in the nonspecific group (NS, n = 6). The other three groups consisted of histologically proven antibody-mediated rejection (ABMR, n = 13), recurrent glomerulonephritis (rGN, n = 15), and acute tubular injury/necrosis (ATN, n = 10). We analyzed the expression of 6 selected miRNAs (miR-29c, miR-126, miR-146a, miR-150, miR-155, miR-223) and compared them with the respective disease process.

Results: When comparing miRNA expression before and after transplantation, there was no statistically significant difference in the expression of the analyzed miRNAs in CG, NS, and rGN, but we observed a statistically significant change in the expression profile of miR-146a and miR-155 after transplantation in patients with ATN and ABMR. Post-transplant biopsies showed differential expression of miR-146a and miR-155 in ABMR and NS compared to CG, miR-146a in ATN compared to CG and miR-223 in NS compared to CG. All but miR-146a showed differential expression in pretransplantation biopsies before transplantation of either NS, rGN, ABMR or ATN compared to CG, but the difference in expression after transplantation was more pronounced.

Conclusions: Our results suggest that miR-146a and miR-155 play an important role in pathological processes after kidney transplantation and also support the hypothesis that there are differences at the molecular level of the donor kidney that may predispose the kidney to certain types of pathohistological damage.

PO2172

Trajectory of Gene Expression Profile and Donor-Derived Cell-Free DNA Before and After Subclinical Acute Rejection
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Background: Subclinical acute rejection (subAR) is associated with poor kidney allograft outcomes. Blood gene expression profile (GEP) and donor-derived cell-free DNA (dd-cfDNA) have been used to exclude or diagnose kidney allograft rejection non-invasively. However, the trajectory of GEP and dd-cfDNA are unknown after subAR. We investigated the changes in GEP and dd-cfDNA after subAR.

Methods: We analyzed 100 subjects with GEP and 87 with dd-cfDNA, with some subjects in both groups. GEP and dd-cfDNA were performed before, at, and after the time of subAR. The cohort was extracted from a previously reported prospective, multicenter observational study. GEP was performed using a microarray-based 120 gene expression profile. The study reported dd-cfDNA as a percentage of donor cell-free DNA over total cell-free DNA. Locally estimated scatterplot smoothing (LOESS) and linear mixed effect models were used to analyze longitudinal changes of GEP and dd-cfDNA scores.

Results: A total of 1,314 blood samples were assessed. The longitudinal changes of GEP scores at a sample level are shown in Figure 1. GEP scores peaked at the time of subAR and decreased after. The slope of GEP scores was significantly different after subAR (slope difference = -0.201 p-value < 0.001) (Figure 2). On the other hand, dd-cfDNA continued to rise even after subAR (Figure 1). There were no significant changes to the slope of dd-cfDNA between pre-subAR and post subAR (p-value = 0.98) (Figure 2).

Conclusions: GEP scores significantly dropped, while dd-cfDNA persistently increased after subAR. How this may inform the biology of gene expression vs. dd-cfDNA after treatment of rejection requires additional study.

Funding: Commercial Support - Vircor-Earlis
PO2174
Sparse Intragraft Molecular Classifiers for Antibody-Mediated and T Cell-Mediated Kidney Transplant Rejection: Development, Validation and Value
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Methods: In a discovery cohort of 224 kidney transplant biopsies, microarray gene expression was applied to build two separate prediction models for presence of ABMR or TCMR. Variable selection for logistic regression was performed by lasso regularization. The diagnostic accuracy and prognostic value of the obtained ABMR and TCMR classifiers were assessed in two external validation cohorts.

Results: From the discovery cohort, a 2-gene ABMR classifier (PLA1A, GNLY) and 2-gene TCMR classifier (IL12RB1, ABPC1B) were derived. In the first validation cohort (N=403 biopsies), diagnostic accuracy was retained for both ABMR (ROC-AUC 0.80, 95% CI 0.75-0.85) and TCMR (ROC-AUC 0.83, 95% CI 0.77-0.89), also allowing discrimination between pure and mixed phenotypes. In the second validation cohort (N=282 biopsies), molecular ABMR and TCMR scores predicted graft failure (respective time-integrated AUC of 0.82 and 0.83) and identified kidneys at risk for graft failure which were not picked up by routine histology.

Conclusions: We identified and validated an intragraft 2-gene ABMR classifier and 2-gene TCMR classifier that can be used as diagnostic and prognostic tools. Robust variable selection models can yield parsimonious molecular classifiers for kidney transplant rejection, facilitating their interpretation and clinical implementation.

PO2175
Evolving Experience with TruGraf® Gene Expression Profile and TRACTM™ Donor-Derived Cell-Free DNA Testing in Kidney Transplantation: First Year Post Transplant and Beyond
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Background: Non-invasive validated rejection biomarkers are available to monitor kidney transplant recipients (KTR). Our program has replaced 3 and 12 month protocol biopsies (BX) with biomarker surveillance using TruGraf (TG) gene expression profile (GEP) validated to rule out subclinical acute rejection (subAR) and TRAC donor derived cell free DNA (dd-cfDNA) as a marker of allograft injury. This is the evolving single center experience of TruGraf-TRACTRAC surveillance for KTR within the 1st year post-transplant (post-txp) and beyond.

Methods: Our immunosuppression (IS) protocol is alentuzumab with tacrolimus maintenance, mycophenolate mofetil added in high risk KTR. TG and TRAC were done at 3, 12 months post-txp, and with IS changes (mTORi/belatacept conversion, IS decrease). Additionally, all KTR to be tested at least once to determine baseline status (immune quiescence). A positive (pos) TG, TRAC, or dynamic changes in post-op course prompts further evaluation and/or repeat TG/TRACTRAC testing. BX were done in cases with equipositive. Donor specific antibodies (DSA) tested in all patients.

Results: To date, 115 KTRs surveilled with TG and/or TRAC (149 TG and 90 TRAC tests). 30/41 KTR spared 3-month BX. Of 11 BX, 6 were for delayed/slow graft function (negative (neg) TG (Transplant eXcellence (TX)) and neg for acute rejection(DSA) and 5 were for pos TG (not-TX) with 3 neg for DSA/acute rejection. 12/16 KTRs avoided 1-year BX. 45 KTRs were > 1 year post-txp at testing (16 KTR > 10 years, 8 KTR >20 years). Table 1: TG/TRACTRAC concordance (n=82). 45% concordant neg, confirming IS adequacy. 50% discordant (TG or TRAC pos) prompting eval and correlation with findings (DSA, proteinuria, renal function). 5% concordant pos prompting BX, diagnosis, and/or subAR treatment.

Conclusions: Non-invasive TruGraf GEP with TRAC dd-cfDNA spares protocol BX in KTR at 3 and 12 months, while providing enhanced monitoring >1 year post-txp by ruling out subAR and assuring IS adequacy. Combined TruGraf and TRAC testing is promising, warranting larger studies for optimal synergy/frequency of serial testing, especially as subAR persists beyond the 1st year post-txp.

TruGraf-TRACTRAC Concordance

PO2176
LIMS1 Risk Genotype and Clinicopathological Features of Kidney Transplant Recipients

Background: LIM Zinc Finger DomainContaining 1 (LIMS1) homoygous risk genotype (rs893403 GG) is associated with increased risk of T-cell mediated rejection (TCMR) after kidney transplantation (KTx). However, prior studies lack detailed histopathological data. We examined the association of LIMS1 genotype with histopathology of allograft rejection.

Methods: A total of 110 KTx recipients underwent allograft biopsy were genotyped for LIMS1 rs893403 variant by Sanger sequencing followed by PCR confirmation of the deletion. The 2013 Banff scores from allograft biopsies were compared between recipients homozygous for LIMS1 rs893403 genotype GG (n=24) versus AA/AG genotypes (n=86).

Results: There were no differences regarding demographic, clinical and laboratory features between the genotype groups (Table 1). Allograft biopsies were performed after a median 6.2 years after KTx. Serum creatinine, proteinuria and donor specific antibody levels at the time of biopsies were similar between groups. Banff median tubulitis score was significantly higher in GG group compared to AA/AG group (1.4±2.65 vs 1.1±0.66, p=0.03) (Figure 1). There were also no significant differences regarding histopathological diagnosis between the groups (Table 1).

Conclusions: Kidney transplant recipients with homozygous LIMS1 deletion had higher tubulitis scores. Our data supports the role of LIMS1 locus in the pathophysiology of allograft rejection and motivates ongoing work to elucidate mechanisms of association of LIMS1 risk genotype and allograft injury.
PO2177
Association of Vascular Endothelial Growth Factor Gene Polymorphism with Allograft Survival in Renal Transplant Recipients
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Background: Endothelial cell dysfunction is a primary cause for late allograft loss in renal transplantation recipients. Vascular Endothelial Growth Factor (VEGF) is a pro-angiogenic factor that has an important role in the development and maintenance of physiological function of endothelium cell thus may determines the allograft function.

Methods: We did genotyping of VEGF SNPs among 320 renal allograft recipients(non-rejecters (160) and rejecters (160)) and 160 donors by PCR- RFLP technique. Intragraft VEGF mRNA and protein expression were analyzed by RT-PCR and immunohistochemistry. Serum VEGF level were analyzed by ELISA.

Results: On comparison between donors and recipients genotypes of VEGF +936 C>T [GT (OR=7.16; 95% CI=4.33-11.84; P<0.001) and TT (OR=49.30; 95% CI=11.84-209.16; P<0.001)], -1154 G>A [AG (OR=2.22; 95% CI=1.40-3.50; P=0.000)], -1190 G>A [GG (OR=2.31; 95% CI=1.22-4.01; P=0.00)], -1455 T>C [CT (OR=3.13; 95% CI=1.07-9.10; P=0.03)] shown risk of allograft rejection whereas mutant genotypes of -2578 C>A [CA (OR=0.45; 95% CI=0.26-0.79; P=0.005) and CC (OR=0.38; 95% CI=0.11-0.46; P=0.000)] and +405 C>G [GG (OR=0.43; 95% CI=0.20-0.91; P=0.02)] have shown protective association with rejection. The VEGF mRNA expression was also significantly higher in rejecters compared to non-rejecters which was found even higher compared to healthy donor. Mean serum VEGF levels was higher in rejecters compared to non-rejecters, which both were higher than those of donors. On IHC percentage of VEGF staining in glomerular capillaries and cortical peritubular capillaries was higher in rejector as compared to non-rejector.

Conclusions: The present study signifies genetic associations of all the mutant genotypes of VEGF +936 C>T, -2578 C>A, -1455 T>C, -1154 G>A, -1190 G>A, -2549 18bp Insertion/Deletion, and -1190 G>A SNPs to be at increased risk for renal allograft rejection.

Funding: Government Support - Non-U.S.
**PO2181**

**Lymphocyte Subpopulations in Clinical Practice After Kidney Transplantation: B Cell Levels Predict Renal Function at 1 Year**

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**Background:** Lymphocytes subpopulations play a key role in the immune response after kidney transplantation. Many different T-lymphocyte have been studied for their suitability to monitor allograft rejection. B cells have been associated with acute and chronic antibody mediated rejection and with poor outcome after transplant but are associated with tolerant kidney transplant recipients.

**Methods:** We retrospectively analyze the lymphocyte subpopulation (total lymphocyte, CD3+, CD4+, CD8+, NK, CD20+) pre transplant, after 1 week, at discharge and after 2 months post transplant in a cohort of kidney transplant recipients and we evaluate the impact of this subsets on kidney outcome.

**Results:** 187 kidney transplant recipients were included in the study and a total of 748 samples were analyzed. We didn’t find any association between lymphocyte subsets and delayed graft function, primary non function and graft rejection. We found an association between low level of B lymphocyte at 2 months and 1-year GFR less than 45 ml/min (p-value <0.05). We also found a significant decrease of B lymphocytes after 2 months post transplant in a cohort of kidney transplant recipients and we associated with tolerant kidney transplant recipients.

**Conclusions:** Combining the GEP and dd-cdDNA can improve the ability to distinguish acute rejection in both stable and unstable patients.

**Funding:** Commercial Support - Viracor-Eurofins

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**PO2182**

**Inflammatory Profile Associated with Non-HLA Antibodies to G-Protein Coupled Receptors in Pediatric Kidney Transplant Recipients**

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**Background:** The inflammatory profiles associated with non-HLA antibodies to G-protein coupled receptors in kidney transplant recipients (KTRs) are unknown. We have recently shown that angiotensin II type 1 receptor antibody (AT1R-Ab) and Endothelin-1 Type A receptor antibody (ETAR-Ab) are prevalent and associated with poor clinical outcomes and elevations in TNF-α, IL-1β, IL-8, IFN-γ, IL-17, and IL-6 in pediatric KTRs. We aimed to expand this analysis by examining the association between these non-HLA antibodies and a broad panel of inflammatory markers in a different cohort of pediatric KTRs.

**Methods:** 157 blood samples from 35 pediatric KTRs followed for 2 years post-transplant were analyzed. ETAR-Ab (ELISA), AT1R-Ab (ELISA), and 38 cytokines (Luminex, Table 1) were measured in blood samples taken at 6 months (m), 12m, and 24m post-transplant and during episodes of rejection. Based on previous receiver operating curve analysis, > 10 and >17 units/ml was considered positive for ETAR-Ab and AT1R-Ab. Patients were serially monitored for viral infections (CMV, EBV, and BK Virus), HLA DSA (Luminex), and rejection (protocol and indication biopsies).

**Results:** Blood samples positive for AT1R-Ab and ETAR-Ab had elevations in 28 of 38 cytokines (Table 1). On principal component (PC) analysis, AT1R-Ab and ETAR-Ab positivity was highly associated with differences in PC1. This relationship remained significant even when controlled for potential confounders, including age, sex, rejection, viral infections, and HLA DSA status (p<0.001, Figure 1).

**Conclusions:** AT1R-Ab and ETAR-Ab positivity is associated with a distinct inflammatory profile in pediatric KTRs in the first 2 years post-transplant. This distinct profile may help inform mechanistic studies and potentially identify new therapeutic targets to treat non-HLA associated allograft injury.

**Funding:** Other NIH Support - NIAID, Private Foundation Support
PO2183
Immunoglobulin G (IgG) Glycosylation, Renal Function, and Anti-body-Mediated Rejection in Renal Transplant
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Background: IgG glycome composition is a key regulator of immune system modulating inflammation at multiple levels. It has been associated to aging, infections response, autoimmune diseases or early kidney failure. Its role in KT has not been studied. Our aim was to analyze the prognostic and diagnostic value of IgG glycans in renal function after 1 year of KT and in antibody-mediated rejection (AMR).

Methods: We analyzed 24 essential IgG glycans by High performance Liquid Chromatography grouped them by biological function, according to the proportion of Galactosylated, Agalactosylated, Sialylated, Fucosylated and Bisecting-GlcNAc structures. We measured baseline IgG glycans and one year after KT in 248 recipients (62%M:38%M) of 55.9±13.6 years, 36 with AMR. Association models were adjusted by donor characteristics, baseline renal function, age/sex, BMI, ATN-postKT and comorbidities.

Results: Differences between IgG glycans at baseline and 1 year were associated with the achieved renal function: Higher Sialylation (Coeff [95% CI] 2.07 [0.23-0.3.9]) and Galactosylation (1.84 [0.0-3.6]) the better renal function and higher proportion of agalactosylated glycans associated worse renal function -2.02 [-4.1- -0.34]. AMR occurred more frequently in patients with a higher proportion of Agalactosylated glycans (OR [95% CI]) 1.7 [1.15-2.51] and less in those with a greater proportion of Galactosylates 0.59 [0.4-0.87], Sialylates 0.67 [0.45-0.9] and Bisecting-GlcNAc 0.66 [0.45-0.9] (Figure)

Conclusions: Glycans, that modulate the IgG function, are a potential prognostic tool for renal function in KT and as a diagnostic support in the identification of patients who develop AMR.

PO2185
Impact of Low-Normal vs. High-Normal Baseline Donor-Derived Cell-Free DNA Levels on Two-Year Allograft Function Following Kidney Transplantation
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Background: Donor derived cell free DNA (dd-cfDNA) is a biomarker that helps to predict acute rejection in kidney allografts. Baseline dd-cfDNA levels are ≤1% in 96% of kidney transplant recipients (KTRs) and a value ≥1% suggests allograft injury usually from acute rejection. dd-cfDNA levels <1% are considered as normal. We tested whether low-normal vs. high-normal baseline dd-cfDNA values would have differing impact on longitudinal allograft function.

Methods: We identified patients who underwent kidney transplantation at our center between September 2017 and June 2020 and had dd-cfDNA levels (<1% and ≥1%) under the surveillance protocol at or around 8 weeks post-transplantation. Those KTRs with dd-cfDNA levels <1% were included in the analysis. Patients were divided into 2 groups based on the dd-cfDNA levels: group 1 with dd-cfDNA <0.5% (low-normal) and group 2 with dd-cfDNA 0.5-0.99% (high-normal). Estimated glomerular filtration rates (eGFR) between the groups at 3 month intervals were compared using box plots and longitudinal eGFR up to 2 years post-transplant were compared between the groups using linear mixed model.

Results: There were 111 patients included in the analysis including 62 males and 49 females. Among the study group, 39 had living and 72 deceased deceased donor kidneys. There were 96 patients in group 1, and 15 patients in group 2. We observed no differences either in 3-month interval cross-sectional eGFRs (fig 1A) or 2-year longitudinal eGFRs (fig 1B) between the groups.

Conclusions: Our analysis found no differences between early post-transplant low-normal and high-normal baseline dd-cfDNA levels in terms of the impact on eGFR up to 2 post-transplant years in KTRs. These findings support the use of 1% cut off as a threshold to separate normal from abnormal dd-cfDNA levels.

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Underline represents presenting author.
PO2186
Baseline Trends in Tacrolimus Intrapatient Variability in Pediatric Kidney Transplant Patients
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Background: High tacrolimus intrapatient variability (IPV) is a known risk factor for inferior graft outcomes in kidney transplant patients. Baseline trends in tacrolimus intrapatient variability have not been well-defined in pediatric kidney transplant patients.

Methods: Pediatric patients who received a kidney-only transplant from 2010-2018 at a single center were considered for inclusion. Patients with follow-up time of at least 1 year were included. Tacrolimus IPV was determined using the mean coefficient of variation over the immediate 6-month time period prior to each tacrolimus level at each year post-transplant. All available tacrolimus levels were included in the analysis. Patients were stratified by age at time of transplantation (ages 1-6, 7-12, 13-18 years). A paired t-test was performed to evaluate the IPV change with increasing time post-transplant, with a specific post-transplant year tested against the prior year for each age group.

Results: 220 pediatric kidney transplant patients met inclusion criteria. Median age was 12.8 years. 117 patients (53.2%) were male, and 54 (24.5%) underwent living donor kidney transplant. IPV trends varied by age group, but IPV was high for all groups during the first year. After the first year, IPV decreased over time for patients in the 1-6 years group while it increased for those in the 7-12 and 13-18 years groups (Figure 1).

Conclusions: Tacrolimus IPV patterns differ in pediatric kidney transplant patients based on age at time of transplantation. It is likely that in the youngest group of patients, factors other than nonadherence explain their initial prolonged high IPV. More research is needed to quantitate and better understand the factors influencing variability in children given the association between IPV and adverse graft outcomes.

Figure 1. Tacrolimus intrapatient variability (IPV) trends over time post-transplant for different age groups

PO2187
The Impact of Intrapatient Tacrolimus Trough Level Variability over 2 Years Post Transplant on the Long-Term Allograft Outcomes in Kidney Transplant Recipients
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Background: The current study aimed to determine the impact of tacrolimus (TAC) trough level (CO) intra-patient variability (IPV) over 2 years after kidney transplantation (KT) on allograft outcomes.

Methods: In total, 1,143 patients with low immunologic risk were enrolled. The time-weighted coefficient variability (TWCV) of TAC-C0 was calculated, and patients were divided into tertile groups (T1: <24.6%, T2: 24.6–33.7%, T3: ≥33.7%) until 2 years after KT. All available TAC-C0 levels at each year post-transplant were included in the analysis. Patients who received a kidney-only transplant from 2010-2018 were divided into tertile groups (T1: <24.6%, T2: 24.6–33.7%, T3: ≥33.7% until 2 years after KT showed the highest risk for death-censored allograft loss (DCGL), and T3 itself was an independent risk factor for DCGL (adj usted hazard ratio (HR) 1.853, P = 0.029). In addition, sustained TWCV ≥33.7% until 2 years after KT showed the highest risk for DCGL (HR 2.395, P = 0.013). Moreover, the changes in TWCV during the 1st–2nd post-transplant year significantly affect to DCGL occurrence (HR of low/high 2.086, P = 0.045, HR of high/low 1.813, P = 0.021). Patients with an average TAC-C0 of ≥5 ng/mL in the high/high group were at highest risk for DCGL as well.

Conclusions: In conclusion, TAC-IPV is an important factor that can significantly affect comprehensive allograft outcomes. TAC-IPV after 1st year of KT was also considered an important factor for allograft outcomes. Moreover, TAC-IPV can significantly affect allograft outcomes even with a high average TAC-C0.

PO2188
The Balance Between Memory and Regulatory Cell Populations in Kidney Transplant Recipients with Operational Tolerance

Background: Donor-reactive memory cells represent a barrier to long-term kidney graft survival. A better understanding of regulatory mechanisms that counterbalance alloreactive memory responses may help to identify patients with operational tolerance.

Methods: The prospective, bacitracin BALANCE study investigated the equilibrium between memory T cell subsets and regulatory T or B cells (Tregs, Bregs) in peripheral blood of kidney transplant recipients with operational tolerance (N=8), chronic rejection (N=8), and different immunosuppressive treatment regimens (N=81). Patients on hemodialysis and healthy individuals served as controls (N=50). In addition, the expression of Treg- and Breg-associated molecule genes was analyzed.

Results: Patients with chronic rejection showed a disrupted memory T cell composition with a significantly increased frequency of circulating CD8+ terminally differentiated effector memory (TEMRA) T cells than in patients with operational tolerance, patients on hemodialysis, or healthy controls (P<0.001). Compared to all other transplant recipients, the lowest ratios between CD8+ TEMRA and naive or effector T cells and the highest frequency of Tregs and transitional Bregs were found in operationally tolerant patients (for all P<0.001). Consequently, operationally tolerant patients showed, as compared to all other transplant recipients with different immunosuppressive regimens, the lowest ratios between CD8+ TEMRA T cells and Tregs or Bregs (for both P<0.001). A specific peripheral blood transcription pattern was found in operationally tolerant patients with an increased expression of Breg- and Treg-associated genes CD22 and FoxP3 and a decreased FcyR1A/FcγRIIB transcript ratio (for all P<0.001, as compared to all other transplant recipients).

Conclusions: Monitoring the balance between circulating CD8+ TEMRA T cells and regulatory cell subsets and their transcripts may help to distinguish transplant recipients with operational tolerance from recipients at risk of graft loss.

PO2189
Steering of Immunosuppression by Virus-Specific T Cells After Pediatric Kidney Transplantation (KTs) in the Randomized Controlled IVIST Trial
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Background: Pharmacokinetic monitoring alone is insufficient to estimate the intensity of immunosuppression after KTxs. Levels of virus-specific CD4 T cells(CD4Tvis) have been shown to identify overimmunosuppression. The IVIST trial has demonstrated that additional steering of immunosuppressive therapy by CD4Tvis levels is safe and reduces exposure to immunosuppressants with significantly lower trough levels but without increasing the risk of acute rejections.

Methods: In the randomized controlled IVIST trial, 64 pediatric KTx recipients were randomized 1:1 to a control group with trough level monitoring of immunosuppressants or to an intervention group with additional steering by CD4Tvis levels against adenovirus(ADV), cytomegalovirus(CMV) and herpes simplex virus(HSV). The immunosuppression consisted of cyclosporine A, everolimus and glucocorticoids. CD4Tvis were quantified by cytokine flow cytometry in 20 visits during the two-year study period. In the intervention group we have analyzed the CD4Tvis levels and the number of Tvis-based dose adjustments of immunosuppressants.
Results: At the time of transplantation, ADV-CD4Tvis were detectable in 30/31 patients (immunogen group), CMV-CD4Tvis and BKV-CD4Tvis only in 12/31. No significant ADV- or HSV-DNAemia was found; only two patients showed transient CMV-DNAemia. The mean level of ADV-CD4Tvis was 1.6 cells/μl (SD 1.6), 2.03 (SD 1.8), 2.18(SD 2.2), and 1.97 cells/μl (SD 3.4) 1,6,12, and 24 months after KTx. In case of CD4Tvis <2cells/μl 125 dose reductions of immunosuppressants (96%) based on ADV-CD4Tvis were performed in 28/31 children with a median of 4 Tvis-based dose reductions (range 0-10) per patient. 48% of these were caused by the combination of ADV-CD4Tvis <2 cells/μl and CMV-DNAemia. Routine monitoring of ADV-CD4Tvis is recommendable especially in the first post-KTx year to prematurely identify overimmunosuppression.

Funding: Government Support - Non-U.S.

PO2190

Regulatory T Cells, BK Virus Infection, and Long-Term Outcomes in Kidney Transplant Recipients

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Background: Regulatory T cells (Tregs) play crucial roles in controlling immune responses. This study evaluated the distribution of Tregs and their role in BK virus infection.

Methods: We evaluated 20 KTx recipients (male:13, mean age:41 ± 12 years, living donor 15) in whom BKV viremia/viruria was detected at a median 12.6 (IQR, 4.6-31.2) months after KTx. Serum and urine BKV DNA levels were measured by real-time PCR at baseline, 1 and 3 months after detection of BKV viremia/viruria. Lymphocyte profile and CD4+/CD8+ lymphocytes were measured by flow cytometry at each time point. Graft outcomes over 8 years were examined in relation to BK viremia, viruria levels, and lymphocyte profiles.

Results: At the time of diagnosis of BKV viremia/viruria, 17 (85%) patients were on calcineurin inhibitor (CNI)-based triple immunosuppression. CNI was discontinued in 9 patients, sirolimus was started in 3 of them. Mycophenolic acid was switched to azathioprine or the dose was decreased in all patients. Reduction in overall immunosuppression was associated with a decrease in serum and urine BKV DNA levels. Tregs and CD8+ T lymphocytes were significantly decreased and CD4(+)/CD8(+) lymphocytes were increased during this period (Figure 1). After a median follow-up of 8.1 years, 6 (30%) patients lost their allografts. There were no significant differences in mean Tregs levels between patients with and without graft failure (p=0.63).

Conclusions: Tregs may play a role in BKV infection, reduction in the overall amount of immunosuppression is associated with improvement of BKV viremia/viruria levels. Reduction in immunosuppression may be associated with allograft failure in patients with BK nephropathy.

PO2191

Expansion and Characterization of Regulatory T Cell Populations from Kidney Transplant Recipients

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Background: Regulatory T cell subpopulation has been an important topic in the kidney transplantation (KT). However, current immunosuppressant regimens cannot achieve adequate immune tolerance and their nonspecific immunosuppressive effects result in many adverse effects. Regulatory T cells (Tregs) play crucial roles in controlling alloimmune responses. This study evaluated the distribution of Tregs and their effect on kidney allograft function in Korean KT recipients.

Methods: We enrolled 144 KT recipients with stable graft function between 1989 and 2018. Differentiation and expansion of Tregs were studied by flow cytometry to compare the Tregs subpopulations. Tregs were defined as CD4+CD25hiCD127−FoxP3+ cells.

Results: Among the 144 patients, 75 patients (65.8%) were males and mean follow-up period was 144.3 ± 111.5 months. All patients received calcineurin inhibitors as maintenance immunosuppressants. Patients with follow-up period more than 144.3 months tended to have more gatings Tregs numbers than that in shorter follow-up period (0.23 ± 0.24 vs. 0.31 ± 0.4, p = 0.061, respectively). There were no significant differences in Tregs subpopulations between patients with creatinine more than 1.5 mg/dl and patients with serum creatinine less than 1.5 mg/dl. In terms of the number of Tregs, when the trough level of tacrolimus was at an appropriate level, the number of Tregs tended to be higher than that of Tregs when the trough level of tacrolimus was low or high, and the organ function of the transplant was also stable.

Conclusions: Tregs counts may be associated with transplant outcomes considering that there is a relationship between these cells and kidney graft function.
Results: Thus far, 64 patient samples have been collected, 11 with DGF. Mean TIMP-2*IGFBP-7 were 3.08 ± 0.63 vs 0.54 ± 0.23 (p-value <0.001) at 4-12 hours, 3.39 ± 0.93 vs 0.38 ± 0.13 at 24-48 hours (p-value <0.001), and 1.73 ± 0.76 vs 0.62 ± 0.27 (p-value <0.09) at 72-96 hours in DGF vs non DGF patients respectively. Mean Scr at 1 week were 6.14 ± 0.71 mg/dL in DGF vs 2.13 ± 0.26 mg/dL (p-value <0.001) in non-DGF. Correlation between peak TIMP-2*IGFBP-7 at 24-48 hours and Scr at 1, 3, 6, 9, and 12 months, was nonsignificant.

Conclusions: These preliminary results confirm the use of TIMP-2*IGFBP product measured by Nephrocheck in the diagnosis and prediction of DGF in the post-kidney transplant period as early as 4-12 hours, and peaking at 24-48 hours. The non-DGF TIMP-2*IGFBP-7 means were higher than prior reports, suggesting mild renal injury in the peritransplant period in those patients without DGF. The current sample size is too small and underpowered as of yet to draw conclusions on prediction of long-term renal dysfunction.

Funding: Commercial Support - Astute Medical Inc

PO2194
The Role of Hyperleptinaemia and Low Values of Interleukin 10 in De Novo Donor-Specific Antibody Production After Kidney Transplantation
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Background: White adipose tissue secretes a number of peptide hormones, including leptin, adiponectin, and several cytokines. The aim of this paper was to determine the role of selected adipocytokines (leptin and adiponectin) and interleukins (IL-10 and IL-6) on the development of graft rejection in protocol biopsy after kidney transplantation.

Methods: In a prospective analysis (n=104), we monitored the values of leptin, adiponectin, IL-6, and IL-10 prior to the transplantation and in the 3rd month after the transplantation. The protocol biopsy of the graft was performed in the 3rd month after the transplantation. The group was divided into the following according to the biopsy result: negative result, IFTA 1, borderline, and DSA positive.

Results: After adjusting for the differences in the baseline recipient and donor characteristics, we identified the hyperleptinaemia baseline (HR=2.044, P=0.0341) and month 3 (HR=49.8043, P=0.0001) as independent risk factors for borderline changes in the protocol biopsy. The hyperleptinaemia baseline (HR=7.4979, P=0.0071) and month 3 (HR=7.4979, P=0.0071) are independent risk factors for de novo DSA positivity. A low value of IL-10 month 3 is a risk factor for de novo DSA positivity (HR=3.0746, P=0.0388).

Conclusions: Higher leptin levels might play a role in rejection and de novo DSA production. We also confirmed the influence of low values of IL-10 on the development of de novo DSA. We assume that values of adipocytokines in context of other risk factors can predict the immunological risk of patients after kidney transplantation.

Funding: Government Support - Non-U.S.

PO2195
Diagnostic Performance of Donor-Derived Cell-Free DNA Assay (AlloSure®) in Kidney transplant Recipients with Graft Dysfunction:
A Single-Center Study
Muhammad S. Naseer, Ayush Singh, Neeraj Singh. Willis Knighton Medical Center, Shreveport, LA.

Background: Circulating donor-derived cell-free DNA (dd-cf-DNA) is a non-invasive biomarker of kidney allograft injury with a high negative predictive value for ruling out active rejection in patients with evidence of graft dysfunction. At our center, we

Funding: Government Support - Non-U.S.
compared the AlloSure® test (CareDx®) for the dd-cfDNA assay using >1% as the cut-off value suggested by the DART study or an increase of ≥30% from the previous value against the gold standard biopsy results and calculated its performance metrics.

**Methods:** From Dec 2019 to Oct 2020, we found 16 patients who had their 21 AlloSure® assays drawn which were within 4 weeks of for-cause biopsy sampling. In assessing this cause of 182 samples, 20 had AKI, 5 had proteinuria, and 3 had clinical symptoms of volume overload.

**Results:** AlloSure® and biopsy results were concordant in 14/21 (66.7%) samples (Table 1). Of the 21 for-cause biopsies, 8 biopsies were positive for rejection (2 borderline, 1 TCMR, 1 mixed AMR/TCMR, 1 chronic). AlloSure® was positive in 2 of these rejections (1 TCMR, 1 mixed AMR/TCMR). However, it was false-negative in the other 6 rejections (2 borderline, 3 AMR, 1 chronic). Out of the 13 negative biopsy results, AlloSure® was negative in 12 samples and false-positive in one sample. The performance metrics for the biopsy results were: sensitivity 92.3%, specificity 92.3%, positive and negative predictive values of 66.7%, and accuracy of 66.7%.

**Conclusions:** Although we had a sample size, it can be concluded from this study that AlloSure® has a high specificity to diagnose acute graft rejection in kidney transplant recipients.

Table 1: 2 x 2 Table

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### PO2198

**Extremely Elevated Donor-Derived Cell-Free DNA Fractions in Kidney Transplant Recipients Are Strongly Indicative of Allograft Rejection**

**Rajesh Govindasamy,1 Sandra L. Siegel,1 Kerry Gaj,2 Heather Wade,2 Sarah McCormick,3 Philippe Gauthier,1 UPMC Hamot, Erie, PA; 4Natera, Inc., San Carlos, CA.**

**Background:** Donor-derived cell-free DNA (dd-cfDNA) is an established non-invasive biomarker for the identification of kidney allograft rejection. The Prospera™ test utilizes a single-nucleotide polymorphism (SNP)-based massively multiplexed-PCR (mmPCR) methodology to quantify dd-cfDNA as a fraction of total cfDNA in kidney transplant recipients. dd-cfDNA fractions ≥1.0% indicate high-risk for rejection and in a small fraction of patients, dd-cfDNA fractions can be elevated significantly over this threshold. Here we present a case series of 18 kidney transplant patients with extremely elevated dd-cfDNA fractions >10% along with clinical data, when available.

**Methods:** To better understand the relationship between highly elevated dd-cfDNA fractions with allograft health, we identified cases from quality assurance data with dd-cfDNA fractions >10% and corresponding clinical follow-up data.

**Results:** Among the 18 cases with dd-cfDNA levels >10%, the median dd-cfDNA fraction was 14.73% (range: 10.8-20.7%). Biopsy data was available for 83.3% (15/18) of the patients indicating mixed rejection in 40% (6/15), TCMR in 40% (6/15), ABMR in 7% (1/15) and chronic AMR in 13% (2/15). In the remaining 3 patients, 1 patient had chronic complicated JC viremia with history of JC nephropathy, 1 had allograft loss associated with diffuse vasculopathy and 1 was admitted and treated for rejection without a biopsy. A 60-year-old female underwent surveillance testing with Prospera and dd-cfDNA results came back at 19.3%. Scr was 1.2 mg/dL compared to a baseline value of 1.1 mg/dL. For the next 8 days, she remained febrile with constitutional symptoms of malaise and general discomfort and low grade fever. The patient underwent allograft biopsy and was diagnosed with TCMR 1a rejection. Patient was subsequently treated with IV methylprednisolone 250 mg x 2 days with a rapid steroid taper. Follow-up Scr levels were 0.9 mg/dL, accompanied by a decline in the dd-cfDNA fraction during a subsequent Prospera test.

**Conclusions:** These results suggest that highly elevated dd-cfDNA fraction in the absence of comorbidities can be a strong indicator of allograft rejection. Further investigation is needed to determine whether there is a relationship between elevated risk for rejection and dd-cfDNA levels elevated significantly above 1%.

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### PO2219

**Can Donor-Derived Cell-Free DNA or Gene Expression Profile Be Used to Monitor Response to Treatment After Subclinical Acute Rejection?**

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**Background:** Subclinical acute rejection (subAR) is defined as acute rejection with stable kidney allograft function. Creatinine is not sensitive enough to detect subAR. Donor-derived cell-free DNA (dd-cfDNA) and gene expression profile (GEP) have been used for acute rejection detection in kidney allograft. We hypothesized that dd-cfDNA and GEP could be used to monitor response to treatment of rejection after subAR.

**Methods:** We analyzed dd-cfDNA and GEP results from 14 unique subjects in the CTOT08 study with subAR who had 8 weeks follow-up biopsy after treatment. Blood samples were paired with kidney biopsies, and collected after subAR during the intensive monitoring periods. We calculated the mean and standard-deviation (SD) for each group at the same time points. A paired T-test was used to generate p-values. We conducted locally estimated scatterplot smoothing (LOESS) and linear mixed effect models for the analysis of serial changes of dd-cfDNA scores.

**Results:** Of 14 patients, subAR resolved in 5 patients (36%) but 9 (64%) patients had persistent rejection after treatment. The slope of dd-cfDNA scores was not significantly different between the resolved and the unresolved group (p-value = 0.43) (Figure 1A). The slope of GEP scores in the resolved group tended to be steeper than unresolved group one after treatment but was not statistically significant between the two slopes (p-value = 0.06) (Figure 1B).

**Conclusions:** GEP scores showed a greater decrease after successful treatment compared to dd-cfDNA scores. Repeating GEP after subAR might be useful to monitor treatment of rejection.

**Funding:** Commercial Support - Viracor-Eurofins

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### PO2199

**Immunosuppression Could Influence De Novo Angiotensin II Type I Receptor Antibodies Development Early After Kidney Transplantation**

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**Background:** Angiotensin II type I receptor antibodies (AT1R-Ab) are non-HLA autoAb associated with graft rejection and detrimental effects on graft function in kidney transplantation (KT). Nevertheless, the data regarding risk factors associated with AT1R-Ab development is scanty. To our knowledge, immunosuppression (IS) has not yet been reported as a potential risk factor. We sought to evaluate the incidence of de novo AT1R-Ab at 1 year after KT and risk factors associated with their formation.

**Methods:** We performed a prospective study on 58 KT recipients, transplanted between October 2018 and October 2019, who were followed for 1 year. Exclusion criteria: age <18 years and preformed AT1R-Ab. AT1R-Ab were evaluated at 1 year after KT using an ELISA technique and the cut-off value for detection was >10 U/ml. Logistic regression analysis was used to identify risk factors associated with AT1R-Ab formation.

**Results:** Twelve out of 58 patients (20.6%) had de novo AT1R-Ab at 1 year of follow-up. Mean age of the study cohort was 40.8±10.5 years, 60.3% were males and 17.2% had a preemptive KT. Glomerular diseases were the main cause for CKD (27.6%). Donors mean age was 48.6±15.6 years, 62.1% were cadaveric donors and 31% of patients had a+ mismatches. Monoclonal Ab directed against IL-2 receptor (84.5%) was the main induction IS used. Immediate-release tacrolimus (TAC) was used in 53.4% and mycophenolate sodium was preferred in 89.7% of cases. Patients with de novo AT1R-Ab had a significantly decreased BMI (21.4±1.8 vs 23.2±2.9 kg/m², p<0.04), received more times antihypertensive drugs (83.3 vs 56.9%, p=0.01) and had a significantly shorter TAC level at 3 months after KT (13.8±5.6 vs 11.4±3.9 ng/ml, p=0.04). By multivariate logistic regression we found that rATG was an independent risk factor for de novo AT1R-Ab development (OR= 5.6; 95%CI: 1.1- 28.34, p=0.03) and immediate-release TAC had a trend of association with Ab (OR= 5.02; 95%CI: 0.93- 27.06, p=0.03) at 1 year after KT.

**Conclusions:** The incidence of de novo AT1R-Ab was 20.6% and rATG induction IS was an independent risk factor for Ab development at 1 year after KT. Our results suggest that IS could influence de novo AT1R-Ab formation.
Results: A total of 10 cadaveric kidney donors (mean KDPI 95.7%) were selected. Diabetic lesions of all cases were present already at pre-implantation biopsies associated with mild IF/TA and vascular damages. At follow-up the lesions showed variable modifications of DN class (fig.1) and moderate evolution of IF/TA and vascular damages. eGFRs were stable and proteinuria was mild.

Conclusions: In the ten patients and at the different follow-ups there was not a uniform trend of DN lesions, we demonstrated an amelioration in 3 cases, stability in 4 and worsening in 3, and did not find a relationship between these changes and the follow up time. Our data suggest that the diabetic kidneys keep after transplantation the histologic stigma that denote their origin and even in this very marginal extended criteria donation the diabetes status in the donor may not represent a limitation to transplantation in favorable conditions as euglycemia.

Utility of Noninvasive Rejection Biomarkers to Assess the Risk of Rejection in Kidney Transplant Recipients with Post COVID-19 Infection

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Introduction: COVID-19 infection is associated with 25% mortality in kidney transplant recipients (KTRs). Treatment of Coronavirus Disease 2019 (COVID-19) infection in KTRs has involved reduction of immunosuppressants (IS). This potentially increases the risk of allograft rejection in the setting of reduced immunosuppression. We reported 6 cases of kidney allograft rejection post COVID infection

Case Description: Total 123 kidney transplant recipients had COVID-19 infection between March 2020 and February 2021. Immunosuppression was reduced routinely in patients who had symptomatic COVID-19 infection. We implemented the protocol of screening tests to assess for rejection which included dd-cfDNA, gene expression profile (TruGraf), donor specific antibody (DSA). Elevated serum creatinine greater than 25% over baseline, dd-cfDNA value greater than 1%, TruGraf value of Non-Tx (NT) or up-trending DSA prompted to allograft biopsy to rule out rejection.

Discussion: Twelve patients out of 123 KTRs received kidney biopsy for above mentioned indications Only 4.8% had kidney rejection (6 out of 123 patients) : 3 patients with acute cellular rejection (ACR) Banff IB rejection, 2 patients with borderline ACR, and 1 patient with antibody mediated rejection (AMR). Of these 6 patients with rejection 5 patients have elevated dd-cfDNA peri COVID infection, 3 patients with elevated Cr and 1 patient had Non-Tx. Three patients with rejection were transplanted within 1 year. The patients with Banff IB rejection were treated with anti - thymocyte globulin (ATG) and 1 patient with AMR due to AT1R antibody was treated with methylprednisolone, IV Ig and Losartan. Only 4.8% had kidney rejection post COVID infection. Despite reduction in IS, COVID infection did not increase the risk of allograft rejection and can monitor the risk of rejection by using non-invasive rejection biomarkers.

PO2201
Donor-Derived Leukocyte Chemotactic Factor 2 Amyloidosis in Renal Allografts

Introduction: Leukocyte chemotactic factor 2 amyloidosis (ALECT2) is a relatively common form of amyloidosis with strong ethnic predilection in the Hispanic population. Patients tend to be older and present with chronic kidney disease with variable proteinuria. Histologically, ALECT2 has a unique preference for interstitial accumulation. We report two cases of donor-derived ALECT2 in renal allografts.

Case Description: Case 1: 69-year-old (yo) Hispanic man with type II diabetes and end-stage renal disease (ESRD) received an 86% Kidney Donor Profile Index (KDPI) deceased donor renal transplant (DDRT) from a 52-yo Hispanic man who died of a stroke. The recipient had delayed graft function and suboptimal nadir serum creatinine (Scr) of 2.6 mg/dL. Proteinuria initially peaked at 2.3 g/g, which decreased to <1 g/g at 4-mo post-transplant (tx). Both time-0 and 3-mo protocol biopsies (bx) revealed widespread interstitial amyloid positive for ALECT2 on immunohistochemistry and mass spectrometry. Case 2: 45-yo Hispanic female with ESRD of unknown etiology received a 78% KDPI DDRT from a 60-year-old female with no medical history who died from head trauma. The recipient experienced immediate graft function with new baseline Scr of 1.2–1.6 mg/dL. She had persistent proteinuria following tx and underwent bx at 2-, 3-, and 6-mo post-ts. The bx showed mostly interstitial amyloid, later confirmed to be ALECT2. Additionally, the patient developed focal segmental glomerulosclerosis (FSGS) as well as CMP infarction of the allograft. She eventually lost her graft ~2 years post-ts, likely from FSGS rather than ALECT2.

Discussion: Rare cases of donor-derived ALECT2 have been reported in the literature and suggest that kidney allografts with limited and localized donor-derived ALECT2 involving <10% of the renal parenchyma have good outcomes. Our cases represent more severely affected donor kidneys. Although the clinical course for our patients were suboptimal, other factors aside from ALECT2 were likely the major contributing factors. Thus, donor-derived ALECT2 is likely of low consequence in the recipient allograft.

PO2202
Regardless of Donor-Specific Antibody, Do Not Forget Non-HLA
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Introduction: Antibody-Mediated Rejection (AMR) remains an important cause of allograft rejection and loss of transplant. This is mainly attributed to donor-specific antibodies (DSA) directed against human leukocyte antigen (HLA). In patients with biopsy findings of AMR and undetectable DSA, non-HLA antibodies must be considered. Here we present two cases of AMR mediated by Angiotensin II type 1 receptor (AT1R) antibody, one of the most widely studied non-HLA antibodies.

Case Description: A 46 yo AA HIV-positive male underwent deceased donor kidney transplant, induced with Basiliximab and methylprednisolone, and maintained on tacrolimus, mycophenolate mofetil and prednisone. His post-op course was complicated by delayed graft function with biopsy performed on day 11 showing acute vascular rejection and severe microcirculation inflammation, highly suspicious for AMR. DSA was negative, but non-HLA panel resulted positive for anti-AT1R at 22 U/mL. He was treated with steroids, PLEX, IVIG, Rituximab, and started on ARB therapy with recovery and most recent creatinine 1.59 mg/dL. To our knowledge, this is the first reported case of an HIV-positive patient with anti-AT1R AMR. A 50 yo AA female underwent deceased donor kidney transplant induced with Alemtuzumab and methylprednisolone and maintained on tacrolimus, mycophenolate mofetil and prednisone. She had immediate graft function, but 5 days after discharge, presented with anuric AKI. Biopsy on day 10 showed thrombotic microangiopathy and diffuse C4d positivity, suggestive of AMR. DSA was negative, but non-HLA panel resulted positive for anti-AT1R at 22 U/mL. He was treated with steroids, PLEX, IVIG, Rituximab, and started on ARB therapy with recovery and most recent creatinine 1.23 mg/dL.

Discussion: Non-HLA antibodies including anti-AT1R have been recognized as possible mediators of allograft injury. They should be suspected in AMR with no identifiable DSA, or in early AMR regardless of DSA. Although no standardized treatment exists for non-HLA antibodies, early recognition may have implications for treatment, particularly in situations with AT1R antibodies in which angiotensin receptor blockade effectively reduces anti-AT1R activity. Along with other AMR therapies, this may improve allograft function as seen in these two cases. To our knowledge, this is the first reported case of an HIV-positive patient with anti-AT1R AMR.
Autoimmune Encephalitis with Concurrent Epstein-Barr Virus Infection in a Renal Transplant Patient

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Introduction: Epstein-Barr virus (EBV) infection following renal transplant is typically associated with post-transplant lymphoproliferative disorder (PTLD). Autoimmune encephalitis is caused by antibodies against N-methyl-D-aspartate receptor (NMDAR), a ligand-gated ion channel with a crucial role in synaptic transmission. We describe a patient who developed encephalitis 1 year after renal transplant with cerebral spinal fluid (CSF) analysis positive for NMDAR antibodies and evidence of EBV infection on brain biopsy without PTLD or malignant processes. To our knowledge, this is the 1st case with tissue evidence of EBV infection on brain biopsy in renal transplant.

Case Description: A 70-year-old female with end stage renal disease from Type 2 Diabetes mellitus who received a deceased donor renal transplant one-year prior was admitted for 3 weeks of progressively worsening mentation. Immunosuppression included tacrolimus, mycophenolate mofetil, and prednisone. Brain MRI did not reveal any acute findings. EEG showed generalized slowing consistent with diffuse encephalopathy. CSF analysis showed lymphocytic pleocytosis and elevated protein level. The infectious workup was negative except for positive EBV PCR in CSF. Cytometry did not reveal any evidence of PTLD. CSF autoimmune panel demonstrated NMDAR antibody. Brain biopsy showed a chronic inflammatory process with features of EBV infection. EBV-infected cells were detected in tissue specimen via in-situ hybridization with EBV-encoded small RNA. Patient initially received ganciclovir, abic twice, and broad-spectrum antibiotics. Treatment then changed to steroids, IVIG and plasmapheresis for autoimmune encephalitis, all of which were stopped and ganciclovir was restarted when brain biopsy was positive for EBV. Unfortunately, patient did not show any clinical improvement possibly due to delayed diagnosis and went home with hospice care.

Discussion: EBV Encephalitis without PTLD following renal transplant is uncommon. Only a few cases have described renal transplant patients with encephalitis and the findings of NMDAR antibodies and EBV DNA in CSF. The relationship between EBV infection and AE remains unclear; however, EBV infection may play a role in the pathogenicity of NMDAR antibodies. AE can occur in the setting of chronic immunosuppression and should not be overlooked to avoid delay in diagnosis and treatment.

2,8-Dihydroxyadenine Crystalline Nephropathy in Transplanted Kidney

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Introduction: 2,8-dihydroxyadeninuria (DHA) disease is a rare autosomal recessive disorder caused by adenine phosphoribosyltransferase (APRT) deficiency, that typically manifests with nephro lithiasis, but rarely can cause chronic kidney disease (CKD). Recurrence of DHA nephropathy after kidney transplant can cause persistent allograft dysfunction with increased risk of early graft failure if diagnosis and treatment are delayed. We describe a case of APRT deficiency which remained undiagnosed until evaluation of a poorly functioning kidney allograft due to DHA nephropathy, successfully managed with allopurinol and conversion to Belatacept.

Case Description: 72-year-old Caucasian male with ESRD secondary to diabetes mellitus type 2 and obstructive uropathy. The patient received a living donor kidney transplant from his daughter on 10/15/2020 with Thymoglobulin and steroid induction followed by maintenance immunosuppression with tacrolimus, mycophenolate, and prednisone. It was a one haplotype mismatch with no pre-formed donor specific antibodies. He had slow graft function with a creatinine of 4 mg/dL on discharge. At 6 weeks post-transplant, his creatinine remained elevated at 2.1 - 2.3 mg/dL with no clear cause for persistent allograft dysfunction. An allograft renal biopsy showed numerous polarizable pigmented brown intratubular crystals, in the absence of triamterene-based diuretics. A diagnosis of 2,8 DHA crystalline nephropathy was made and he was started on allopurinol and a low purine diet. To minimize tubular injury, Belatacept was added to maintenance immunosuppression and tacrolimus dose was reduced with a goal to wean over 9 months. To further confirm the diagnosis, a kidney gene panel was performed confirming homozygous ARPT deficiency with an autosomal recessive inheritance pattern. Kidney function continued to improve with creatinine of 1.5 mg/dL (GFR 45 mL/min/1.73m2) at 7 months post-transplant.

Discussion: DHA nephropathy due to APRT deficiency is a rare but preventable cause of CKD and can remain undiagnosed until its recurrence after kidney transplant. To prevent allograft failure, high index of suspicion and early biopsy is important. In addition to allopurinol, low purine diet, and increased hydration, CNI minimization and utilization of Belatacept is an effective strategy to minimize vascular and tubular injury and prevent further precipitation of crystals.

Anti-MDA5 Dermatomyositis as a Paraneoplastic Syndrome of Myelodysplastic Syndrome After Kidney Transplant in Autosomal Dominant Polycystic Kidney Disease

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Introduction: Malignancy after solid organ transplantation is increasing, there is 3 to 5-fold greater incidence than in general population. Major risk factors for non-cutaneous neoplasms are male sex, older age and Caucasians, there are no data on the prevalence of hematologic malignancies after kidney transplantation. We report a case of kidney allograft infections causing acute dysfunction secondary to myelodysplastic syndrome and amyopathic dermatomyositis as a paraneoplastic syndrome (PS).

Case Description: A 40-year-old man with chronic kidney disease (CKD) secondary to autosomal dominant polycystic kidney disease (ADPKD) was programmed for preemptive kidney transplant (KT); basiliximab induction and mycophenolate mofetil (1 year), tacrolimus and steroid was the maintenance therapy. Three years after KT he was admitted to the hospital with AKI (SO 4.7mg/dL, baseline 1.7mg/dL), unexplained weight loss (17kg) and rash in face, hands and feet. Kidney biopsy showed cortical segmental infarction, focal hyperperfusion with negative C4d. MDA-5, Anti-Jo-1 and PL-7 were positive and Gottron papules were reported in skin biopsy, myopathy was excluded. PS was our conclusion, so PET-CT and BMA were done, with no metabolic activity and hypoplastic myelodysplastic syndrome with high risk for acute myeloid leukemia, respectively.

Discussion: Kidney infarctions were the etiology of AKI as a expression of a hypercoagulable state secondary to amyopathic dermatomyositis (paraneoplastic syndrome) presents and precedes hematologic malignancies in almost 50% cases, awarding poor prognosis at 1, 3 and 5 year with 96.9%, 78.1% and 51.4% overall survival, respectively. Dermatomyositis coexistence with kidney transplant has been described, nevertheless, ADPKD and dermatomyositis is anecdotal. In any case, the diagnosis of Anti-MDA5 dermatomyositis requires ruling out neoplasms.
Discussion: This is a rare case of bilateral pyomyositis in a kidney transplant patient. The inability to culture an organism is likely due to preceding IV antibiotic treatment. This case underscores the importance of keeping a broad differential diagnosis and obtaining a detailed history when treating immunosuppressed patients.

Figure 1

**PO2207**

Dihydroxyadenine Crystals Leading to Renal Graft Loss

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Introduction: Adenine phosphoribosyltransferase (APRT) deficiency is an autosomal recessive disease which leads to excessive production and renal excretion of poorly soluble 2,8-dihydroxyadenine (DHA). This causes crystal-induced acute kidney injury and progressive chronic kidney disease (CKD). We describe a case of DHA nephropathy in a renal transplant recipient leading to graft failure.

Case Description: A 69 year old female with ESRD secondary to recurrent nephrolithiasis underwent a deceased donor kidney transplant. The stone composition was previously unknown but she underwent genetic testing and was found to be homozygous for APRT c.81-3C>G mutation which was reported as a variant of uncertain significance. APRT activity level was checked and was within normal range. As a result, allopurinol was stopped. Her serum creatinine which was 1.6 mg/dl started to gradually increase to 5.5 mg/dL. She underwent a kidney biopsy which showed extensive tubular cytoplasmic and luminal 2,8-DHA crystal deposits. Despite restarting allopurinol, renal function continued to worsen and she developed uremic symptoms. She was initiated on hemodialysis.

Discussion: APRT deficiency is a rare condition and novel mutations are being reported. It is likely that the mutation of unknown significance which our patient has might be another novel mutation associated with APRT deficiency. DHA stone formation can occur even when APRT levels are normal or detectable. It is of utmost importance to continue allopurinol in patients with known DHA stones as genetic testing and APRT level may be misleading and stopping allopurinol will result in irreversible kidney damage.

Figure 1

**PO2208**

Hypercalcemia in Immuno-compromised Host: Beware of Zebras


Introduction: Hypercalcemia has varied etiology with treatment dictated by underlying cause. We present an immunocompromised host with weight loss, lymphadenopathy and hypercalcemia masquerading as malignancy.

Case Description: A 74 year old male construction worker with deceased donor liver transplant 4 months earlier on tacrolimus/mycophenolic acid (MPA) maintenance and stage 4 chronic kidney disease presented with constitutional symptoms and 20 pound weight loss. Serum creatinine was 2.5 mg/dl and corrected calcium 11.9 mg/dl. CT scan showed mediastinal and bilateral axillary lymphadenopathy. Serum E BV and CMV PCR were negative. Work up for hypercalcemia revealed: intact PTH 6.8 picogram/ml (11.0-68.0), 25 OH vitamin D 44.6 ng/ml (30-100), iCa ratio 1.45 (0.26-1.65) and absent M-spike on serum protein electrophoresis. Blood culture grew Cryptococcus neoformans and serum Cryptococcal antigen titer was positive at 1:4096. Lumbar puncture revealed CSF lymphocytic pleocytosis and positive cryptococcal antigen titer at 1:32. Axillary lymph node biopsy showed cryptococcal lymphadentis with diffuse involvement by encapsulated yeast forms within non-necrotizing granulomatous inflammation (fig 1). Patient was started on induction treatment with intravenous liposomal amphotericin B and oral flucytosine till 2 weeks after negative blood cultures followed by 8 weeks of consolidative therapy with oral fluconazole. MPA was stopped and tacrolimus continued. Hypercalcemia resolved a week after initiating antifungal therapy. Patient doing well 4 months later on maintenance fluconazole.

Discussion: Hypercalcemia is a rare manifestation of disseminated fungal infection. The exact etiology is unclear but 1, 25 di(OH) vitamin D and PTHrp are implicated. Weight loss and lymphadenopathy in our immunosuppressed patient raised concern for malignancy. However, blood culture and lymph node histology clinched the diagnosis enabling prompt therapy with resolution of the symptoms and hypercalcemia.

Figure 1

**PO2209**

A Rare Case of Collapsing Focal Segmental Glomerulosclerosis Caused by Cytomegalovirus in a Renal Transplant Recipient

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Introduction: Cytomegalovirus (CMV) is a DNA virus that is associated with several clinical manifestations in renal transplant recipients (RTR), presenting often with asymptomatic viremia, CMV syndrome, and tissue invasive disease in the lungs, colon,
esophagus, and retina. CMV infection may occur in the renal allograft presenting as interstitial nephritis. We present a rare case of CMV nephritis in a RTR that presented as a collapsing focal and segmental glomerulosclerosis (FSGS).

Case Description: A 55 year old caucasian male with a history of end-stage renal disease due to hypertension on hemodialysis for 4 years received a living donor renal transplant with immediate graft function. Induction was with Thymoglobulin, maintenance immunosuppression was with MMF, Prednisone, and Tacrolimus. He completed valganciclovir prophylaxis for CMV, and soon after presented to an outside hospital with hypotension, lower extremity swelling, and diarrhea of 2 weeks duration. He had a proteinuria value of 22.1g/m with hypoalbuminemia and an acute kidney injury. A presumptive diagnosis of FSGS was made and he received IV Solumedrol. Chart review revealed CMV viremia 4 weeks prior to presentation. He was transferred to a tertiary center for management, where a kidney biopsy was done that revealed interstitial inflammation, widespread collapse of glomerular tufts, podocyte hyperplasia and hypertrophy, extensive podocyte foot process effacement, microthrombi and CMV staining in tubular epithelial cells. He was treated with IV ganciclovir, and both viremia and proteinuria resolved (Figure 1).

Discussion: The patient’s de novo collapsing-FSGS is a rare manifestation of CMV infection. While CMV is the most common opportunistic viral infection in RTR, renal involvement is unusual. This may be a cytokine related injury to podocytes in the setting of a viral infection. Our patient had complete recovery following treatment with renal function returning to baseline.

PO2210
Use of Lipoprotein Apheresis in Recurrent Focal Segmental Glomerulosclerosis Following Transplant
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Introduction: Primary focal segmental glomerulosclerosis (FSGS) recurs in 20-30% of transplanted kidneys and has a high rate of transplant failure. We report a case of recurrent FSGS treated with lipoprotein apheresis (LDL-A).

Case Description: A 27-year-old male with primary FSGS underwent a DBD kidney transplant. He was ESRD on PD and anuric. ATG and steroids were given for induction. On post-op day (POD) 2, his spot urine protein was > 2000 mg (unable to calculate urine protein/creatinine ratio (UPCR)). Serum creatinine was 1.47 mg/dL (pre-transplant: 9.65 mg/dL). With concern for recurrent FSGS, emergent therapeutic plasma exchange (TPE) and Iosartan were started. On POD 3 and 4, proteinuria was > 2000 mg; TPE was done daily and adrenocorticotropic hormone (ACTH) and rituximab started. Despite 5 days of TPE and medical therapy, proteinuria was > 2000 mg. On POD 8, LDL-A was started. Prior to second LDL-A run, his proteinuria was 1900 mg but 294 mg afterwards. Proteinuria rebounded between treatments, but steadily decreased: by week 3, UPCR was 686 mg/g and by final LDL-A, was 200 mg/g. Renal function was stable and biopsy had no podocyte effacement. He completed LDL-A biweekly for 3 weeks, then weekly for 6 weeks. ACTH and rituximab were continued. Currently, his UPCR is 9 mg/g.

Discussion: Treatment of recurrent FSGS centers on plasma exchange and immunosuppression. By lowering LDL levels, LDL-A is thought to reduce proteinuria by reducing vascular permeability and improving response to immunosuppressive agents. Case reports indicate efficacy, but currently the use of LDL-A is designated as a humanitarian device exemption for drug resistant recurrent FSGS in transplanted kidneys by the FDA. Although this modality is uncommon, our case suggests that patients with recurrent FSGS may benefit from early initiation of LDL-A.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

Iron Overload Syndrome and Primary Focal Segmental Glomerulosclerosis Recurrent with Monthly Plasma Exchange Therapy: Long-Term Second Kidney Allograft Survival
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Introduction: Patients who lose their allograft due to recurrent FSGS are usually not retransplanted since the risk of recurrence (80-100%). Proteinuria as a result of glomerular damage is linked to tubulointerstitial injury, which is associated with increased filtration of transferrin-bound iron and can lead to tubular accumulation.

Case Description: A 32-year-old female with a history of collapsing FSGS, living related kidney transplant with loss of the allograft function due to recurrent disease underwent a 2nd kidney transplantation in October 2018. At 2 months post transplantation elevated levels of proteinuria (6 g/g), kidney biopsy (KB) demonstrated recurrent FSGS. She received treatment with high-dose steroids, CsA and an intensive course of plasma exchanges (PEs) due to persistent proteinuria. There is no history of blood transfusions, iron treatment and diseases with ineffective erythropoiesis. Ferritin levels (15000 ng/ml) and a MRI with liver and spleen iron deposition pointed to the diagnosis of Hereditary Hemochromatosis (HH), common mutations (C282Y, H63D and G320V genes) were negative. KB of 2020 demonstrated iron deposition (ID) in tubular epithelial cells.

Discussion: Histological evidence of ID in the tubulointerstitium can be related to persistent proteinuria. The negative genetic testing is common in the Hispanic race in which there is a lesser prevalence for the most frequent mutation, C282Y homozygosity (0.03% compared to 0.44% in Whites). We assume that this patient has a genetically unknown type of HH. To our knowledge this is the first reported case in which an Iron Overload Syndrome (IOS) is associated with FSGS. PEs is a therapeutic option in patients with recurrent FSGS, also used in IOS.
PO2212
Is One Allele Enough to Cause APOL1-Associated Nephropathy?
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Introduction: The high risk APOL1 genotype are associated with an increased risk of developing non-diabetic kidney disease. In the post-kidney transplant setting, a high-risk donor APOL1 genotype (but not recipient genotype) is associated with an increased risk of graft failure and proteinuria, indicating that it is local glomerular APOL1 gene expression that confers disease rather than systemic gene expression. Here, we present 2 patients that developed post-transplant focal segmental glomerulosclerosis (FSGS) after an initial diagnosis and treatment of Antibody-mediated rejection (AMR).

Case Description: Two patients with end stage kidney disease, highly sensitized, received deceased donor kidney transplants from African American donors (one in 2019 and the other a regraft in 2020). Donors were without discernable proteinuria on urine dipstick. Initial post transplant courses were complicated by AMR treated as per center protocol. Tissue-based whole biopsy gene expression studies on kidney biopsy specimens (MMdx, using Molecular Microscope, Alberta, Canada) confirmed AMR along with grossly elevated interferon-γ expression. Subsequently each developed nephrotic range proteinuria with biopsy-confirmed FSGS and ongoing AMR. In both patients, in the absence of a prior history of FSGS and a delayed development of proteinuria in the first case (2019, patient1), an absence of recurrence in the first allograft in the second case (2020, patient2), a diagnosis of donor-derived APOL1 nephropathy was considered and retrospective donor genotyping revealed the intermediate G1/G0 genotype. See Figure for more details.

Discussion: We hypothesize that extreme local interferon-γ activation due to AMR was the primary trigger that could have resulted in local APOL1 gene activation and subsequent podocytopathy. Similar data was recently reported by Shetty et al, in a kidney transplant patient with COVID associated collapsing nephropathy and G1/G0 donor genotype. Based upon these data we hypothesize that the G1/G0 genotype may represent intermediate risk for podocytopathies. Further research is needed in this area to confirm these initial associations.

PO2213
Early Recurrence of Fibrillary Glomerulonephritis After Kidney Transplantation
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Introduction: Fibrillary glomerulonephritis (FGN) is a rare glomerulonephritis characterized by glomerular congo red negative nonbranching fibrils on electron microscopy (EM). The optimal treatment for FGN is unclear and the renal prognosis is poor, with up to half of patients progressing to end-stage kidney disease (ESKD) by four years. Kidney transplantation has a variable recurrence rate after transplant ranging from 9 to 50%.

Case Description: A 57-year-old male with a history of cirrhosis secondary to nonalcoholic fatty liver disease and ESKD secondary to FGN was hospitalized for acute kidney injury. The patient underwent simultaneous liver and kidney transplantation four weeks prior to presentation. The patient underwent induction with basiliximab and started on tacrolimus, mycophenolate mofetil, and prednisone for maintenance immunosuppression. The patient’s serum creatinine had increased from the previous nadir of 2.0 mg/dL to 2.7 mg/dL. Given worsening allograft function, a transplant kidney biopsy was performed. The patient’s biopsy showed evidence of recurrent fibrillary glomerulonephritis, including positive immunohistochemical staining for DNAJB9 and ultrastructural findings of mesangial nonbranching fibrils averaging 21.5 nm in diameter. The biopsy also showed acute tubular necrosis, secondary global and focal segmental glomerulosclerosis, and tubular atrophy and interstitial fibrosis in 20-30% of the cortex. There was no evidence of acute T-cell mediated rejection or antibody-mediated rejection. The patient’s allograft function improved and ranged from 1.5 -1.7 mg/dL at the time of discharge. The patient is now six months from transplant and has stable allograft function and minimal proteinuria.

Discussion: FGN recurrence after kidney transplantation has been described in case reports and case studies. In the most recent and largest study, utilizing DNAJB9 and protocolized post-transplant biopsy, the authors showed a recurrence rate of 21% and a median time to recurrence of 10.2 years. Additionally, all biopsies before five years were negative in their cohort. Allograft failure was seen in 33% of patients with recurrent FGN. To our knowledge, this case is the earliest reported recurrence of FGN after transplantation. In patients with a history of FGN, recurrent disease should be considered in the differential of early allograft dysfunction.

PO2214
Donor-Derived Fibrillary Glomerulonephritis in a Renal Allograft

Introduction: Fibrillary glomerulonephritis (FGN) is a rare progressive renal disease that is defined by the presence of randomly oriented non-branching fibrils showing positive immunostaining for Dnal homolog subfamily B member 9 (DNAJB9). Recurrent FGN in renal allografts have been described with an indolent course. We report a case of donor-derived FGN in a renal allograft.

Case Description: A 73-year-old female with history of end-stage renal disease (ESRD) due to anti-myeloperoxidase antibody-associated pauci-immune glomerulonephritis received a preemptive deceased donor renal transplant from a 62-year-old 79% Kidney Donor Profile Index female. The patient experienced slow graft function and nadir serum creatinine (Cr) of 1.7 mg/dL at 4 months post-transplant with subsequent Cr stabilizing in the 2.0-2.3 mg/dL range. Proteinuria mainly fluctuated between 1-2 g/g. Time-0 biopsy demonstrated mild mesangial widening/hypercellularity with rare glomerular capillary double contours. Ancillary studies revealed positive staining for DNAJB9 and kappa light chain-restriction, consistent with donor-derived FGN. 4-month surveillance biopsy showed similar findings. Background renal parenchyma showed moderate chronicity with prominent chronic vascular disease. At 10-months post-transplant, Cr remains at ~2 mg/dL and proteinuria remained in the 1-1.6 g/g range.

Discussion: FGN carries a poor prognosis with nearly half of patients progressing to ESRD within a few years. A case series of recurrent FGN after kidney transplantation suggests a relatively benign clinical course including a single report of donor-derived FGN (from a living related donor) without proteinuria in the recipient. Our case shows a more severely affected allograft that resulted in persistent low-grade but stable proteinuria in the recipient. Suboptimal Cr was also observed following transplant as well, although the allograft had other factors such as chronicity and chronic vascular disease.
**PO2215**

**A De Novo Case of C1q Nephropathy in a Renal Allograft**

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**Introduction:** C1q nephropathy (C1qN) is a rare idiopathic glomerulopathy that is characterized by mesangial C1q deposition in the absence of systemic lupus erythematosus or membranoproliferative glomerulonephritis. Clinical manifestations vary, but can include proteinuria, hematuria, and renal dysfunction. C1qN is not usually responsive to corticosteroids and outcomes are poor for most patients. We describe a de novo, but clinically silent case of C1qN in a renal allograft incidentally detected on surveillance biopsy.

**Case Description:** A 20 year old male, with history of end stage renal disease secondary to congenital renal hypoplasia, on maintenance tacrolimus, mycophenolate mofetil, and oral prednisone, underwent a surveillance biopsy 1 year after a deceased donor kidney transplantation. Laboratory studies revealed a baseline serum creatinine of 1.7 mg/dl and a spot urine protein to creatinine ratio of 258 mg/g. Urinalysis did not show hematuria and the rheumatologic workup was unremarkable. Light microscopy revealed minimal mesangial hypercellularity without endocapillary proliferation. Immunofluorescence microscopy demonstrated granular mesangial staining for C1q with positive staining for IgG, IgM, C3, C4, and kappa and lambda light chains. Electron microscopy revealed mesangial and paramesangial electron-dense immune deposits.

**Discussion:** Unlike other C1qN cases described in the literature, our patient did not have evidence of an underlying autoimmune disease or viral infection. Renal biopsy demonstrated positive immunofluorescence staining of IgG, IgM, C3, C4, and kappa and lambda light chains, in addition to C1q. Moreover, there was no evidence of proteinuria, hematuria, or renal dysfunction. One question that arises is whether this patient, with a history of congenital renal hypoplasia, was susceptible to developing an autoimmune process that was otherwise being masked by immunosuppression. This case emphasizes the following: (1) further research is needed to determine the frequency and duration of monitoring of de novo C1qN in renal transplant recipients, and (2) further research is needed to determine the optimal therapeutic regimen.

**PO2216**

**Repository Corticotropin (Acthar®) in Treating De Novo C3 Glomerulonephritis Post Transplantation**

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**Introduction:** De-novo C3 glomerulonephritis (C3GN) post-transplant is uncommon. Although ecclizumab has been used successfully in several cases, the response is heterogeneous and treatment strategies remain undefined. The use of repository corticortropin in C3GN has not been described in the literature.

**Case Description:** A 48-year-old African American male with kidney transplantation secondary to diabetic nephropathy presented 6 years post-transplant with lower extremity edema and nephrotic range proteinuria of 8.2 g/g of creatinine. His renal allograft biopsy confirmed the diagnosis of C3GN (Figure 1). He was treated with ecclizumab (Soliris®) 900 mg IV once weekly for 4 weeks and repository corticortropin (H.P. Acthar® gel) 80 units subcutaneous twice weekly for 6 months with complete resolution of proteinuria within 3 months of the treatment. However, the patient presented again after 6 months of completing therapy with a recurrence of proteinuria which peaked at 11.6 g/g of creatinine. The kidney allograft biopsy was consistent with C3GN. He was started on Acthar® 80 units subcutaneous twice weekly and the proteinuria was reduced to <50% within 2 months of therapy. When ecclizumab 900 mg IV once weekly for 4 weeks was added with Acthar®, the proteinuria fully resolved within 10 weeks of treatment. Since then, the patient has been maintained on Acthar® monotherapy of 40 units subcutaneous twice weekly and has stayed in complete remission of proteinuria for more than a year till his last follow-up.

**Discussion:** In conclusion, this is the first case report describing the role of repository corticortropin as an effective therapy in reducing proteinuria and maintaining patients with C3GN in complete remission.

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**PO2217**

**Rare Presentation of Disseminated Nocardia as Syndrome of Inappropriate Antidiuretic Hormone (SIADH) in Renal Transplant**

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**Introduction:** Nocardia is a rare opportunistic pathogen that typically affects the immunocompromised host. Recently, Williams et. al. reported a third of patients have disseminated cerebral nocardiosis at presentation with most common isolate Farcinica species. SIADH has been reported in association with disease progression.

**Case Description:** A 31-year-old renal transplant recipient presented 4 years post-transplant with dyspnea and left upper extremity jerking. Immunosuppressives (IS) included Mycophenolate, Tacrolimus and Prednisone. He had non focal exam. Blood work showed Na 129, Uosm 500 mosm/kg, UNa 92. MRI brain showed multiple lesions, largest in left frontal area. CT chest revealed right pleural effusion. Biopsy of resected brain abscess and pleural fluid analysis both confirmed Nocardia Araoensis and Bejingensis. Imipenem and Bactrim were started, IS regimen was tapered down. Repeat scans month later showed resolution of vasogenic edema, pleural effusion and SIADH.

**Discussion:** Cerebral nocardiosis is life-threatening opportunistic infection that often presents with no specific clinical signs to guide diagnosis. High index of clinical suspicion is the key to early diagnosis. Presence of SIADH should prompt search for Nocardia which needs to be identified down to its species for targeted antibiotic treatment.
William Patient with Subsequent Immune Reconstitution Inflammatory Transplantation: Clinical - Noninvasive Biomarkers, Immune Regulation, and Fascinomas

Left frontal ring-enhancing lesion.

PO2218
Disseminated Mycobacterium Avium Complex in a Renal Transplant Patient with Subsequent Immune Reconstitution Inflammatory Syndrome Post Transplant Nephrectomy

Introduction: Mycobacterium avium Complex (MAC) are a group of pathogenic mycobacteria present in soil and water. Infection can present with respiratory symptoms, but in immunocompromised patients disseminated disease with fevers, weight-loss or diarrhoea is more common. Immune Reconstitution Inflammatory Syndrome (IRIS) is an excessive but protective inflammatory response against an existing pathogen when immune function is restored. It is usually seen in patients with Human Immunodeficiency Virus but has been described in renal transplant patients with MAC infection. It can lead to hypercalcaemia via increased macrophage 1α-hydroxylase activity, causing increased 1,25(OH)2D3 production.

Case Description: A 54-year-old male presented 3 years post renal transplant with recurrent fevers, night sweats and pancytopenia with a haemoglobin of 76 g/L, leucocytes of 1x10⁹/L and platelets of 72x10⁹/µL. He was on Tacrolimus, Mycophenolate and Prednisolone, and was previously treated with anti-thymocyte globulin for cellular rejection. Bone marrow and blood cultures were positive for MAC at 8 weeks. He was started on clarithromycin, ethambutol and rifampicin, with reduction in leucocytes of 1x10⁹/L and platelets of 72x10⁹/µL. Septic rejection treatment was performed for acute T cell mediated rejection and prednisone was added to her maintenance immunosuppressive regimen. 2 months later she presented with a necrotic lesion with pain over the hard palate with a couple of more oral lesions with similar characteristics. She underwent debridement with excision and biopsy that confirmed oral aspergillosis. She was treated with isavuconazole for 3 months. The oral lesions eventually recovered after 12 weeks of treatment.

Discussion: Oral aspergillosis is very rare but associated with high morbidity and mortality if not treated timely. The diagnosis is based on tissue culture and histopathologic findings. The treatment is surgical combined with systemic fungal therapy for at least 3-6 months. Our patient developed the infection early post kidney transplant due to her recent extensive immunosuppression before and after kidney transplant.

PO2219
A Very Rare Presentation of Oral Invasive Aspergillosis Immediately Post Kidney Transplant
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Introduction: Although oral candida infection is very common opportunistic infection after kidney transplant, there are incidences of other fungal infections like aspergillosis, cryptococcosis, histoplasmosis, coccidioidomycosis, Blastomycoses dermatitii etc. that are also important to be considered. Here we are reporting a very rare presentation of oral aspergillosis in very early phase post kidney transplant.

Case Description: 38 years old Hispanic female with history of systemic lupus erythematosus and lupus nephritis since 2005, last lupus flare in June 2020 was treated with rituximab and high dose prednisone followed by maintenance with azathioprine and hydroxychloroquine. She received preemptive directed deceased donor kidney transplant in November 2020 with thymoglobulin induction followed by Tacrolimus and Mycophenolate mofetil maintenance therapy. 1 month post-transplant she received pulse dose intravenous Methylprednisone for acute T cell mediated rejection and prednisone was added to her maintenance immunosuppressive regimen. 2 months later she presented with a necrotic lesion with pain over the hard palate with a couple of more oral lesions with similar characteristics. She underwent debridement with excision and biopsy that confirmed oral aspergillosis. She was treated with isavuconazole for 3 months. The oral lesions eventually recovered after 12 weeks of treatment.

Discussion: Oral aspergillosis is very rare but associated with high morbidity and mortality if not treated timely. The diagnosis is based on tissue culture and histopathologic findings. The treatment is surgical combined with systemic fungal therapy for at least 3-6 months. Our patient developed the infection early post kidney transplant due to her recent extensive immunosuppression before and after kidney transplant.

PO2220
Simultaneous Occurrence of Actinomyces Gastritis and Severe Rejection in a Kidney Pancreas Transplant Recipient
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Introduction: We are presenting a 33 year old lady with history of Kidney Pancreas transplant admitted for rejection treatment and found to have co infection, actinomycyes and CMV in gastric mucosa. Patient was managed well with modified net immunosuppression and discharged safely on long term antibiotics.

Case Description: 33 year old woman with h/o stage V CKD from type I diabetes mellitus had Simultaneous kidney pancreas transplant in 2018 admitted directly from clinic for rejection treatment. admission vitals were temperature 97.6, blood pressures of 151/99, heart rate 83, respiratory rate 18, on room air. exam unremarkable. home. Immunosuppression is cyclosporine, sirolimus and prednisone. baseline creatinine
PO222
Recurrent Renal Allograft Torsion After Simultaneous Kidney and Pancreas Transplantation: Is Still Possible to Salvage the Graft?
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Introduction: Kidney Allograft Torsion (KAT) is defined as a rotation of the renal allograft around its vascular pedicle. It is a rare complication with high rate of graft loss. The nonspecific presentation and inability to provide a definitive diagnosis by imaging, mainly in cases of partial torsion, often delay the diagnosis and treatment. We report a case of recurrent complete torsion of the renal allograft after simultaneous kidney and pancreas transplantation (SKPTx), requiring two emergency exploratory laparotomies.

Case Description: A 38-year-old woman with a history of intraperitoneal SKPTx underwent two separate emergency exploratory laparotomies secondary to complete renal allograft torsion, respectively seven and eleven months after the transplant. In both episodes, no adhesions were encountered. During the first operation, nephropyexy was performed. During the second operation, an abdominal wall mesh was placed and fixed to the abdominal wall. Acute kidney injury (AKI) related to KAT recovered in both occasions with a creatinine of 1.3 mg/dL after four months follow-up.

Discussion: Renal torsion should be always suspected in intraperitoneally placed kidneys presenting with nonspecific symptoms, abdominal pain, oliguria and worsening kidney function. Surgical exploration should be considered to salvage the renal graft. This case illustrates the reversibility of a severe injury related to this vascular complication with an adequate return to baseline kidney function even when diagnosis and surgical treatment of KAT might be delayed secondary to its misleading clinical presentation.

PO2222
New-Onset Antibiotic Anaphylaxis Post Kidney Transplant: A Role of Calcineurin Inhibitors?
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Introduction: Calcineurin inhibitors (CNIs), such as tacrolimus and cyclosporin, are a mainstay of post-transplant immunosuppression. Immunosuppressive medications typically suppress type I allergic reactions, however, there have been reports of allergic sensitization post-transplantation, despite no known drug allergies.

Case Description: We report two cases of antibiotic-related anaphylaxis post kidney transplant. In case one, a 63-year-old male was admitted for an elective transurethral prostate section having received an NDD renal allograft two-months prior and maintained on tacrolimus, mycophenolate and prednisone. Preoperatively, creatinine was given for antibiotic prophylaxis, but he developed an anaphylactic reaction leading to hemodynamic collapse requiring ICU admission. Serum tryptase (37.6ug/L, normal <11.4ug/L) and histamine (20-40ng/mL, normal <1ng/mL) levels were markedly elevated confirming anaphylaxis. In case two, a 56-year-old female received a DCD renal allograft on immunosuppression with prednisone, mycophenolate and tacrolimus), eleven months prior to admission for suspected sepsis. He was empirically treated with cefazidime and vancomycin but developed an anaphylactic reaction, requiring intubation and ICU admission. Serum tryptase and histamine levels were not assessed. A comprehensive medication review revealed that both patients had received the offending antibiotics without issues prior to transplantation. In both cases, neither donor had a documented allergy to these medications.

Discussion: In these clinical vignettes, we describe two patients with anaphylaxis post transplantation, despite previously tolerating the offending medications without issue. Furthermore, these reactions were not donor derived. Type I allergic reactions are typically suppressed post-transplant, yet there is literature to suggest that allergic sensitization may be CNI mediated. The rates of CNIs causing allergy are cited to be as high as 10% in liver and kidney recipients. Risk factors for sensitization are not described, although we note both of our patients had anaphylactic events within one-year post transplant. Given the importance of CNIs in allograft immunosuppression balanced against the morbidity of anaphylaxis, these cases highlight the need to better identify high risk patients for such events.

PO2223
Immunosuppression Cessation During Chemotherapy for Post-Transplant Lymphoproliferative Disorders in Kidney Transplant Recipients
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Introduction: Kidney transplant patients have a 20-fold higher risk to develop Post-Transplant Lymphoproliferative disorder (PTLD). PTLD requires reduction in immunosuppression (IS) medications to the lowest dose that prevents rejection. Here we report the safe withdrawal of IS in three kidney transplant recipients with PTLD receiving chemotherapy.

Case Description: Case 1: A 44-year-old male received a deceased donor renal transplant with alemtuzumab induction. He developed cellular rejection that was treated with steroids and thymoglobulin. He was maintained on cyclosporine, mycophenolate, and prednisone. Later on, he developed resistant EBV viremia and a retroperitoneal mass with diffuse lymphadenopathy. Biopsy revealed a high-grade, EBV-negative, monomorphic diffuse large B cell lymphoma (DLBCL). IS medications were stopped except for low-dose prednisone. Creatinine remained stable post six cycles of chemotherapy, with complete response after three cycles. Case 2: A 59-year-old male with a history of membranous nephropathy (MN) treated with rituximab. Removed a living-related donor renal transplant (LRDRT), with alemtuzumab induction. MN recurred three years after transplantation and was treated with modified Ponticelli protocol. He was maintained on cyclosporine and mycophenolate. Ten years post-transplant, he had a large mesenteric soft tissue mass with lymphadenopathy. Biopsy showed EBV-negative, monomorphic high-grade DLBCL. IS medications were stopped. The patient received six cycles of chemotherapy and achieved a complete response. Creatinine remained at baseline. Case 3: A 36-year-old male with a history of IgA nephropathy, received a LRDRT with alemtuzumab induction. He was maintained on tacrolimus and mycophenolate. Five months later, he was diagnosed with stage IIIB, EBV-positive, monomorphic DLBCL via tonsorial mass biopsy. IS medications were stopped and he went into complete remission after eight cycles of chemotherapy. He was started on sirolimus monotherapy post-chemotherapy. Creatinine remained at baseline for five years.

Discussion: IS withdrawal seems to be a safe option during chemotherapy for PTLD. Chemotherapy causes prolonged immunosuppression or immune tolerance to the allograft. The safe cessation of IS while receiving chemotherapy for PTLD has been described, with reinitiation of low-dose IS post-remission.

PO2224
Sirolimus and Chylorperitoneum: A Rare Pair
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Introduction: The mammalian target of rapamycin inhibitors (mTORi) are associated with complications like hyperlipidemia, lymphocytosis, lymphedema and rarely chylous ascites (CA), characterized by a milky colored, triglyceride (TG) rich fluid leading to dehydration, electrolytes imbalances and immunosuppression. We present a case of sirolimus induced chylorperitoneum in an ESKD patient.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Case Description: 44 year old woman with heart failure reduced ejection fraction (HFrEF) secondary to transposition of great vessels and orthotopic heart transplant in 2007, NASH cirrhosis and ESKD from calcineurin inhibitor toxicity, switched to sirolimus in 2018. Renal function declined requiring initiation of peritoneal dialysis (PD) in December 2020. 3 months prior patient presented with right upper extremity (RUE)/ipsilateral breast swelling, erythema and dull pain. US doppler ruled out DVT. Lymphangiogram showed diffuse skin/right breast soft tissue edema. PD catheter was placed, incidentally found mild clear ascites, liver cirrhosis and bilateral ovarian cysts, work up for malignancy was negative and discharged. She trained for PD and efficient for K/TV had milky appearance. Fluid analysis showed nucleated cell count 1151mcL, RBCs 1391mcL, total protein 2.4g/dl, albumin 1g/L, amylase <30u/L, glucose 160mg/dL, LDH 248U/L and TG level 141mg/dl consistent with CA. Sirolimus was held and 2 weeks after PD fluid cleared and RUE lymphedema slowly improved with right breast enlargement to date.

Discussion: CA results from disruptive lymphatic system and posterior leakage of lymph into the abdominal cavity. Diagnosis requires TG levels >110mg/dl and gold standard imaging test is lymphangiography. Multiple etiologies are proposed: malignancy, traumatic surgical injury, liver cirrhosis and cardiovascular disease. Less common, standard imaging test is lymphangiography. Multiple etiologies are proposed: malignancy, traumatic surgical injury, liver cirrhosis and cardiovascular disease. Less common, resolution of symptoms. Their current average sirolimus level is 5.05 ng/dL.

Discussion: This case presents a unique instance of extended-release tacrolimus induced psychosis. While immediate-release tacrolimus is well known to cause neurotoxicity (5, 13), extended release is generally felt to be safer (12, 9). This case illustrates that while extended-release Tacrolimus formulations may have a reduced incidence of neurological side effects, they are not devoid of them. The SIMPLE trial is currently ongoing and its data may shed more light on Tacrolimus induced neurotoxicity (10). Regardless of the outcome of this research, the treatment for tacrolimus induced neurotoxicity should always be to decrease the dose or withdraw the medication (14).

PO2225
Renal Transplant Recipient with Large Periorbital Basal Cell Carcinoma (BCC) Cured Nonsurgically with Vismodegib

Introduction: Renal transplant recipients (RTR) live a delicate balance between preserving allograft function with immunosuppression medications (IS) and the side effects (e.g malignancies). Skin cancers are prevalent with Squamous (SCC) & BCC (SCC), comprising 90% of skin cancers. These tumors are aggressive, exhibiting unique pathophysiologic characteristics. We present a case of a RTR who developed invasive periorbital BCC; successfully treated with novel chemotherapeutic Vismodegib.

Case Description: A 66-year-old man with history of kidney transplant had a stable graft function with Cr 1.6 on IS for 35 years, on Prednisone and Tacrolimus. With a history of recurrent SCC and BCC treated with surgical and radiation therapy. During clinic, he was found to have a large tumor in the lateral canthus of the left eye. Patient was referred to dermatology, biopsy revealed BCC. Tumor grew rapidly, further invading the eye within a few weeks. Given the proximity to visual organs; ENT, Ophthalmology, Dermatology, and Transplant team decided to treat the BCC nonsurgically with Vismodegib. Patient achieved complete remission in 6 months of treatment with successful preservation of eyesight.

Discussion: Surgical excision is considered first line therapy in BCC. Patients with periorcular BCC can place visual organs at risk with surgical and/or radiation therapy. Vismodegib is indicated for metastatic BCC or locally advanced BCC that has recurred following surgery. Vismodegib binds and inhibits the smoothened receptor, leading to hedgehog signaling pathway inhibition and decreased tumor cell proliferation. Recent studies assessing Vismodegib benefit recruited patients with median tumor size of 22mm. Our case highlights that Vismodegib is efficacious in preserving essential visual structures and eyesight even in much larger tumor burden; 55mm. In conclusion, Vismodegib is now emerging in critical management of large and fast growing BCC affecting vital facial structures, especially in RTR on long term IS meds.

PO2226
Psychosis as a Neurotoxic Manifestation of Extended-Release Tacrolimus

Introduction: Tacrolimus is a calcineurin inhibitor used in renal transplant to reduce the risk of rejection. Common side effects include infection, nephrotoxicity, and neurotoxicity (7). The neurotoxic effects can manifest as psychosis, paraesthesia, and bipolar mania (4, 2). The unpredictable nature of tacrolimus pharmacokinetics has led to the development of extended-release tacrolimus such as Envarsus XR (8, 9, 12). While data is lacking, Envarsus XR is thought to have a lower incidence of neurotoxic side-effects (10, 11). To our knowledge, there are no recorded cases in the literature of psychosis related to Envarsus XR (3, 6). We present a case of acute paraesthesia related to Envarsus XR.

Case Description: Ms. H is a 62 year old woman who underwent allogenic renal transplant and was placed on immediate-release tacrolimus 0.5 mg twice daily. Due to high tacrolimus levels (average 9.6 ng/dl) she was switched to Envarsus XR 0.75 mg daily and subsequently reported new onset emotional disturbance. She was initially treated with fluoxetine then switched to citalopram without relief. She then developed paranoid ideation and refused to sleep. The patient and family felt this behavior correlated with starting Envarsus XR. This was discussed with her transplant team and Envarsus XR was continued as her tacrolimus levels were within goal (average 5.3 ng/dl). Her paranoia worsened and she was seen by psychiatry and placed on risperidone 2 mg daily. She continued to experience paranoid delusions and behavioral disturbance. She was then switched from Envarsus XR back to immediate-release tacrolimus and had complete resolution of symptoms. Her current average tacrolimus level is 5.05 ng/dL.

Discussion: This case presents a unique instance of extended-release tacrolimus induced psychosis. While immediate-release tacrolimus is well known to cause neurotoxicity (5, 13), extended release is generally felt to be safer (12, 9). This case illustrates that while extended-release Tacrolimus formulations may have a reduced incidence of neurological side effects, they are not devoid of them. The SIMPLE trial is currently ongoing and its data may shed more light on tacrolimus induced neurotoxicity (10). Regardless of the outcome of this research, the treatment for tacrolimus induced neurotoxicity should always be to decrease the dose or withdraw the medication (14).
PO2228

Dual Diagnosis of Thrombotic Thrombocytopenic Purpura and Atypical Hemolytic Uremic Syndrome in Pregnancy

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Introduction: Thrombotic thrombocytopenic purpura (TPP) and atypical hemolytic uremic syndrome (aHUS) are thrombotic microangiopathy (TMA) disorders which may initially occur in pregnancy. TPP, caused by severe ADAMTS13 deficiency, is treated with plasma exchange (PEx); whereas aHUS, caused by uncontrolled complement activation, is treated with complement inhibition (e.g., eculizumab). Because TPP and aHUS have different causes, the term TPP-hUS is no longer used. However, we describe a patient diagnosed and treated for both TPP and aHUS in pregnancy.

Case Description: A 38-year-old female at 9 weeks’ gestation presented with hematuria. Labs revealed severe thrombocytopenia (platelets 5 k/ul), hemolytic anemia, and acute kidney injury. TPP was suspected, so PEx was initiated, but she did not fully respond (Fig 1). ADAMTS13 activity was low (11%) but with negative inhibitor, arguing against acquired TTP; genetic testing revealed no cause of TTP, and eculizumab was initiated. Complement-mediated aHUS (aHUS) was considered given low C3, C4, and proteinuria; Lupus and Anti-Phospholipid Syndrome were ruled out. Genetic testing revealed a rare C3 variant and polymorphisms in CFH and MCF, which are enriched in aHUS patients. After multidisciplinary review, the diagnosis of aHUS was made. PEx was stopped, and eculizumab was started with good response. At 35 weeks’ gestation she presented with hypertension and petechiae, and labs showed recurrence of hemolytic anemia and thrombocytopenia (platelets 7 k/ul). She had cesarean delivery, after which PEx was initiated. Two years later she was admitted with worsened renal function, severe anemia (Hb 4 g/dl), thrombocytopenia (36k/ul), and poor controlled HTN, needing 6 different classes of drugs to control her blood pressure. Eculizumab was started and she received 14 cycles of PEx, prednisone, and rituximab for refractory TPP (Fig 1).

Treatments were stopped after 6 weeks, and she remains in remission after 1 year.

Discussion: This case illustrates dual diagnosis of TPP and aHUS in pregnancy. Key points: a) Rarely, TPP and aHUS can coexist; b) ADAMTS13 activity and complement genetic testing may help identify TMA etiology; and c) Treatment of TMA in pregnancy with PEX or complement inhibition should be clinically-based.

PO2229

Pregnancy-Associated Atypical Hemolytic Uremic Syndrome in the Setting of a Rare THBD Mutation and Successful Treatment with Eculizumab

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Introduction: Pregnancy-associated atypical hemolytic uremic syndrome (PaHUS) is a rare but fatal thrombotic microangiopathy that results from uncontrolled complement activation during the peripartum and postpartum periods. Underlying complement gene mutations are found in a majority of cases. THBD, the gene responsible for encoding thrombomodulin, is a known risk variant associated with PaHUS. We present a case of PaHUS complicated by intrathoracic fetal demise and acute renal failure in the setting of a rare THBD gene variance which was successfully treated with the terminal complement inhibitor eculizumab.

Case Description: 20-year-old G1P0 female presented at 30w+4d with severe abdominal pain and diffuse vaginal bleeding. An emergent cesarian section revealed a placental abortion with intrathecial fetal demise. Hospital course was complicated by anuria with a maximum serum creatinine 8.43 mg/dL, hemoglobin 5.5 g/dL, platelets 35 x10^3/µL, lactate dehydrogenase 9051 U/L, and schistocytes seen on peripheral smear. She was initiated on renal replacement therapy, daily plasma exchange, and steroids. Despite this, she experienced persistent hemolysis, dialysis dependence, and worsening respiratory failure ultimately requiring intubation. ADAMTS13 activity was normal at 83%. Eculizumab was initiated, and after one week, hematologic parameters normalized with evidence of renal recovery. Outpatient genetic testing revealed a rare variant in THBD. Six months following discharge, the patient remains in remission on maintenance eculizumab.

Discussion: The diagnosis of PaHUS is very challenging; however, prompt recognition and subsequent genetic testing for complement variants are crucial given association with more severe outcomes, progression to ESRD, and increased risk of relapse. Pathologic variances in THBD account for 5% of aHUS cases and have been associated with earlier onset and higher mortality; however, risk of disease relapse with mutations in this gene is unknown. Although eculizumab has been shown effective in PaHUS, there is little data on treatment duration and recurrence rate with therapy in subsequent pregnancies. Further expansion of genetic testing is required to enhance our knowledge of all PaHUS susceptibility factors and improve management of patients similar to the presented case.

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Underline represents presenting author.

PO2230

Efficacy of Eculizumab Therapy in Delayed-Diagnosed, Hemodialysis-Dependent, Pregnancy-Triggered, Complement-Mediated Thrombotic Microangiopathy


Introduction: Pregnancy associated atypical hemolytic uremic syndrome (p-aHUS) is provoked by pregnancy and affects 1/25,000 pregnancies in the general population. The delivery is vital for halting the disease process. The course of complement-mediated thrombotic microangiopathy (C-TMA) is not affected by delivery, but condition improves with anti-complement therapy. We are presenting a rare case of delayed diagnosed, pregnancy provoked C-TMA with significant improvement in blood pressure, stabilization of anemia, and resolution of thrombocytopenia after treatment with Eculizumab.

Case Description: A 25-year-old Hispanic woman with history of CKD stage IIIIB presented with syncope. She developed renal failure, required hemodialysis (HD) and HTN during her first pregnancy. During postpartum, HD was stopped and HTN resolved. Two years later she was admitted with worsened renal function, severe anemia (Hb 4 g/dl), thrombocytopenia (36k/ul), and poor controlled HTN, needing 6 different classes of drugs to control her blood pressure. Blood smear showed schistocytes. Our extensive work up ruled out: TTP, HUS, DIC, lupus, scleroderma, and other disorders. Complement work up was low. Renal ultrasound showed obstructive and renal artery stenosis, but showed echogenic kidneys. Given echogenic kidneys and increased bleeding risk, renal biopsy was not performed. The diagnosis of C-TMA was established. Regular HD was resumed. She was started on Eculizumab and with maintenance treatment her HTN became wellcontrolled with only two medications.

Discussion: Timely diagnosis and management are the key points to improve C-TMA prognosis. It may be a difficult diagnosis and mimic eclampsia, HELLP syndrome, or p-aHUS. Although it is related to inherited defects of complement alternative pathway or the proteins that regulate it, lack of linked gene mutations cannot exclude C-TMA. In this patient, the diagnosis of C-TMA was not made until two years after onset. Our case report showed that even though Eculizumab cannot completely reverse the renal injury at the late stage of C-TMA, it may still improve the blood pressure control, normalize platelets, help anemia, and prevent further damage.

PO2231

Therapeutic Plasma Exchange Improved Pregnancy Outcomes in a Patient with Triple Positive Anti-Phospholipid Antibody Syndrome

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Introduction: Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by antibodies directed at platelet, monocyte, endothelial cell, and thrombast hemotoies potentially causing venous and arterial thromboses. The placental vasculature is particularly vulnerable to these antibodies resulting in a marked increased risk of fetal growth restriction, placental infarction, abortion, stillbirth, and preterm severe preeclampsia. APS is diagnosed by clinical criteria in conjunction with laboratory findings, and the circulating anti-phospholipid antibodies commonly tested are lupus anticoagulant, anti-cardiolipin, and anti-beta-2-glycoprotein-1. The simultaneous presence of all three antibodies is associated with the highest risk of thrombotic complications in APS.

Case Description: A 29-year-old nulligravida with medical history was significant for APS on lifelong coumadin. Her APS labs at the time of preconception visit showed elevated lupus anticoagulant ratio, anticardiolipin and anti-beta-2-glycoprotein-1antibodies (Triple- positive antibodies). Medications included twice daily LMWH 60 mg and hydroxychloroquine 200 mg. Fetal anatomic survey at 20 weeks demonstrated normal fetal growth, however, by 21 weeks 6 days ultrasound showed absent-end diastolic flow of the umbilical artery Doppler waveform. She was admitted to the hospital. A pre-eclampsia workup was completed due to hypertension and new onset proteinuria. LDA daily, pravastatin 20mg was added. Due to the diagnosis of preeclampsia with severe features, the decision was made to treat with therapeutic plasma exchange.

Discussion: High-risk obstetric APS profiles are linked to specific serological markers such as triple antibody positivity, clinical features such as a history of thrombosis, and the presence of pregnancies result in a liveborn infant, with that rate dropping to 30% in patients who are triple system autoimmune diseases. Therapeutic plasma exchange every 48 hours successfully prolonged the pregnancy for 11 weeks, resulting in an optimal pregnancy outcome for both mother and infant given the initial dire clinical situation at a pre-viable gestation. The rationale for TPE every 48 hours was based on the experience in plasmapheresis use in Cstatrophic Antiphospholipid Syndrome (CAPS)
Lupus Nephritis Kidney Biopsy Characteristics and Preterm Birth
Monica L. Reynolds, Caroline J. Poulton, Lauren N. Blazek, Keisha L. Gibson, Vimal K. Derebail. University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC.

Background: Lupus nephritis (LN) in pregnancy is associated with high rates of preterm birth (PTB). Hypocomplementemia, elevated creatinine, proteinuria and hypertension serve as risk factors. Outside of pregnancy, class IV LN and interstitial fibrosis at initial biopsy associate with progressive disease. We performed a retrospective chart review to assess if timing of kidney biopsy and histologic features increased PTB.

Methods: We included women with LN enrolled in the Glomerular Disease Collaborative Network registry who delivered at University of North Carolina (UNC) Hospital from 2001-2019. Delivery data came from the UNC perinatal database. Fishers exact test assessed biopsy characteristics and PTB (< 37 weeks).

Results: There were 36 deliveries in 32 women. Figure 1 describes the cohort. Among preconception biopsies (n=25), pregnancy occurring ≥ 24m after biopsy was more likely to result in PTB than if biopsy was performed ≥ 24m prior to conception (82% vs 29%, p < 0.02). A UPVR > 0.5 mg/mg in the first trimester was also associated with PTB (81% vs 36%, p=0.04). PTB occurred in 69% with proliferative LN vs 50% without (ie primary diagnosis class II or V), p=0.44. Class IV LN was not significantly associated with PTB; neither was the presence of crescents (n=21/36), activity ≥ β (n=16/25), chronicity ≥ 3 (n=12/27), or more than mild interstitial sclerosis (n=6/33).

Conclusions: Biopsy occurring within 2 years of conception and first trimester proteinuria were significantly associated with PTB. While this presumes greater LN activity, no specific biopsy characteristic impacted the outcome. This data may aid in preconception counseling for optimal timing of conception. Calcineurin inhibitors were not used in the first trimester in this cohort; their antiproteinuric qualities and effect on PTB requires evaluation.

Comparison of Clinical Features of Pregnant and Non-Pregnant Women with Primary Hyperoxaluria
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Background: Primary hyperoxaluria (PH) is a rare monogenic disease characterized by oxalate overproduction in the liver, hyperoxaluria, and risk of kidney stones and chronic kidney disease. Data about the effects of pregnancy on women with PH are lacking. We aimed to compare clinical features and risk of incident kidney failure in women with PH with and without pregnancy.

Methods: Women with PH were identified from the Rare Kidney Stone Consortium registry, and pregnancy was identified by phone interview and medical record review. Kidney survival and risk of time-dependent kidney failure were estimated using the Kaplan-Meier method and adjusted proportional hazard Cox’s model.

Results: We identified 47 women with PH and a history of pregnancy and 39 women without pregnancy. PH was diagnosed later in women with pregnancy vs. women without pregnancy (median age 32.4 vs. 13.4 years, p<0.001). Other clinical characteristics such as PH type, eGFR and 24-hour urine oxalate excretion (Uox) at PH diagnosis did not differ between the 2 groups. Fig 1A shows the time course of the PH diagnosis, pregnancy and kidney failure in 29 women with known delivery date. In women with pregnancy versus non-pregnancy, the hazard ratio for incident kidney failure was 0.81 (95% CI 0.25-2.6, p=0.73) when adjusted for PH type, age, and eGFR and Uox at PH diagnosis. Among patients with PH1 who did not have kidney failure by the time of the 1st pregnancy (n=20), kidney survival estimates at 10, 20, and 30 years after delivery were 79%, 60%, and 45%, respectively (Fig 1B).

Conclusions: These results suggest that pregnancy did not greatly impact renal prognosis in women with PH.

Second Trimester eGFR and Adverse Pregnancy Outcomes in Women with Systemic Lupus Erythematosus
Anika Lucas, Amanda Eudy, Christina M. Wyatt, Megan Clowse. Duke University, Durham, NC.

Background: Adverse pregnancy outcomes are more common in women with SLE.2nd trimester eGFR was shown to predict adverse pregnancy outcomes in a general population cohort. We sought to evaluate 2nd trimester eGFR as a predictor of adverse pregnancy outcomes in women with SLE.

Methods: We evaluated 684 women with SLE(22% of Black race)who received care in North America and Europe from 1995-2017.2nd trimester eGFR was stratified based on studies demonstrating women with an eGFR 120-135 ml/min/1.73m2 had the lowest odds of adverse outcomes. Outcomes of interest included preterm birth, preeclampsia, fetal loss and poor pregnancy outcome(composite outcome). 2nd trimester GFR was computed using the CKD Epi equation without adjustment for race. In sensitivity analysis, 2nd trimester GFR computed using the conventional race-based equation. Polynomial and logistic regression models used to evaluate 2nd trimester eGFR and adverse outcomes.

Results: Very low eGFR(<90ml/min/1.73m2)and very high eGFR (>135ml/ min/1.73m2)were associated with higher adverse outcomes. In univariate and multivariable regression models adjusted for age, race, and SLE disease activity, very low eGFR was associated with preterm birth, preeclampsia, fetal loss and poor pregnancy outcome. Very high eGFR was associated with poor pregnancy outcome and preterm birth. In sensitivity analyses using race based GFR estimates, very low eGFR remained associated with adverse outcomes observed. No association was observed between very high eGFR and adverse outcomes.

Conclusions: We found a U-shaped relationship between 2nd trimester eGFR and adverse pregnancy outcomes. Women with eGFR <90ml/min/1.73m2 and >135ml/ min/1.73m2 had higher odds of adverse outcomes. 2nd trimester GFR may be a helpful tool to identify women with SLE at greater risk for adverse outcome. Our results further suggest that kidney hyperfiltration may become pathologic during pregnancy. There were notable differences using non-race based and race-based GFR estimating equations. These differences may have clinical implications when utilizing GFR estimating equations to predict health outcomes.

Funding: Private Foundation Support
PO2235
Narrowing Communication Gaps to Optimize Patient-Centered Pregnancy Counseling for Women with CKD
Andrea L. Oliverio, Maryn Lewallen, Kassandra Weber, Sarah Havley, Julie A. Wright Nunes. University of Michigan, Ann Arbor, MI.

Background: Women with chronic kidney disease (CKD) face unique pregnancy decision-making challenges. Although there is an increased risk of adverse pregnancy outcomes in women with CKD, many women report strong pregnancy desires. There is little evidence on how to support pregnancy communication and decision-making needs in women with CKD.

Methods: We performed semi-structured interviews with 18-45 years of age who have CKD stages 1-V (n=30), and their practicing nephrologists (n=12) at one academic medical center. The average age of patients was mean(3D) 32.4(6.9) years; 50% already had children. 50% (n=15) identified as white, 23.3% (n=7) as Black, 13.3% (n=4) as Hispanic, 6.7% (n=2) as Asian, and one declined to answer. CKD etiologies included lupus nephritis (n=7, 23.3%), other nephritic/nephritic syndromes (n=9, 30%), diabetes (n=4, 13%), hypertension (n=3, 10%), other (n=4, 13%), and unknown (n=3, 10%). Interview questions probed patients about counseling experiences and reproductive health outcomes in CKD, approaches to pregnancy decision-making, barriers and facilitators to effective counseling, and desires for future support. A codebook was iteratively developed, with double coding of transcripts and discrepancies resolved via consensus.

Results: Most women with CKD preferred their nephrologist introduce the concept of reproductive planning to elicit their values in care and reduce barriers to pregnancy counseling. Specific information about individual pregnancy risks and risks to potential offspring were desired. Women with strong reproductive intentions more often sought counseling, and desires for future support. A codebook was iteratively developed, with double coding of transcripts and discrepancies resolved via consensus.

Conclusions: Patient-provider pregnancy communication and decision-making are critical for women who have CKD. Further research is needed to ensure nephrologists have tools to support pregnancy decision-making that incorporates patients’ needs, values and goals in care.

Funding: NIDDK Support

PO2236
Maternal Hypertension and Hypertensive Disorders of Pregnancy Are Associated with Increased Risk of Hypertension in Offspring

Background: Hypertensive disorders of pregnancy (HDP) have significant effects on perinatal outcomes for offspring. Although there is increasing evidence of adverse effects of HDP exposure on long-term health outcomes in offspring, the impact of maternal hypertension beyond HDP is limited.

Methods: We conducted genetic testing for 20 complement genes in a cohort of patients with C3G from the University of Iowa Health System C3G Natural History Study (n=76) and at least one pregnancy (n=17). Genetic and/or acquired drivers of disease studies were assessed. Standard peri-pregnancy outcomes were considered.

Results: Autosomal recessive inheritance was observed in most patients (n=9, 53%). Mutations were identified in complement genes in 12 patients (71%). The most common CFH-related variant was CFH R266Q (n=9, 53%). Mutations were classified as, Level 1: pathogenic; Level 2: likely pathogenic; Level 3: variant of uncertain significance (VUS); Level 4: likely benign; Level 5: benign.

Conclusions: Complement genetic variants are associated with thrombotic microangiopathy (TMA). Atypical hemolytic uremic syndrome (aHUS) is a classic complement-mediated TMA characterized by hemolytic anemia, thrombotic thrombocytopenia and acute kidney injury. Clinical features of aHUS resemble those of preeclampsia and HELLP syndrome (Hemolysis, Elevated Liver Enzymes, Low Platelets) syndrome. Therefore, we sought to determine if complement genetic variants also predispose to these hypertensive diseases of pregnancy.

Funding: NIH Support
Results: 44 pregnancies and 34 deliveries were identified. Non-live birth pregnancy outcomes included eight miscarriages, one ectopic pregnancy and one elective abortion. The presumed driver of disease was known for eight patients; gene variants of unknown significance (n=3), nephritic factors (n=4), and a mononuclear protein (n=1). Six patients presented first C3G symptoms during pregnancy. Preeclampsia developed in 11. Six infants were premature. Five were born with low birthweight. One infant suffered a stroke. One infant presented with AKI. [Maternal nephritic factor was identified in neonatal sera.]

Conclusions: We provide a summary of maternal-fetal outcomes in C3G mothers. Our data supports an increased risk of preeclampsia in C3G mothers as compared to healthy women. There was no excess risk of miscarriage, cesarean section, ectopic pregnancy, prematurity, or low birth weight. This data indicates a relatively higher risk of preeclampsia and lower risk of cesarean section compared to women with IgA Nephropathy. A similar risk of miscarriage, prematurity, and low birth weight as other glomerular diseases was evident. Our data supports a reasonable maternal-fetal risk profile for C3G patients.

Figure 1 - Peri-Pregnancy Outcomes in C3G Mothers

PO2239
Maternal Health in Autosomal Dominant Tubulointerstitial Kidney Disease
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Background: Autosomal dominant tubulointerstitial kidney disease due to MUC1 mutations (ADTKD-MUC1) and UMOD mutations (ADTKD-UMOD) are becoming increasingly recognized as causes of chronic kidney disease (CKD). Genetic testing allows women to determine if they are affected with these conditions, and data on the outcomes in pregnancy in ADTKD would be of great interest to them as they prepare for future pregnancies.

Methods: We surveyed women with ADTKD and genetically unaffected family regarding past pregnancy outcomes. We also analyzed survival to end-stage kidney disease (ESKD) according to number of pregnancies.

Results: We received completed standardized questionnaires surveys from 52 women with ADTKD-MUC1 (113 pregnancies), 74 women with ADTKD-UMOD (136 pregnancies), and 35 genetically unaffected women (64 pregnancies). At the time of pregnancy, only 16.5% of genetically affected women were aware that they had ADTKD. Results are summarized in Table 1. There was a nonstatistical increase in HTN and hospitalization for HTN, 10% of births to affected mothers were premature vs. 0% in unaffected (p=0.01); 12% of babies required a NICU stay vs. 6% in unaffected (p=0.06), but child outcomes were good. Survival analysis showed no statistical differences in age to ESRD based on number of pregnancies for affected women.

Conclusions: Patients with ADTKD had an increased prevalence of hypertension, anemia, and early delivery than controls, but overall pregnancy outcomes were good for mother and child. More information is needed on changes in glomerular filtration rate with pregnancy in ADTKD.

Funding: Private Foundation Support, Government Support - Non-U.S.

Characteristics and Pregnancy Complications Reported.

PO2240
Effect of Reproductive History on Kidney Structure and Function in Women
Andrea G. Kattah,1 Aidan F. Mullan,1 Vesna D. Garovic,1 Maxwell L. Smith,2 Aleksandar Denic,1 Mark D. Stegall,1 Andrew D. Rule,1 Mayo Clinic Minnesota, Rochester, MN; 2Mayo Clinic, Scottsdale, AZ.

Background: Varying estrogen levels from menarche to menopause and physiological changes of pregnancy may impact kidney health in women.

Methods: Female kidney donors from 2000 to 2017 were sent a survey on reproductive health, including menarche, pregnancy, and menopause. At the time of donation, donors had a medical evaluation, measured GFR, 24h urine albumin, CT angiography of kidneys, and a kidney biopsy. Kidney volumes were calculated from CT images. Non-sclerosed and globally sclerosed glomeruli counts and % interstitial fibrosis/tubular atrophy (IFTA) were assessed via kidney biopsy. Kidney function and structural findings at the time of donation were assessed by differences in reproductive factors prior to donation adjusting for age.

Results: There were 673 women studied with a mean (SD) age at donation of 47.4 (11.4) and 74% had at least one pre-donation birth. As compared to non-parous women, parous women had a higher total cortical volume (6.1%, p=0.009) and medullary volume (6.7%, p=0.038). However, among parous women, additional parity was not associated with further increases in kidney volumes. Among the 218 post-menopausal women, each year since menopause was associated with a higher likelihood of IFTA > 0% on biopsy independent of age (OR=1.052, p=0.027). With each 5-year increase in reproductive lifespan (years from menarche to menopause), there was a lower likelihood of having IFTA > 0% (OR=0.81, p=0.048). We did not find any significant association between past reproductive factors on GFR, urine albumin, glomerulosclerosis, or nephron number at the time of donation.

Conclusions: Past pregnancy is associated with larger kidneys among healthy women suggesting that the enlargement of kidneys with pregnancy does not fully resolve after delivery. Among healthy post-menopausal women, longer duration of menopause and shorter reproductive lifespan associated with detectable IFTA on kidney biopsy consistent with a protective effect of estrogen on preventing subclinical kidney injury.

Funding: NIDDK Support, Clinical Revenue Support

PO2241
Kidney Disease Prevalence in Transgender Individuals
Hannah Eckenrode,1 Orlando M. Gutierrez, Gunars Osis, Anupam Agarwal, Lisa M. Curtis. The University of Alabama at Birmingham Department of Medicine, Birmingham, AL.

Background: Kidney disease in the transgender population is understudied which precludes the ability to derive appropriate care guidelines for promoting kidney health. The term transgender includes individuals for whom their assigned sex at birth doesn’t align with their gender identity. Transgender individuals often choose gender-affirming hormone therapy (GAHT) to achieve greater alignment. The impact of this necessary treatment on their kidney health has not been studied.

Methods: We performed a cross-sectional study of 360 transgender individuals, using medical records from 2009-2019. Diagnosis codes were used to identify individuals with acute kidney injury (AKI) and chronic kidney disease (CKD), and comparisons were performed between the groups.

Results: The mean age of the population was 42 (SEM 0.91) and 40% were of black race. Black individuals made up a greater proportion of the transfeminine population who received GAHT but a lower proportion of transmasculine individuals who received GAHT. The term transgender includes individuals for whom their assigned sex at birth doesn’t align with their gender identity. Transgender individuals often choose gender-affirming hormone therapy (GAHT) to achieve greater alignment. The impact of this necessary treatment on their kidney health has not been studied.

Methods: We performed a cross-sectional study of 360 transgender individuals, using medical records from 2009-2019. Diagnosis codes were used to identify individuals with acute kidney injury (AKI) and chronic kidney disease (CKD), and comparisons were performed between the groups.

Results: The mean age of the population was 42 (SEM 0.91) and 40% were of black race. Black individuals made up a greater proportion of the transfeminine population who received GAHT but a lower proportion of transmasculine individuals who received GAHT.

Conclusions: This single-center study of prevalence of kidney disease in the transgender patients demonstrates significant differences in kidney disease conditions in those who did vs. did not use GAHT. These studies highlight the need for further research to define the health and disease manifestations seen in the transgender population.

Funding: NIDDK Support
Dietary Inflammatory Potential and the Risk of Incident ESKD in the Women’s Health Initiative

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Background: Inflammation is implicated in the pathogenesis and progression of chronic kidney disease (CKD). Diet is an important modulator of chronic inflammation, and possibly kidney health. We evaluated the association of diet-associated inflammation with risk of incident end-stage kidney disease (ESKD) in the Women’s Health Initiative (WHI) study.

Methods: Participants enrolled between 1993-1998 in the Observational Study and Dietary Modification Trial of the WHI with completed food frequency questionnaires (FFQs), Medicare enrollment data, and serum creatinine (cCr) measurements were included in our study. Dietary inflammatory potential was assessed from FFQs using the dietary inflammatory index (DII®). The index has been previously validated in the WHI. Medicare claims data were used to ascertain ESKD status. Analyses used DII® scores adjusted for energy-intake (E-DII®), which were categorized into quartiles (Q): scores in Q1 (reference group) having the lowest dietary inflammatory potential and Q4 being the most pro-inflammatory. We performed multivariable Cox proportional hazards models adjusted for important covariates of interest to compare dietary quartiles for risk of incident ESKD. Participants were censored at the time of study withdrawal, loss-to-follow-up, or death.

Results: Of the 15,722 women included in our study, the mean age was 64.2 years (standard deviation 7.01); 35% self-identified as African American, 12% as Hispanic, 27% as Asian, and 50% as White; 40% had hypertension and 9% had diabetes mellitus at baseline. The mean baseline cCr and estimated glomerular filtration rate were 0.74 mg/dL and 89 ml/min/1.73m², respectively. African American and Hispanic women compared to White women (30% vs 19%) were more likely to report consuming diets with scores in Q4. Over mean follow-up of 11.5 years, 515 women developed ESKD. Women with dietary patterns in Q4 compared to those in Q1 had a 20% higher risk of developing ESKD (hazard ratio 1.20 [95% confidence interval 1.05–1.38]; P=0.02) after adjusting for age, race/ethnicity, comorbidities, body mass index, education, medications, trial vs cohort study status, and region.

Conclusions: A pro-inflammatory dietary pattern is associated with a higher risk of new-onset ESKD among Medicare-eligible post-menopausal women without baseline CKD.

Age-Stratified Sex Differences in the Risk of Cardiovascular Disease in Patients with CKD

Ester Oh, Zhiying You, Kristen L. Nowak, Anna Jovanovich. University of Colorado Denver School of Medicine, Aurora, CO.

Background: In the general population, females (vs. males) and younger individuals have a lower cardiovascular risk. However, little is known whether this age- and sex-specific risk pattern of cardiovascular disease (CVD) translates to individuals with chronic kidney disease (CKD). The purpose of this study was to examine if sex-specific risk of CVD differed across the age groups approximating premenopause (<45 y), perimenopause (45-54 y), and postmenopause (≥55 y) association between sex and time to a composite of CVD events (heart failure, myocardial infarction, ischemic stroke, and peripheral artery disease). Secondary outcomes were individual components of the CVD composite.

Methods: Cox proportional-hazards models were used to examine the age-stratified (<45 y, 45-54 y, and ≥55 y) association between sex and time to a composite of CVD events (heart failure, myocardial infarction, ischemic stroke, and peripheral artery disease). Secondary outcomes were individual components of the CVD composite.

Results: The median follow-up time was 7 years. In the entire cohort, males had a 32% higher risk of incident CVD (95% CI: 15-53%; Figure) than females after adjusting for age, race, clinic site, and traditional CVD risk factors, but not after further adjustment for markers of kidney disease (fully adjusted model). In the 45-54 y group, there was a 63% higher risk for CVD (95% CI: 4-157%) in males than females in the fully adjusted model. However, no sex-specific CVD risk was observed in the <45 y and ≥55 y groups having the lowest dietary inflammatory potential and Q4 having the most pro-inflammatory. Secondary outcomes were individual components of the CVD composite.

Conclusions: Our findings suggest that CKD may be a strong risk factor for CVD in females. Moreover, females may have a lower risk of CVD than males, particularly in the perimenopausal, but not premenopausal and postmenopausal ages.

Funding: NIDDK Support

Elevated Triglyceride-Glucose Index Predicts Renal Hyperfiltration in Young Adults

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Background: Insulin resistance increases the risk for renal hyperfiltration (RHF), a proposed mechanism for kidney injury in diabetes. However, the association between triglyceride-glucose (TyG) index, a novel marker for insulin resistance, and RHF is not well established in young adults. This study aimed to investigate the association between TyG index and RHF in Korean young adults.

Methods: Data were retrieved from the Korean National Health and Nutrition Examination Surveys (2010-2019). A total of 15,764 participants aged 19–39 years with normal kidney function were enrolled. The participants were divided into tertile based on TyG index [ln(fasting triglyceride[mg/dL] x fasting glucose [mg/dL]/2)]. RHF was defined as eGFR with residuals >90th percentile after adjusting for sex, age, weight, and height.

Results: The mean age of the study participants was 30.4±6.1 years, and 43.8% were male. The mean levels of TyG index were 7.70±2.05, 8.28±1.95 and 9.07±0.45 in tertile 1, 2, and 3 respectively. The prevalence of RHF was significantly higher tertile 9.1%, 10.0%, and 10.9%, respectively, for trend=0.03. When the association between TyG index and the risk for RHF was evaluated by multivariable logistic regression analysis, the higher tertiles showed increased risks for RHF compared to lowest tertile. (odds ratio [OR],1.24; 95% confidence interval [CI],1.08-1.41, P=0.002 in tertile 2 and OR,1.64; 95%CI, 1.41-1.90, P<0.001 in tertile 3). This association was consistent when TyG index was treated as continuous variable (OR,1.53; 95% CI,1.39-1.38; P<0.001). When subgroup analysis stratified by hypertension or diabetes were performed, no significant interactions were found, suggesting TyG index is an independent predictor for RHF regardless of hypertension or diabetes.

Conclusions: This study showed that higher TyG index is associated with increased risk of RHF in Korean young adults with normal kidney function. Longitudinal studies are need to investigate whether elevated TyG index levels associated RHF is an early risk factor for kidney injury in young adults.
PO2244

Screening for Early CKD in School Children in Kano, Nigeria
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Background: There has been an ongoing debate on the benefits of CKD screening in general especially as it relates to cost effectiveness and absolute relevance. However, screening for CKD in children will make a huge impact especially in low- and middle-income countries (LMIC) where treatment for End Stage CKD is not readily available due to high cost, shortage of skilled personnel and donor organs. This NIH/VEC Fogarty Funded research aimed to determine the burden of early CKD among school children in Kano, Nigeria.

Methods: The study screened 228 school children (5-15 years) within Kano metropolis for CKD from February 2020 to February 2021. Information of participants’ socio-demographic profile and medical history was obtained through questioning. Participants’ height, weight and blood pressure were measured. They also had their spot urine measured for albumin to creatinine ratio (ACR), and blood for serum creatinine and estimated glomerular filtration rate (eGFR). Participants with abnormal findings had a repeat assessment after three months for BP, ACR and eGFR.

Results: The median age of the children was 13.0 (11.1-14.0) years, with a male:female ratio of 1:1.1:1. Seventy-eight (34%) of the children (34%) had at least one abnormality in the form of hypertension, decreased eGFR (<90 ml/min/1.73m^2) or increased ACR (>30 mg/g) at recruitment. Following re-assessment, 43 of the 78 children had persistent abnormal findings suggestive of early CKD (19%). Factors such as age, sex, type of school, parent’s education, history of family member with kidney disease, and nutritional status were not significantly associated with early CKD.

Conclusions: The outcome of this study indicates that a significant number of school children had persistent abnormal findings suggestive of early CKD. Thus, further emphasizing the need for large scale CKD screening programmes in our setting. A long-term follow-up of these children will help determine the clinical significance of these findings and provide more information on the epidemiology of CKD. Abdullahi Mudi was supported by a VECG Global Health Fellowship, funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Fogarty International Center (FIC) of the NIH (D43 TW009337). The views expressed are solely those of the authors and do not necessarily represent the views of the NIH.

Funding: NIDDK Support, Other NIH Support - National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Fogarty International Center (FIC) of the NIH (D43 TW009337).

PO2246

Advanced Liver Fibrosis Predicts CKD Development in Patients with Nonalcoholic Fatty Liver Disease
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Background: Nonalcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD) are progressive chronic conditions that share important cardiometabolic risk factors and pathogenic mechanisms. We investigated the association between liver fibrosis and the risk of incident CKD in patients with NAFLD.

Methods: A total of 5,933 patients with NAFLD (defined as controlled attenuation parameter >222 dB/m) but without CKD who underwent transient elastography (TE) between March 2012 and August 2018 were selected. The primary outcome was incident CKD, defined as the occurrence of estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 or proteinuria (a+ or dipstick test) on two consecutive measurements during follow-up. The secondary outcome was a 25% decline in eGFR measured on two consecutive visits.

Results: The mean age was 51.8 years and 3,756 (62.8%) participants were male. During a median follow-up of 3 years (2.0), 62 participants (1.0%) developed incident CKD. When stratified into TE-defined fibrosis stages, multivariable Cox models revealed that risk of incident CKD was 3.63-fold (95% CI, 1.64-8.06, P=0.001) higher in the F3-4 group (a9.5 KPa), compared to the F0 group (<5.5 KPa). During 17,577 person-years of follow-up (mean follow-up of 3.0 years), 201 participants (3.4%) experienced the secondary outcome, for which the F3-4 group had a 2.69-fold increased risk (95% CI, 1.70-4.27, P<0.001), compared to the F0 group.

Conclusions: In this large cohort of NAFLD patients without baseline CKD, advanced liver fibrosis measured by transient elastography was significantly associated with a higher risk of incident CKD.
Methods: We conducted a cross-sectional study among 8,105 US adults aged 20-69 years old in the National Health and Nutrition Examination Survey (NHANES) 2011-2012 and 2015-2016. CKD was defined as eGFR < 60 ml/min/1.73m². We calculated the prevalence of HI among CKD population by using analytic survey weights and design factors. We also examined the association between CKD and HI using multivariable logistic regression.

Results: The prevalence of speech frequency HI among patients with CKD was 33.1% vs 14.0% among control (p=0.001). The prevalence of high-frequency HI among patients with CKD was 74.9% vs 38.7% among control (p=0.001) (Table 1). The prevalence of speech frequency HI was 31.5% among CKD stage 3, 47.0% among CKD stage 4 and 53.6 among CKD stage 5 (p-trend = 0.26). The prevalence of high frequency HI was 74.8% among CKD stage 3, 75.9% among CKD stage 4 and 75.2% among CKD stage 5 (p-trend = 0.99). After adjusting for age, sex, race, income, diabetes, hypertension, history of smoking, alcohol drinking, history of cardiovascular diseases, and loud noise exposure, CKD was significantly associated with higher odds of overall speech frequency HI (OR = 1.94, 95% CI [1.03, 3.64]; p=0.04) and overall high-frequency HI (OR = 3.03, 95%CI [1.83, 5.02]; p<0.001).

Conclusions: Nearly one-third of CKD patients have speech frequency HI and about 75% have high frequency HI. Both speech frequency and high-frequency HI are common even in the early stage of CKD. CKD is independently associated with speech frequency and high frequency HI. Early screening and intervening on HI among CKD patients may even in the early stage of CKD. CKD is independently associated with speech frequency HI (OR = 1.94, 95% CI [1.03, 3.64]; p=0.04) and overall high-frequency HI (OR = 3.03, 95%CI [1.83, 5.02]; p<0.001).

Table 1. The prevalence of speech frequency and high frequency hearing impairment

<table>
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<tr>
<th>CKD Stage</th>
<th>Overall</th>
<th>Unilateral</th>
<th>Bilateral</th>
<th>High Frequency</th>
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<tbody>
<tr>
<td>No CKD</td>
<td>11.1%</td>
<td>3.6%</td>
<td>7.5%</td>
<td>12.3%</td>
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<tr>
<td>CKD stage 3</td>
<td>24.1%</td>
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<td>15.5%</td>
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<tr>
<td>CKD stage 4</td>
<td>47.0%</td>
<td>17.0%</td>
<td>29.9%</td>
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</tr>
<tr>
<td>CKD stage 5</td>
<td>53.6%</td>
<td>18.4%</td>
<td>34.3%</td>
<td>68.9%</td>
</tr>
</tbody>
</table>

Conclusions: We identified several related metabolites associated with ESRD and kidney failure. Additional work is needed to determine whether the relationship is causal.

Funding: NIDDK Support

Table 1. Association between Significant Clusters and Adverse Renal Outcomes

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>P adj.</td>
<td>n</td>
</tr>
<tr>
<td>2</td>
<td>1.31 (1.11-1.51)</td>
<td>0.001</td>
</tr>
<tr>
<td>5</td>
<td>0.77 (0.54-1.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>10</td>
<td>0.78 (0.56-0.99)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Background: Multiple observational studies indicate an association between circulating levels of interleukin-6 (IL-6) and end-stage renal disease (ESRD). However, these studies are prone to confounding and reverse causation, limiting their utility in identifying causal relationships. Mendelian Randomization (MR) studies can provide evidence for causality by examining the relationship between genetically-determined biomarker levels and outcomes. We used MR to evaluate whether genetically predicted higher IL-6 levels are associated with the risk of ESRD.

Methods: We performed two-sample MR of the relationship between IL-6 and ESRD. We selected 5 single nucleotide polymorphisms (SNPs) robustly associated with IL-6 levels at genome-wide significance among 30,931 individuals in the SCALLOP consortium as instrumental variables and examined their association with the odds of ESRD in the Million Veteran Program (MVP) among 5,503 ESRD cases and 6,354 controls.

Results: A genetically-driven increase in IL-6 levels was associated with a 30% higher odds of ESRD (95% confidence interval [CI] 1.01 to 1.67; p = 0.04). In race stratified models, among 3,112 Caucasians and 3,170 controls, there was a weaker association (OR 1.17, 95% CI 0.86 – 1.59) compared to 2,062 American Blacks (OR 1.30, 95% CI 0.83 – 2.04).

Conclusions: IL-6 levels might be causally associated with the risk of ESRD. This association was stronger among African Americans, although was underpowered. Additional studies are needed to clarify the role of IL-6 in ESRD, and if inhibition of this cytokine could be a target for delaying kidney disease progression to ESRD. Co-senior authors: Robinson Cohen & Hung

Funding: Veterans Affairs Support

PO2250 Association Between Serum Metabolites and Adverse Renal Outcomes: The Atherosclerosis Risk in Communities (ARIC) Study Lauren Bernard,1 Linda Zhou,1 Aditya L. Surapinanji,1 Jinghia Chen,1 Casey Rebholz,1 Bing Yu,1 Eric Boerwinkle,1 Josef Coresh,1 Pascal Schlösser,1 Morgan Grams,1 Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD; 2The University of Texas Health Science Center at Houston, Houston, TX; 3Johns Hopkins Medicine, Baltimore, MD; 4Albert-Ludwigs-Universität Freiburg, Freiburg im Breisgau, Germany.

Background: Few metabolomic studies have characterized associations between metabolites and end-stage renal disease (ESRD) and kidney failure. Better characterization of the biological underpinnings may help identify at-risk individuals.

Methods: A total of 3,799 participants with serum samples collected at ARIC visit 1 (1987-1989) were included in this analysis. Starting with 318 individual metabolites, we formed clusters of metabolites using Netboost. We then examined longitudinal associations with ESRD and kidney failure using Cox regression. For significant clusters, we also assessed associations of component metabolites with the outcomes. Because the meta-analytic profiling was performed in two studies, analyses were performed within each study and then meta-analyzed.

Results: There were 160 ESRD events and 357 kidney failure events during a median follow-up of 23.5 and 23.3 years, respectively. Overall, mean age was 53.5 years, 59.9% were women, and 61.4% were African American. Mean GFR was 107.5 (SD 16.7). We classified metabolites into 43 clusters. Four clusters were significantly associated with ESRD, and all were associated with kidney failure in a directionally consistent manner. Cluster 26 was primarily sugars involved in glycolysis and anaerobic metabolism. Cluster 35 included amino acids involved in liver metabolism using glutathione and gamma glutamyl transferases. Cluster 34 was an assortment of lysophosphids involved in creating phospholipid components of cell membranes. Significant component metabolites included: mannose and glucose from cluster 26; gamma-gluatomyl tyrosine, gamma-glutamyl threonine, and 5-oxoproline from cluster 5; and 6 lipids in the phosphocholine family from cluster 34. With the exception of mannose and glucose, higher levels of these metabolites were significantly related to lower risk of ESRD and kidney failure.

Conclusions: We identified several related metabolites associated with ESRD and kidney failure. Additional work is needed to determine whether the relationship is causal.

Funding: Veterans Affairs Support
Results: Mean eGFR decreased with higher POx quartiles. eGFR modified the association of higher POx with CKD progression (P=0.01) and death (P=0.02). In participants with eGFR<45, higher POx quartiles were associated with CKD progression after adjusting for demographic factors, comorbidities, medications, lab values (including hemoglobin, serum albumin, urine protein-to-creatinine ratio), and eGFR (Q3 vs Q1: HR 2.07, 95% CI 1.12-3.82; Q4 vs. Q1: HR 2.23, 95% CI 1.24-3.99). Higher POx was associated with death in participants with eGFR<45 after multivariable adjustment (Q4 vs. Q1, HR 1.94, 95% CI 1.10-3.44). POx doubling was associated with a 34% increased risk of CKD progression and 28% increased risk of death (Table 1A). In those with eGFR<45, higher POx was associated with CKD progression after adjusting for demographic factors, comorbidities, medications, and lab values. Adjusting for eGFR attenuated these associations, with higher POx trending towards being protective of CKD progression. Associations of POx and death were not significant after adjusting for covariates and trended towards being protective after adjusting for eGFR (Table 1B). Sensitivity analyses adjusting for 24-hour urinary oxalate did not change these associations.

Conclusions: Higher plasma oxalate may be an independent risk factor for CKD progression/ESKD and death in persons with eGFR<45.

Funding: NIDDK Support, Private Foundation Support

PO2253

Associations of CKD Risk Factors and Longitudinal Changes in Urine Biomarkers of Kidney Tubules Among Women Living with HIV

Results: Of the 647 women in this analysis, 67% were Black, median age at baseline was 45 years and eGFR was 104 ml/min/1.73m². Each CKD risk factor associated with distinct changes in urine biomarkers (Figure). For example, baseline hemoglobin a1c (Hba1c) associated with worse tubular injury (higher interleukin-18 [IL-18]), proximal tubular reabsorptive dysfunction (higher alpha-1 microglobulin), tubular reserve (lower uromodulin) and heightened immune response to injury (higher chitnase-3-like protein [C3L3]) and 47.4 ml/min/1.73m² was 47.4 ml/min/1.73m². Among women with HIV (WWH), urine biomarkers of tubule dysfunction and injury allow detection of antiretroviral toxicity and prediction of CKD risk and mortality. However, risk factors for changes in urine biomarkers are unclear.

Methods: We assessed traditional and infection-related CKD risk factors and measured 14 urine biomarkers at baseline and at follow-up (median 2.5 years) among WWH in the Women’s Interagency HIV Study. We used simultaneously adjusted multivariable linear regression models to evaluate the associations of CKD risk factors with changes in biomarker levels concurrently.

Results: Of the 647 women in this analysis, 67% were Black, median age at baseline was 45 years and eGFR was 104 ml/min/1.73m². Each CKD risk factor associated with distinct changes in urine biomarkers (Figure). For example, baseline hemoglobin a1c (Hba1c) associated with worse tubular injury (higher interleukin-18 [IL-18]), proximal tubular reabsorptive dysfunction (higher alpha-1 microglobulin), tubular reserve (lower uromodulin) and heightened immune response to injury (higher chitnase-3-like protein [C3L3]) and 47.4 ml/min/1.73m² was 47.4 ml/min/1.73m². Among women with HIV (WWH), urine biomarkers of tubule dysfunction and injury allow detection of antiretroviral toxicity and prediction of CKD risk and mortality. However, risk factors for changes in urine biomarkers are unclear.

Conclusions: CKD risk factors associated with unique patterns of biomarker changes among WWH, suggesting that longitudinal biomarker measurements may help in detecting and monitoring kidney disease in WWH.

Funding: NIDDK Support

PO2254

Correlation Between Urinary Sodium and Protein Excretion in CKD

Results: The mean age ± SD of the cohort was 74.4 ± 9.5 years. Mean estimated GFR was 47.4 ml/min/1.73 m² and UPCR was 1.0 g/g. About 97% of subjects were male and 51% had diabetes. Using multivariable linear regression, we found that weight, height,
Liver Disease Is a Predictor of Recurrent Hyperkalemia

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Background: Liver disease is a well-established predictor for recurrent hyperkalemia (HK) independent of mineralocorticoid receptor antagonist (MRA) therapy, which is a common treatment in this population. This study explores the relationship between liver disease and recurrent HK independent of MRA therapy and Renin Angiotensin System Inhibitors.

Methods: In a cohort of 9,894,683 US veterans that had at least one potassium measurement between 0.5-8 mEq/L during year 2004 and 2018, we identified 2,169,401 patients who had a HK event (≥5.0 mEq/L) and complete data on covariates and examined the association of possible predictors of HK recurrence within 1 year after index HK event. Liver disease was defined according to the presence of mild, moderate, or severe liver disease ICD 9/10 codes using 1 inpatient or 2 outpatient records in one year prior to index HK event. HK recurrence was defined as the 3rd or later potassium measurement after index HK measurement subsequent to one or more normal (≤5 mEq/L) potassium measurement. Fine and Gray competing risk regression model was used to evaluate the association between liver disease and HK recurrence, where HK recurrence was the outcome and the competing event was all-cause mortality within 1 year after index HK occurrence. The model was adjusted for demographics, comorbid conditions, medications, and pre-existing conditions.

Results: Of 2,169,401 patients, 93,141 (4%) patients had liver disease with a median age of 75.6 years and 47.5% were male. The median follow-up was 90 and 91-180 days during the follow up, restricted to patients remaining on patiromer. 90% of patients stayed on treatment past 30 days, with 53% staying on treatment past 1 year.

Conclusion: Liver disease is a predictor of 1 year HK recurrence independent of MRA therapy. Further studies are needed to understand the possible cause underlying this association.

Funding: Commercial Support - AstraZeneca.

Urinary Sodium-to-Potassium Excretion Ratio Is Associated with Incident CKD in the General Population

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Background: Previous study suggests that urinary sodium to potassium (UNAK) ratio is associated with cardiovascular event and mortality, but the association of incident chronic kidney disease (CKD) and UNAK ratio in a preserved kidney function adult showed contrast results.

Methods: Data from the Korean Genome and Epidemiology, a prospective community-based cohort study were used to evaluate the between UNAK ratio and CKD development. 24 hour estimated sodium and potassium excretion amounts were calculated by a Kawasaki equation using spot urine potassium and sodium measurements. A total of 85,288 person-year were analyzed as incident primary outcome of Incident CKD defined as estimated glomerular filtration ratio (eGFR) <60 mL/min/1.73m² in a2 consecutive measurements during the follow-up period.

Results: The mean age was 52.1 ± 8 years and 47.5% were male. The median estimated 24h urinary sodium excretion, potassium excretion, UNAK ratio were 4.9 (4.1-5.8) g/day, 2.1 (1.8-2.5) g/day, and 2.3 (1.9-2.7), respectively. During 37,950 person-year of follow-up (median 11.5 years), the primary outcome developed in 513 participants and corresponding incidence rate was 14.0 (95% Confidence interval [CI], 12.9 to 15.3) per 1000 person-year. When the participants were categorized into quartiles according to UNAK ratio, age, sex and baseline eGFR adjusted hazard ratios (HR) (95% CI) for the Cox proportional hazard model were 0.76 (0.59-0.96), 0.89 (0.70-1.14), and 1.15 (0.91-1.46) from UNAK ratio quartile 1, 2, and 3, respectively as compared with the highest UNAK ratio. This finding was further confirmed in the follow-up time on patiromer. When UNAK ratio was observed when log-transformed UNAK ratio was treated as a continuous variable; for one increase in UNAK ratio, there was a 51% higher risk of adverse kidney outcome (HR 1.51, 1.12-2.04). Spline regression analysis show that HR increased more steeply up to 1 log-transformed UNAK ratio, but there was no significant increase of risk after that.

Conclusions: UNAK ratio is significantly associated with a decreased risk of CKD development.

PO2256

Associations of Urinary and Dietary Sodium-to-Potassium Ratios with Albuminuria in Community-Dwelling Japanese Adults

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Background: Urinary sodium-to-potassium (Na/K) ratio is an indicator of dietary sodium intake and is associated with reduced kidney function. However, it is not known whether urinary Na/K ratio is also associated with albuminuria, the other key component of CKD, in community-dwelling adults.

Methods: We quantified the association of urinary Na/K ratio with albuminuria in 2,169,401 Japanese adults (age 40-97 years; 51.0% women) by using spot urine samples. Linear and logistic regression analyses were performed with adjustment for potential confounders. We also evaluated dietary Na/K ratio based on a food-frequency questionnaire.

Results: Median values of urinary and dietary Na/K ratios were 2.70 (interquartile interval: 1.87, 3.83) and 1.50 (1.20, 1.84), respectively, with median albumin-to-create amino ratio (ACR) of 11.0 (6.0, 24.0) mg/g and mean eGFR of 74.7 (SD 15.7) mL/min/1.73 m². In multivariable linear regression analysis, urinary Na/K ratio (per one-unit increment) was significantly associated with log-ACR (e.g., 0.023 [95% CI, 0.008, 0.039] in Model 3) (Table). Similarly, dietary Na/K ratio was independently associated with ACR (Table). The results were consistent with those of multivariable logistic regression analysis with urinary ACR ≥30 mg/g as a dependent variable.

Conclusions: Both urinary and dietary Na/K ratios were associated with elevated albuminuria in community-dwelling Japanese adults. Our findings further support the potential usefulness of urinary Na/K ratio as an indicator of sodium intake and suggest a link between sodium intake and kidney damage.

Funding: Government Support - Non-U.S.

PO2257

Time on Patiromer Therapy and Impact on Serum Potassium Levels in Real-World German CKD Patients

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Background: Hyperkalemia (HK) (serum K ≥5.0 mEq/L) is a frequent condition in patients with chronic kidney disease (CKD) associated with high morbidity and mortality and it is a common reason for RAASi discontinuation and dose limitation. Patiromer is a non-absorbed, sodium-free, potassium (K) binder that has been shown to chronically reduce serum K in patients with HK, enabling RAASi therapy, which is supported by randomized trial evidence in CKD patients. Data on patiromer use in patients with renal-to-advanced CKD in the real-world setting in Europe is lacking. We describe time to discontinuation and changes in serum K levels among CKD stage 3-5 patients starting patiromer using 2018-21 data from German participants in CKD Outcomes and Practice Patterns Study (CKDopps).

Methods: Duration of patiromer use was estimated by Kaplan-Meier curve, starting at patiromer initiation and censoring for death, dialysis, transplant, or loss of follow-up. Serum K levels are described as mean/median at the baseline and in ranges of 1-30, 31-90 and 91-180 days during the follow up, restricted to patients remaining on patiromer.

Results: Patiromer use was limited to 34 of 90 clinics. We identified 155 patiromer users, 131 with K measurements at baseline and 110 with at least one follow-up value. 79% of patiromer users were CKD stage 4/5, v. 28% of non-patiromer users in the sample. A large proportion (95%) of patiromer users stayed on treatment past 1 month, with 53%...
of surviving users continuing for over a year (Fig 1A). Mean serum K levels decreased after patiromer initiation and remained stable under treatment during follow-up (up to 180 days) (Fig 1B).

**Conclusions:** Most patients were not observed to discontinue patiromer prior to one year after initiation. Mean levels of serum K were lower after patiromer initiation and remained stable during the follow-up period.

**Funding:** Commercial Support - Vifor Pharmaceutical

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**PO2259**

**Kidney Outcomes in Pediatric Non-Kidney Solid Organ Transplant Patients**

**Methods:** A retrospective chart review was done in children who underwent non-kidney solid organ transplant between 2011-2019 at UPMC Children’s Hospital of Pittsburgh. AKD and AKI are defined using the Kidney Disease Improving Global Outcomes criteria. AKD is defined as serum creatinine >/= 50% times baseline or a decrease in eGFR by >/= 35% times baseline for > 7 days and up to 3 months. Patients with a new eGFR of <60 ml/min/1.73m² persisting for > 3 months met criteria for CKD. Variables associated with AKI, AKD and CKD were analyzed.

**Results:** Among 338 patients 37.9% met criteria for severe AKI, 11.5% for AKD and 8% for a new diagnosis of CKD. Stage 3 AKI was independently associated with AKD (OR: 4.10; 95% CI: 1.64-10.25). AKD but not severe AKI was associated with new onset CKD (Table 1). There was a dose dependent relationship between nephrotoxic medication use and incidence of AKD (Figure 1).

**Conclusions:** In conclusion, children with AKD after transplant are particularly vulnerable to developing CKD and there are modifiable risk factors that could decrease the risk of progression of AKI to AKD and CKD in this population.

**Multivariable logistic regression of risk factors for CKD**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.00 (0.99-1.01)</td>
<td>0.91</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2.07 (1.06-4.13)</td>
<td>0.05</td>
</tr>
<tr>
<td>Race</td>
<td>2.55 (0.88-7.57)</td>
<td>0.09</td>
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<tr>
<td>Sever AKI</td>
<td>11.03 (3.52-37.09)</td>
<td>0.00</td>
</tr>
<tr>
<td>All AKI</td>
<td>1.58 (0.45-5.48)</td>
<td>0.00</td>
</tr>
<tr>
<td>CKD</td>
<td>20.45 (7.47-59.77)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

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**PO2260**

**Cardiovascular Outcomes in Pediatric CKD: A CKiD Study**

**Methods:** We performed control-match analysis of CKD patients with renal cystic disease (PKD, MCDK, BOR) compared to a group of aplastic/dysplastic/hypoplastic kidney patients or those with obstructive uropathy. Variables were normalized using the Kolmogorov-Smirnov test; categorical variables were summarized as percentages while continuous variables as medians and inter-quartile ranges. Univariate associations were tested using chi-square statistic or Fischer exact test for categorical variables and Mann-Whitney T test for continuous variables.

**Results:** 41 patients in the renal cystic group were compared to 294 patients in the non-renal non-cystic group. Renal cystic patients demonstrated statistically significant increases in creatin-C with no difference in iGFR or serum creatinine. Blood pressure was decreased [103 (97-112) vs. 107 (99-115) mmHg; p=0.004] in the renal cystic group but cardiac parameters of ascending aortic stiffness [3.1 (2.11 - 5.21) vs. 2.53 (1.87 - 3.56); p=0.001] and incidence of left-ventricular hypertrophy (LVH) [12 (15.2%) vs. 44 (8.3%); p=0.049] was increased.

**Conclusions:** CV mortality is the primary cause of death in patients with CKD, especially ADPKD. Previous literature conceptualized link between renal cystic disease and hypertension leading to poorer CV outcomes however our analyses show this is an incomplete picture with almost 50% higher incidence of LVH but lower blood pressure in renal cystic group compared to other CKD pediatric patients. This suggests a need for further exploration of cardiac remodeling and structural changes to improve the understanding of CVD development in renal cystic pediatric patients.
PO2262
Ideal Cardiovascular Health and Risk for Incident CKD: Findings from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL)

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Background: Prior studies have reported that measures of ideal cardiovascular health influence the risk of developing chronic kidney disease (CKD). However, U.S. Hispanic/Latino adults were not well represented in these studies.

Methods: We analyzed data from 8,770 U.S. Hispanic/Latino adults aged 18-64 years enrolled in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) who completed a baseline (2008-2011) and a follow-up (2014-2017) visit and did not have CKD at baseline (estimated glomerular filtration rate [eGFR] ≥ 60 ml/min/1.73m² and urine albumin-to-creatinine ratio [UACR] <200 mg/g). Cardiovascular health metrics were assessed using the American Heart Association’s Life’s Simple 7 (LS7, nonsmoker; body mass index <25 kg/m²; physical activity ≥30 minutes/day; healthy diet; total cholesterol ≤200 mg/dL; blood pressure <120/<80 mm Hg; and fasting blood glucose <100 mg/dL). The association between LS7 and the outcomes was evaluated using Poisson regression with robust variance while accounting for the complex sampling design of HCHS/SOL.

Results: At baseline, the weighted mean age was 42.1 years, 56.3% were female, mean eGFR was 107 ml/min/1.73 m², median UACR was 7 mg/g, and 49% had at least one ideal health factor. After a median follow-up of 5.9 years, there were 598 incident albuminuria events, and 201 low eGFR events. Compared with the presence of <4 ideal factors, at least one ideal health factors was associated with lower risk for incident albuminuria but there was no additional reduction in incident eGFR (Table).

Conclusions: Among U.S. Hispanic/Latino adults, the presence of a higher number of ideal health factors was associated with a lower risk of incident albuminuria. These findings may have implications for public health strategies for CKD prevention in this population.

*Adjusted for center, age, sex, background, education, eGFR, and log(UACR)

PO2263
Inflammatory Biomarkers and Proteinuria Progression in CKD Patients: The CRIC Study

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Background: Proteinuria progression is considered a surrogate endpoint for CKD progression. We studied prospective association of inflammatory biomarkers with proteinuria progression in the Chronic Renal Insufficiency Cohort (CRIC) Study participants.

Methods: The CRIC Study recruited 3939 CKD patients in the U.S. After excluding those without urine protein measures at baseline or follow-up and those with missing covariables at baseline, 3177 patients were included in this analysis. Proteinuria progression was defined as a ≥30% increase in urine protein-to-creatinine ratio (UPCR) from baseline and UPCR ≥150 mg/g at follow-up visits. Incident proteinuria was defined as UPCR ≥150 mg/g among patients without proteinuria at baseline. Cox proportional hazards models were used to examine multivariate association of inflammatory biomarkers with proteinuria progression and incidence, adjusting for age, sex, race, current smoking, body mass index, systolic blood pressure, total cholesterol, hemoglobin A1C, eGFR, baseline UPCR, and use of ACE-Is/ARBs, statins, and aspirin.

Results: Over a mean follow-up of 6.6 years, 1478 participants developed proteinuria progression and 625 participants developed proteinuria. Multivariable-adjusted hazard ratios (95% confidence intervals [CI]) of proteinuria progression for the highest quartile vs. lowest quartile of inflammatory biomarker levels were 1.20 (1.01-1.42; P=0.03) for fibrinogen, 1.21 (1.03-1.43; P<0.002) for interleukin-6 (IL-6), 1.54 (1.30-1.81; P=0.0001) for tumor necrosis factor-α (TNF-α), and 1.22 (1.04-1.42; P=0.01) for CXCL12. Among 1635 patients without baseline proteinuria, similar relationships of fibrinogen, IL-6, TNF-α, and CXCL12 with incident proteinuria were identified. C-reactive protein, white blood cells, IL-1β, IL-1 receptor antagonist, fetuin-A, transforming growth factor-β, and fractalkine were not significantly associated with proteinuria progression or incidence.

Conclusions: Our findings suggest that higher levels of fibrinogen, IL-6, TNF-α, and CXCL12 are independently associated with proteinuria progression and incidence. Future studies may test whether targeting specific inflammatory pathways will improve proteinuria and reduce CKD progression.

Funding: NIDDK Support, Other NIH Support - National Institute of General Medical Sciences (NIGMS)

PO2264
Racial Disparities in Progression to ESRD and Mortality in Rural vs. Urban Veterans

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Background: Little is known about how race and ruralicity interact to influence progression of CKD to ESRD and mortality in CKD patients.

Methods: We analyzed a national cohort (n=915,039) of veterans with CKD (eGFR ≤ 60 on two or more outpatient serum creatinines ≥60 days apart) who received care from 1/1/2010-12/31/2015 and who had information on demographics, comorbidities, and residence coding available. ESRD data was obtained by linkage to USRDs. Cox linear regression models were used to relate rural and urban residence defined by RUCA codes with time to incidence of ESRD, as well as time to all-cause mortality. The models were adjusted for age, gender, and comorbidities. The full cohort was examined as well as two subgroups divided by race. Hazard ratios were calculated using the urban (RUCA 1.0 & 1.1) veterans within the full cohort or each subgroup as a reference.

Results: When compared to urban veterans, veterans who reside in rural regions had lower risk of ESRD (HR 0.89, 95% CI 0.87-0.91) but had a slightly higher risk of mortality (HR 1.03, 95% CI 1.02-1.03). Within race subgroups, White rural veterans had lower risk of ESRD compared to White urban veterans (HR 0.88, 95% CI 0.85-0.91) but not in Black rural versus Black urban veterans (HR 0.99, 95% CI 0.93-1.05). While rural White veterans had slightly higher risk of mortality compared to urban White veterans (HR 1.02, 95% CI 1.01-1.02), the difference in mortality between rural and urban veterans was much larger in the Black subgroup (HR 1.11, 95% CI 1.08-1.14).

Conclusions: Examination of CKD patients cared for by the VA reveals an intersection between race and rurality in which mortality is increased and CKD progression is decreased for Black rural veterans with CKD. Interventions to improve preESRD care in rural Black veterans are needed.

Funding: NIDDK Support, Other NIH Support - NHLBI, Veterans Affairs Support
PO2265

Trends in Prevalence of Comorbid Conditions at Onset of CKD Among US Veterans with Incident CKD, 2004-2018

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Background: Many comorbid conditions are strong risk factors for adverse outcomes in people with CKD. We examined trends in prevalence of major comorbidities at CKD onset in the US Veterans Health Administration (VHA).

Methods: Incident CKD was defined as the first time estimated glomerular filtration rate (eGFR) decreased to <60 mL/min/1.73 m² for >3 months. We excluded veterans recorded in the VHA for <2 years prior to the first eGFR <60, or with CKD stage ≥4 when first identified. We identified 15 comorbidities at CKD onset using ICD-9/ICD-10 codes during the 2 years before and 6 months after CKD onset and calculated the Charlson comorbidity index (CCI), a composite score of total disease burden.

Results: The cohort included 892,005 veterans with new-onset CKD between 2004 and 2018. The mean age (72 years), eGFR (52 mL/min/1.73 m²), and body mass index (30 kg/m²) at CKD onset were similar in 2004 and 2018. Among the 8 comorbidities with >20% prevalence (left panel, Table), hypertension, cardiovascular disease, chronic obstructive pulmonary disease, and cancer declined from 2004 to 2018, with the largest decline (21%) for cancer. Diabetes, anemia, depression, and obesity increased in prevalence, with the largest increases for obesity (58%) and depression (42%). The percentage of patients with a CCI ≥6 increased from 9% in 2004 to 14% in 2018.

Conclusions: In US veterans, obesity, depression and the CCI score have significantly increased at CKD onset over the recent 15 years, underscoring the importance of a multifaceted approach to management of CKD and its risk factors.

Funding: NIDDK Support, Other U.S. Government Support

Prevalence of comorbidities at CKD onset among US veterans, 2004-2018

*P-values were all <0.001, controlling for demographics.

PO2266

Association Between Cardiac Autonomic Function and Coronary Artery Calcification in Persons with Type 2 Diabetes with and Without CKD

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Background: Cardiac autonomic neuropathy and cardiovascular disease are concomitant complications to diabetes but the link between these complications are largely unknown, especially in relation to kidney function. We examined the association between measures of cardiac autonomic function and coronary artery calcification (CACS) in persons with type 2 diabetes stratified by presence of chronic kidney disease (CKD).

Methods: Post-hoc analysis of baseline data from a randomized clinical trial including 84 persons with type 2 diabetes. Cardiac autonomic function was evaluated using heart rate variability (HRV) indices and cardiovascular autonomic reflex tests (CARTs). Lower response in CARTs and HRV measures were taken as indicators of impaired cardiac autonomic function. CT based CACS was calculated using Agatston method.

Results: The participants had a mean age of 64.7 (SD=7.8) years, 31% were men, mean eGFR was 83.5 (SD 16.2) ml/min/1.73 m², median albumin creatinine ratio 5.5 [Q3R.3, 11.8] mg/g and 10 (11.5%) had CKD (eGFR < 60 ml/min/1.73 m²). In persons without CKD, a higher CACS was associated with a lower 30-to-15 ratio (-1.27, SE: 0.33), p < 0.0001, E-to-I ratio (-1.33, SE:0.32, p < 0.0001), standard deviation of normal-to-normal intervals (0.73 ms, SE:0.34, p=0.03), high frequency power (-0.49 ms, SE:0.24, p=0.045) and total power (0.86 ms, SE:0.33, p<0.01). All these associations remained significant after adjustment for age, heart rate (only for HRV measures), sex, LDL, Hba1c, systolic blood pressure, diabetes duration and weight (except for standard deviation of normal-to-normal intervals and high frequency power). In persons with CKD, no significant associations were demonstrated between measures of cardiac autonomic neuropathy and CACS.

Conclusions: In persons with type 2 diabetes but without CKD, we demonstrated an association between impaired cardiac autonomic function and higher coronary artery calcification. This association could not be demonstrated in persons with CKD.

PO2267

Characterization of Metabolome-Wide Biochemicals Associated with Kidney Function

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Background: Chronic kidney disease (CKD) is a global public health problem. Identifying sensitive filtration biomarkers is a key diagnostic value contributing to an understanding of CKD at the molecular level. A metabolomics study indicated a snapshot of the biochemical activity of the human body at a particular time in the progression of CKD. This metabolome-wide study verified whether blood metabolite profiles are significantly different in CKD stages and characterized potential markers to assess kidney function in Chinese population.

Methods: An analysis of plasma and serum metabolites using ultrahigh-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) was performed on 198 participants (55 serum samples and 145 plasma samples) based on their measured GFR (by iohexol plasma clearance).

Results: A large number of metabolomics related to the mGFR were selected as the top 30 metabolites by the random forest method, and we found 15 amino acids, 8 nucleotides, and 2 carbohydrates strongly related to kidney function in the combined group (serum and plasma). Thirteen amino acids, 9 nucleotides, and 3 carbohydrates were identified in the plasma group, while 13 amino acids, 7 nucleotides, and 3 carbohydrates were found in the serum group. We observed that 10 of the top 15 ranked metabolites were concordant between the plasma and serum groups. Major differences in metabolite profiles with increasing stage of CKD were observed.

Conclusions: Our study identified 6 novel and potential metabolites that reproducibly strongly associated with mGFR, including pseudouridine, C-glycosylthiopan, N-acetylanalamin, myo-inositol, and N-acetylhomoserine. However, pseudouridine may be an ideal biomarker that is nondependent on race. Specifically, a potential negative biomarker of kidney disease may be 1,5-anhydroglucitol (1,5-AGI).

Future studies will utilize the potential 3-5 novel biomarkers in estimating the glomerular filtration rate without race influence.

Funding: Government Support - Non-U.S.

PO2268

Lipid Accumulation Product Index and CKD

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Background: Obesity, a well-known risk factor for chronic kidney disease (CKD), is generally assessed using body mass index (BMI). However, because BMI does not take body composition into account, it may not reflect the metabolic abnormalities associated with obesity. Recently, lipid accumulation product index (LAP) has been proposed to effectively recognize metabolic syndrome. Therefore, the association between LAP and risk of incident CKD was investigated in a general population cohort.

Methods: A total of 180,268 subjects without CKD, who participated in the Korean Genome and Epidemiology Study from 2001 to 2018, were analyzed. LAP was calculated as [waist(cm)−65] × triglyceride(mmol/l) for males and [waist(cm)−58] × triglyceride(mmol/l) for females. The association between LAP and risk of incident CKD was investigated in a general population cohort.

Results: The participants were concordant between the plasma and serum groups. Major differences in metabolite profiles with increasing stage of CKD were observed.

Conclusions: Chronic kidney disease (CKD) is a global public health problem. Identifying sensitive filtration biomarkers is a key diagnostic value contributing to an understanding of CKD at the molecular level. A metabolomics study indicated a snapshot of the biochemical activity of the human body at a particular time in the progression of CKD. This metabolome-wide study verified whether blood metabolite profiles are significantly different in CKD stages and characterized potential markers to assess kidney function in Chinese population.

Funding: Government Support - Non-U.S.

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PO2269

Comparison of Two Immunoassay Technologies for Plasma Biomarker Measurement

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Background: Anti-double-stranded DNA (anti-dsDNA) antibodies in autoimmune diseases such as systemic lupus erythematosus (SLE) may interfere with immunoassay technologies that use oligonucleotide-based antibodies (Olink) or aptamers (SomaScan). In this study, we compare measurements of plasma kidney injury molecule-1 (KIM-1), a well-known marker of tubular injury, across two different immunoassay technologies in patients with and without SLE.

Methods: We measured plasma KIM-1 levels in 444 individuals enrolled into a prospective, observational cohort study of patients with chronic kidney disease using microbead-based sandwich ELISA (Olink) and the proximity extension assay (PEA; Olink). The PEA uses oligonucleotide-labeled antibodies that bind to the target protein. We investigated differences in plasma KIM-1 measurements between the two assays in individuals with SLE (n=68) and individuals with other diseases than SLE (n=376) using Bland-Altman plots and Spearman correlation coefficients.

Results: Mean eGFR was 85.2±37 and 52.3±33 ml/min/1.73m² and the median proteinuria (IQR) was 1.5 (0.7, 3.2) and 1.7 (0.4, 4.2) g/g creatinine in individuals with and without SLE, respectively. The correlation between paired plasma KIM-1 measurements from both assays was 0.7 (p<0.001) in individuals with SLE and 0.9 (p=0.001) in individuals with other diseases than SLE (Figure 1A). The Bland-Altman plots show the bias between the mean differences in plasma KIM-1 in individuals with and without SLE, indicating that the bias in measurements was significantly greater in those with than without SLE (2.8 vs. -3 units, p=0.008, Figure 1B).

Conclusions: Anti-dsDNA antibodies in SLE may interfere with measurements by oligonucleotide-labeled antibodies.

Funding: NIDDK Support

Figure 1.
Results: The mean age of participants was 58 years, 43% were women, and 43% Black. During a median follow-up of 6.0 years, 684 participants developed moderate-to-severe pruritus, with an overall unadjusted incidence rate of 4.6 per 100 person-years. The 5-year unadjusted cumulative incidence of pruritus was: overall 21%, eGFR ≥60 18%, eGFR 45 to <60 20%, eGFR 30 to <45 24%, and eGFR <30 20%. In the fully adjusted model, compared to eGFR ≥60, an eGFR of 30-45 was associated with a 39% (95% CI 1.08 - 1.80) higher risk of pruritus, and an eGFR <30 was associated with a 56% (95% CI 1.15 - 2.11) higher risk of pruritus (Figure 1). Female sex, diabetes, current smoking, and opioid use were associated with increased risk of pruritus, independent of eGFR. Notably, serum albumin and e-reactive protein were independently associated with pruritus, whereas calcium, phosphorous, and parathyroid hormone were not.

Conclusions: A significant proportion of patients with CKD develop pruritus, even at modestly reduced eGFR ≤ 45 mL/min/1.73 m². Careful assessment and management of pruritus should be considered as a part of routine CKD care.

Funding: NIDDK Support

Adjusted cumulative incidence of pruritus by eGFR in the CRIC study

PO2273

Subtle Changes in Uremic Symptoms with CKD Progression
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Background: Uremic symptoms are a major contributor to symptom burden in CKD and related to lower quality of life. However, factors associated with uremic symptom progression have not been rigorously examined.

Methods: We included 3,504 participants with CKD not on dialysis from the Chronic Renal Insufficiency Cohort (CRIC) study with at least two assessments of estimated GFR (eGFR) and uremic symptoms. The uremic symptoms fatigue, anorexia, and pruritus were assessed annually by the Kidney Disease Quality of Life instrument. Responses were transformed to a scale from 0-100, with lower scores indicating worse symptom severity. We used multivariate linear mixed effects models with random intercepts and random slopes to estimate the association between eGFR change and the change in uremic symptoms over time.

Results: The mean age of participants was 58 years, 45% were women, 41% Black, and the mean eGFR at baseline was 45 mL/min/1.73 m². Over a median follow-up of 7 years (IQR 3-11), the average annual decline in eGFR was -1.3 mL/min/1.73 m²/year. The average annual change in the symptom scores for fatigue, anorexia, and pruritus were -0.27 (95% CI: -0.35, -0.19), -0.26 (95% CI: -0.33, -0.19), and -0.49 (95% CI: -0.59, -0.39), respectively. A 1-unit change in eGFR was significantly associated with worsening fatigue, anorexia, and pruritus (Table 1). The association was stronger for those with eGFR <30 than those with higher eGFR.

Conclusions: Decreasing kidney function is associated with worsening fatigue, anorexia, and pruritus; however, the absolute change in symptom severity scores is small and unlikely to be clinically meaningful. Regular symptom assessment should be incorporated into routine CKD care; however, caution should be used when attributing large changes in symptom severity solely to changes in the level of kidney function.

Funding: NIDDK Support

Factors influencing providers to consider conservative kidney management

PO2274

Conservative Kidney Management Practice Patterns in the United States: A CKDopps Analysis
Jennifer S. Scherer,1 Daniel G. Muenz,2 Brianieber,3 Benedicte Stengel,4 Talshin Masad,5 Bruce M. Robinson,6 Roberto Pecocits-Filho,7 Keith S. Goldfeld,1 Joshua Chodosh,1 David M. Charytan.1 CKDopps Investigators (NTU Langone Health, New York, NY; Emory University, Atlanta, GA; Arbor Research Collaborative for Health, Ann Arbor, MI; Centre de Recherche en Epidemiologie et Sante des Populations, Villejuif, France.

Background: Conservative kidney management (CKM) of kidney failure is an important treatment option for many patients. However, its availability in the United States (US) is not well described. We describe CKM resources and provider practice patterns in US Chronic Kidney Disease (CKD) clinics.

Methods: Cross sectional analysis of provider surveys (n=22) from unique clinics in the US from the CKD Outcomes and Practice Patterns Study (CKDopps) collected between 2014-2017.

Results: Only eight (36%) providers reported involving palliative care in planning for and educating patients about kidney failure. A majority (59%) were extremely comfortable discussing CKM and nearly 100% typically discussed CKM as a treatment option. Nearly all (95%) reported their clinics had the ability to routinely deliver CKM, but only one had a CKM protocol or guideline, and none offered a specific CKM clinic. Most providers said their clinics used the word “conservative” to describe CKM, with 24% choosing “palliative” or “supportive” terminology. Regardless of involvement of PC, most providers estimated that 5% of their patients with or approaching kidney failure were managed with CKM. Patient preference, functional status, frailty, and comorbidities were the most important factors influencing provider decisions in contemplating the suitability of CKM for patients. (Figure 1)

Conclusions: Most providers report feeling comfortable discussing CKM, yet almost no clinics report resources or dedicated infrastructure for CKM delivery. Despite reported high frequency of discussing CKM, few patients were described as choosing this treatment pathway. Factors that influence consideration of CKM are consistent with elements that generally influence well-informed geriatric and end-of-life care. Efforts to improve assessment of those elements may allow for more informed recommendations of CKM.

Funding: NIDDK Support

Factors influencing providers to consider conservative kidney management

PO2275

Association Between Monocyte Counts and All-Cause Mortality in Patients with CKD
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Background: In the general population, monocyte counts are strongly associated with a higher risk of all-cause mortality. However, little is known whether this association translates to individuals with chronic kidney disease (CKD). The purpose of this study was to examine if monocyte counts are associated with the risk of all-cause mortality in patients with non-dialysis CKD who participated in the Chronic Renal Insufficiency Cohort (CRIC) observational study.

Methods: Patients were divided in tertiles according to their monocyte counts at baseline, and survival analysis was performed using Kaplan-Meier curve with statistical comparison by the log rank test. Cox models with time interaction effects were used to examine the association between monocyte counts and all-cause mortality.

Results: Among the 3,939 CRIC participants, a total of 3,391 participants (1,838 males and 1,553 females) were included in the final analytic cohort, with a mean ± SD eGFR of 45 ± 15 mL/min/1.73 m² and age of 58 ± 11 years. Participants in the highest tertile of monocyte count had a lower rate of survival than those in the lowest tertile (P<0.001, Figure). At follow-up time of 5 years, there was a 39% higher risk for all-cause mortality (95% CI: 22-59%) with every 2-fold increase of monocyte count after adjusting for age, sex, race, clinic site, traditional cardiovascular risk factors, markers of kidney disease, and e-reactive protein (fully adjusted model).

Funding: NIDDK Support

Factors influencing providers to consider conservative kidney management

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Conclusions: There may be an elevated risk for all-cause mortality in patients with CKD who have higher monocyte counts.

Funding: NIDDK Support

PO2276

Kidney Disease and Longitudinal Changes in Muscle Strength in Older Adults
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Background: Persons with chronic kidney disease (CKD) experience lower physical function and increased risk of disability, both of which have strong prognostic importance for poor clinical outcomes. To date, functional status studies in populations with CKD have focused on physical activity and/or individuals with end-stage kidney disease, and have largely neglected measures of muscle strength, especially among those with non-dialysis dependent CKD.

Methods: Participants were from the Health, Aging and Body Composition Study, a longitudinal cohort focused on functional decline in adults aged 70-79 years at baseline. Kidney function was defined by estimated glomerular filtration rate (eGFR) using the CKD-EPI Cystatin C Equation at each available visit (up to 5) during 10 years of follow up. Participants were grouped based upon their longitudinal eGFR: no CKD (eGFR ≥60 mL/min/1.73 m²), prevalent CKD (baseline eGFR <60 mL/min/1.73 m²), and incident CKD (baseline eGFR ≥60 but <60 mL/min/1.73 m² during follow up). Grip and quadriceps strength were also assessed longitudinally (8 and 6 visits, respectively). Linear mixed models stratified by sex tested associations between kidney function groups and grip and quadriceps strength over time.

Results: Of the 2,630 participants with median age 73 years, 64.9% had no CKD, 23.4% had prevalent CKD, and 11.7% developed incident CKD. At baseline, men and women without CKD had higher adjusted grip and quadriceps strength compared to those with CKD. In adjusted linear mixed models for grip strength, men with CKD had faster decline over time, compared to men without CKD (Table). For women, changes in grip strength were not different across kidney function groups. In adjusted models of quadriceps strength over time, there were no differences among kidney function groups.

Conclusions: Men with CKD had faster decline in grip strength compared to those without CKD. Future studies can determine if recognizing decreased muscle strength and intervening can change this functional trajectory among those with CKD.

Funding: NIDDK Support

PO2277

Health-Related Quality of Life in Patients with Inflammation and Non-Dialysis-Dependent CKD
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Background: Inflammation is common in chronic kidney disease (CKD) and can affect treatment of anemia, which is a common complication of CKD. Both inflammation and anemia in CKD have been linked with poor health-related quality of life (HRQoL), though evidence is limited. We aimed to assess the association between inflammation and HRQoL in patients with non-dialysis-dependent CKD (NDD-CKD).

Methods: Data were drawn from the Adelphi CKD Disease Specific Programme, a point-in-time survey of physicians and their patients with CKD (stage 3-5D) collected in the United States in 2018. Patients were also invited to complete a questionnaire which included subjective assessment of the impact of CKD, as well as the Kidney Disease Quality of Life-36 questionnaire (KDQoL-36). Patients with NDD-CKD who filled out the KDQoL-36 were included in this analysis. Inflammation was defined as C-reactive protein ≥4.9 mg/L, ferritin ≥700 ng/mL, or albumin ≤3.6 g/L. T-tests were conducted to assess differences in KDQoL-36 scores between patients with and without inflammation.

Results: Inflammation was present in 136 (28%) patients. Mean KDQoL-36 scores reported by patients with inflammation were lower than scores reported by patients without inflammation across all 5 domains (all p<0.05; Table 1). Most differences in KDQoL-36 scores between patients with and without inflammation exceeded the distribution-based minimal clinically important difference (MCID).

Conclusions: We found that patients with inflammation in NDD-CKD reported poorer HRQoL compared with those without. Reducing inflammation in CKD may improve HRQoL.

Funding: Commercial Support - FibroGen Inc

Table 1: KDQoL-36 scores* by inflammation status

PO2278

Higher Frequency of Physical Activity Reduces the Risk of Kidney Function Loss in a General Non-Diabetic Population
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Background: Physical activity (PA) reduces the risk of diabetes and hypertension, known risk factors for chronic kidney disease (CKD), but there is limited data on the independent association between PA and loss of kidney function. Previous population studies of PA have reported mixed results and relied on estimated glomerular filtration rate (eGFR). All eGFR equations are biased by non-GFR related factors such as muscle mass and inflammation, making confounding likely, particularly in studies of PA. We investigated the association between self-reported PA and the annual change of measured GFR in a general population cohort.

Methods: 1627 subjects aged 50-62 years, without diabetes, cardiovascular disease or CKD were recruited from the general population in Tromsøe, Norway, and included in the Renal Iohexol Clearance Survey (RENIS) in 2007. Participants completed a questionnaire regarding frequency, intensity and duration of leisure-time PA, medication and comorbidities. GFR was measured using iohexol clearance at baseline and follow-up in 2013-15 and 2018-20. Linear mixed regression was used to analyze the association of PA with annual change in GFR, and logistic regression was used to assess the risk of accelerated GFR decline, defined as being those with the 10% steepest GFR decline.

Results: Mean (SD) age was 58 (3.8) years and 51% were female, median follow-up time was 11 years. Relative to participants that never exercise, the annual GFR decline rate for participants with PA once a week, 2-3 times a week or almost every day was slower by 0.40% (95% CI 0.05-0.76, p=0.026), 0.49% (95% CI 0.15-0.84, p=0.005) and
Polypharmacy and Potentially Inappropriate Medication Use in Patients with CKD Managed in Primary Care

**Background:** Polypharmacy and the use of potentially inappropriate medications (PIMs) are increasingly serious public health challenges attributable to aging populations and multimorbidity. This study assessed the prevalence of polypharmacy and use of PIMs in chronic kidney disease (CKD).

**Methods:** A cross-sectional analysis using the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) database (January 1, 2010 through December 31, 2018). Polypharmacy was defined as the use of 5 medications, excessive polypharmacy as a 10 medications, and PIMs as medications recommended to be avoided in CKD.

**Results:** The cohort was comprised of 70,331 patients (mean [SD] age, 73.1 [11.4] years; 40,502 [57.6%] female) with CKD stages G3a to G5. The most common chronic conditions were hypertension (60.8%), diabetes (29.4%), and osteoarthritis (25.4%). Overall, the prevalence of polypharmacy and excessive polypharmacy was 91.5% and 74.9%, respectively. The median number of medications was 14 (IQR 9-23). The most commonly prescribed medications were atorvastatin (29.8%), amiodipine (28.9%), and rosuvastatin (27.2%). About 45% of patients with CKD had at least one PIM, 11.1% had two PIMs, and 3.6% had three or more PIMs. The most commonly prescribed PIMs were metformin (21.7%), nitrosulfurantin (16.2%), and rivaroxaban (4.5%).

**Conclusions:** Polypharmacy and use of PIMs are highly prevalent among patients with CKD managed in primary care. These findings highlight opportunities for interventions aimed at improving prescribing practices in the management of CKD.

**Funding:** Government Support - Non-U.S.

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Polypharmacy and Potentially Inappropriate Medication Use in Patients with CKD Managed in Canadian Primary Care

**PO2282**

**Astonishment of SGLT2 Inhibitors and DPP-4 Inhibitors vs. GLP-1 Agonists with Incident CKD in US Veterans**

**Background:** Randomized controlled trials (RCTs) have demonstrated that SGLT2 inhibitors (SGLT2i) reduce the risk of eGFR decline and ESRD as compared with placebo in patients with pre-existing CKD. These RCTs showed an initial dip in eGFR with initiation of SGLT2i that stabilized over time. Little is known about the impact SGLT2i vs. other newer anti-diabetic medications (DPP-4 inhibitors [DPP4i], GLP1 agonists [GLP1a]) upon risk of developing de novo kidney dysfunction in patients without underlying CKD.

**Methods:** Among US Veterans with diabetes and absence of pre-existing CKD (normal eGFR and no proteinuria) followed over 2004-18, we identified incident (new) users of SGLT2i vs. DPP4i vs. GLP1a therapy, excluding combined users of the examined classes. We examined associations of SGLT2i vs. DPP4i vs. GLP1a use with the risk of incident CKD (primary outcome) and ESRD (secondary outcome) using multivariable Cox models.

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**PO2279**

**Serum Uric Acid Levels and Nephrosclerosis in a Population-Based Autopsy Study: The Hisayama Study**

**Background:** The association of the unpleasant upper gastrointestinal symptoms with CKD and diabetes. Anti-emetic medication users had an almost 2-fold higher incident rate of frequencies of comorbidities such as chronic obstructive pulmonary disease, cancer, and diabetes. Anti-emetic medication users had an almost 2-fold higher incident rate of frequencies of comorbidities such as chronic obstructive pulmonary disease, cancer, and diabetes.

**Results:** Higher serum uric acid levels were associated significantly with greater levels with arteriolar hyalinosis index and the presence of advanced arteriolar hyalinosis. The presence of the advanced degree of glomerular sclerosis, kidney arteriolar hyalinosis, and kidney arteriolosclerosis were determined by the 90th percentile or more of a glomerular sclerosis index and an arteriolar hyalinosis index, and the 10th percentile or less of a wall-lumen ratio, respectively. A logistic regression model was used to evaluate odds ratios and their 95% confidence intervals of serum uric acid levels on advanced kidney arteriosclerosis than in subjects in the Q1 group after adjusting for potential covariates. There was no evidence of significant associations of serum uric acid levels with arteriolar hyalinosis index and the presence of advanced arteriolar hyalinosis.

**Conclusions:** Elevated serum uric acid levels were associated significantly with advanced glomerular sclerosis and advanced kidney arteriosclerosis, but not with advanced arteriolar hyalinosis in community based autopsy samples of Japanese.

**Funding:** Government Support - Non-U.S.
Results: Among 39,065 diabetic patients without pre-existing CKD, 15%, 70%, vs. 15% were new users of SGLT2i, DPP4i, vs. GLP1a, respectively. Compared to DPP4i, use of SGLT2i and GLP1a were each associated with higher risk of incident CKD: adjusted HRs (aHRs) (95%CI) 1.32 (1.18-1.47) and 1.20 (1.11-1.31), respectively (Figure 1A). However, use of SGLT2i and GLP1a were not associated with higher risk of de novo ESRD adjusted HRs (aHRs) (95%CI) 1.20 (0.15-9.32) and 0.62 (0.24-1.57), respectively (Figure 1B).

Conclusions: In a national cohort of diabetic US Veterans without pre-existing CKD, SGLT2i and GLP1a use were each associated with higher risk of incident CKD as compared with DPP4i use. However, neither medication was associated with incident ESRD, suggesting that early decline with SGLT2i and GLP1a use may be an acute/ subacute effect that stabilizes over time.

Funding: Veterans Affairs Support

**PO2283**

Insulin Use and CKD Are Risk Factors for Mild Cognitive Impairment (MCI) or Dementia in Persons with Type 2 Diabetes

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Background: Both insulin use and CKD are risk factors for hypoglycemic episodes in patients with diabetes. Recurrent hypoglycemia is associated with increased risk of dementia. Hence, we examined whether insulin use and CKD are associated with increased risk of MCI/dementia.

Methods: We analyzed a national VA cohort (N =855,133) with T2DM defined by ICD-9 codes and outpatient serum creat from 1/2008 to 12/2010. Index date was the date of first outpatient serum creatinine measurement. Baseline comorbidities were defined by ICD-9 codes from 10/1999 to the index date. MCI/ dementia were defined by ICD-90 codes. Those with baseline MCI/dementia were excluded and new onset of MCI/dementia was tracked from index date to 12/31/2020. A multivariate logistic regression model of baseline variables was used to develop propensity scores of baseline insulin use (24% were on insulin at baseline). A propensity score matched cohort (N = 288,374) was used to calculate adjusted HRs (aHRs) (95% CI) of incident MCI/dementia in persons with diabetes.

Results: Baseline mean age was 65 ± 11 yrs, 20% black and mean eGFR 72 ± 18 ml/min/1.73 m². Recurrent hypoglycemia was associated with increased risk of MCI/dementia, adjusted HR (aHR) 4.05 (95% CI 3.32-4.99) compared to non-hypoglycemic persons (Fig 1). Both insulin use and advanced CKD were associated with higher risk of MCI/dementia (Fig 2).

Conclusions: Both insulin use and advanced CKD are associated with increased risk of MCI/dementia in persons with T2DM.

Funding: NIDDK Support, Other NH Support - NHLBI, Veterans Affairs Support

**PO2284**

Incidence of CKD Stages 3-5 Among Patients on Lithium Therapy

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Background: The association between lithium use and chronic kidney disease (CKD) is not well understood, and the impact of comorbidities and other factors remains unknown. The aim of this study was to examine the risk of developing CKD stage 3 and above among individuals using lithium.

Methods: This was a retrospective cohort study of all patients in Iceland treated with lithium in the years 2008-2018. A control group was comprised of patients with affective disorders (ICD-10 codes F30-F39) who attended the outpatient clinics of the Landspitali–The National University Hospital Mental Health Services in 2014-2016 and had not been prescribed lithium. CKD stages 3-5 was defined according to the KDIGO 2012 guidelines and eGFR was calculated from serum creatinine (SCr) using the CKD-EPI equation. Individuals with CKD 3-5 prior to 2008 and those with fewer than 2 SCr measurements during the study period were excluded. Risk assessment was performed using logistic regression.

Results: A total of 2682 persons had received lithium treatment, of whom 2051 (76.5%) were included in the study. Of those 221 (10.8%) developed CKD 3-5. Lithium use was significantly associated with CKD development (OR 1.94, 95% CI 1.25–3.11) after adjusting for sex, age and comorbid diseases (Table).

Conclusions: Lithium treatment is a highly significant independent risk factor for the development of CKD in individuals with affective disorders.

Funding: Government Support - Non-U.S.

Factors associated with CKD, multivariable logistic regression.

**PO2285**

Effect of Serum Testosterone on Kidney Function in Men and Women from the General Population

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Background: Testosterone may prevent kidney function decline, but at population level evidence is sparse in males, and even lacking in females. Therefore, we investigated the association between serum testosterone and kidney function in males and females from a large population-based cohort study.

Methods: Linear regression and linear mixed models were used to assess the associations of serum free and total testosterone with kidney function, including baseline assessments of estimated glomerular filtration rate (eGFR) based on serum creatinine (eGFRcrea) or serum cystatin C (eGFRcys), and the urine albumin-to-creatinine ratio (ACR), and repeated assessments of eGFRcrea. Betas with their 95% confidence intervals (CI) were reported per 1 nmol/L increase in testosterone. Analyses were conducted for males and females separately.

Conclusions: Testosterone may prevent kidney function decline, but at population level evidence is sparse in males, and even lacking in females. Therefore, we investigated the association between serum testosterone and kidney function in males and females from a large population-based cohort study.

Methods: Linear regression and linear mixed models were used to assess the associations of serum free and total testosterone with kidney function, including baseline assessments of estimated glomerular filtration rate (eGFR) based on serum creatinine (eGFRcrea) or serum cystatin C (eGFRcys), and the urine albumin-to-creatinine ratio (ACR), and repeated assessments of eGFRcrea. Betas with their 95% confidence intervals (CI) were reported per 1 nmol/L increase in testosterone. Analyses were conducted for males and females separately.

Factors associated with CKD, multivariable logistic regression.
Results: Our study population comprised 9,484 participants (mean age 65.2 years). In multivariable models, higher free testosterone was associated with lower eGFR(creat) (beta -0.63, 95% CI -1.05;-0.21), but higher eGFR(creatinine) (beta 0.56, 95% CI 0.07;1.05), and lower ACR (beta -0.25, 95% CI -0.35;-0.16) at baseline. Higher total testosterone was associated with higher eGFR(creat) at baseline and over time, but with lower eGFR(creatinine) when additionally adjusted for sex hormone-binding globulin. In females (n=5,449), higher free testosterone was associated with lower eGFR(creat) and eGFR(creatinine) at baseline (beta -1.03, 95% CI -1.36;-0.71, beta -1.07, 95% CI -1.44;-0.70) and lower eGFR(creat) over time (beta -0.78, 95% CI -1.10;-0.46), but not with ACR. Similar results were obtained with total testosterone.

Conclusions: The association between serum testosterone and kidney function is sex-dependent, with a positive association in males and a negative association in females. The discrepant results with eGFR(creat) in males may be explained by the effect of testosterone on muscle mass. Whether treatment with testosterone replacement therapy may be beneficial for kidney function in males with low serum testosterone still needs to be investigated. The association between testosterone and lower eGFR in females requires further study.

PO2287
Disturbance of Circadian Rhythm and CKD in Korean Adult Population
Yina Fang, Sewon Oh, Jihyun Yang, Ko Yoon Sook, Hee Young Lee, Sang-Kyung Jo, Won-Yong Cho, Myung-Gyu Kim. Korea University Anam Hospital, Seoul, Republic of Korea.

Background: Disturbances in circadian rhythm are known to cause a number of health problems (psychosis, metabolic syndrome, cancer, etc.), however their contribution to kidney disease is not well understood. Therefore, this study evaluated the association of chronic kidney disease (CKD), sleep disturbance, and shift work in a Korean adult population.

Methods: A total of 32,429 participants who completed the National Health and Nutrition Examination Survey from 2010 to 2018 were assessed for their sleep patterns, shift work, and renal function. CKD was defined by eGFR ≤60 mL/min/1.73 m² or urinary albumin-to-creatinine ratio ≥30 mg/g.

Results: First, sleep disturbances were assessed according to sleep onset time and total sleep duration. We observed that the early bedtime group (starting sleep before 9pm) had a significantly higher CKD prevalence (OR 2.757, p < 0.001) compared to the regular bedtime group (9pm-2am), but inadequate sleep duration (≤6hr) had minimal effect on CKD (OR 1.052, p=0.745), which suggest that alterations in circadian rhythms due to sleep disturbance are associated with CKD development. In particular, there was a strong association between sleep disturbance and renal dysfunction in patients with comorbidities younger than 65 years of age. Next, work schedules were divided into two types; regular work (day or evening work) and shift work (fixed night shift, 24-hour shift, split-work). The shift-work group also had a higher prevalence of CKD compared to the regular work group (OR 1.32). However, in a multivariate analysis that adjusted for age, sex, BMI, smoking, drinking, diabetes, and hypertension, neither sleep disturbance nor shift work showed an independent association with the occurrence of CKD.

Conclusions: Our results suggest that impaired circadian rhythm may be associated with CKD development and that sleep disturbance can be an important therapeutic target for circadian rhythm.

PO2288
Mortality Risk and Life-Years Associated with CKD for Young and Older Adults
Alexander J. Kula,1,2 David K. Prince,3,2 Ronit Katz,2 Nisha Bansal,1,2 Seattle Children’s Hospital, Seattle, WA; 2University of Washington, Seattle, WA; 3Kidney Research Institute, Seattle, WA.

Background: Younger individuals living with CKD face a lifetime at risk for complications, including an increased risk of mortality. There is limited data to inform individual patients with CKD across the lifespan how their risk for mortality compares with equivalently aged individuals without CKD. The objective of this study is to provide age-specific contexts to the risk of mortality associated with a diagnosis of CKD.

Methods: We created a pooled study cohort using participants with CKD enrolled in the Chronic Renal Insufficiency Cohort along with participants aged 21-75 years with an eGFR >70mL/min/1.73m² included in the 2002-2008 NHANES surveys. Age-stratified mortality rates, along with unadjusted and adjusted hazard ratios (HR) for mortality were generated to compare differences between those with and without CKD. Mean life-years-lost (LYL) relating to CKD were calculated using CDC life tables.

Results: A total of 17,550 participants (3,746 with CKD) were included. The adjusted HR for mortality relating to CKD was highest in the 21-35yr strata (HR [95% CI]: 3.6 [3.5, 9.0]) and lowest in the 65-75yr strata (HR [95% CI]: 1.9 [1.6, 2.1]). Mean LYL secondary to CKD was inversely related with increasing age (Fig. 1). An individual aged 21yrs old with CKD could expect a mean of 15.6 LYL compared to age-matched peers without CKD. A similar comparison in a 70-yr-old would translate to 2.9 LYL.

Conclusions: Compared to age-matched peers without CKD, the risk for mortality and LYL associated with a diagnosis of CKD is highest in younger individuals. Further research is needed to elucidate the societal and personal costs of premature mortality in young adults with CKD.

Funding: NIDDK Support

Disturbance of Circadian Rhythm and CKD in Korean Adult Population
Yina Fang, Sewon Oh, Jihyun Yang, Ko Yoon Sook, Hee Young Lee, Sang-Kyung Jo, Won-Yong Cho, Myung-Gyu Kim. Korea University Anam Hospital, Seoul, Republic of Korea.

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Conclusions: Our results suggest that impaired circadian rhythm may be associated with CKD development and that sleep disturbance can be an important therapeutic target for circadian rhythm.

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Alexander J. Kula,1,2 David K. Prince,3,2 Ronit Katz,2 Nisha Bansal,1,2 Seattle Children’s Hospital, Seattle, WA; 2University of Washington, Seattle, WA; 3Kidney Research Institute, Seattle, WA.

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Conclusions: Compared to age-matched peers without CKD, the risk for mortality and LYL associated with a diagnosis of CKD is highest in younger individuals. Further research is needed to elucidate the societal and personal costs of premature mortality in young adults with CKD.

Funding: NIDDK Support
**PO2290**

Renal Biopsy Is Mandatory in Normal Urinary Findings with Unknown Origin Hypertension or CKD

Byoung-Soo Cho, Dr. Cho’s kidney Center, Deoul, Seoul, Republic of Korea.

**Background:** One of the most common causes of end-stage renal disease is diabetes mellitus, hypertension and chronic glomerulonephritis, however, many centers do not try to find the origin of hypertension especially in chronic kidney disease patients. Most chronic glomerulonephritis patients usually associated with hematuria and or proteinuria. Most kidney centers do not recommend renal biopsy if proteinuria is absent even though associated with persistent hematuria. In order to clarify the causes of hypertension or chronic kidney diseases, our center performed renal biopsy who showed unknown origin chronic kidney disease or unknown origin hypertension even though urinalysis findings showed no abnormalities.

**Methods:** From 2014 to 2020, we performed 1,300 cases of renal biopsy, of which 272 cases showed no urinary abnormalities when performing renal biopsy. We performed renal biopsy not only in unknown origin hematuria and unknown origin proteinuria but also we performed renal biopsy in unknown origin CKD and unknown origin hypertension even though urinary findings were normal at that time of renal biopsy.

**Results:** Of the 1,300 renal biopsy patients, 272(20.9%) showed normal urinalysis findings at that time of renal biopsy. Minor changes were detected in 2 cases among 272 cases. Most cases were serious chronic glomerulonephritis. Biopsy results were as follows:  IgA nephropathy 98cases(36%), Mild focal nonspecific glomerulonephritis 43 cases(15.8%), Focal segmental glomerulosclerosis 39 cases(14.3%), Diffuse mesangial proliferative glomerulonephritis 39 cases(14.3%), Podocyte disease 8 cases(2.9%), Membranous nephropathy 6 cases(2.2%), C1q nephropathy 5 cases(1.8%), Lupus nephritis 4 cases(1.5%), malignant hypertension 3 cases(1.1%), Obesity related glomerulopathy 2 cases(0.7%), Minor change 2 cases(0.7%), C3GN 1 case(0.3%).

**Conclusions:** Most patients with CKD /hypertension patients without urinary abnormalities showed serious chronic glomerulonephritis such as IgA nephropathy, FSGS, diffuse mesangial proliferative glomerulonephritis etc. kidney biopsy is mandatory in unknown origin CKD hypertension to clarify the original causes before considering antihypertensive medicine.

**PO2291**

Association Between Diabetes and Major Bleeding Complications of Renal Biopsy: Analysis of 76,304 Patients Using a National Inpatient Database in Japan


**Background:** Nephrologists have recently recognized the heterogeneity of kidney diseases in patients with diabetes and actively performed percutaneous renal biopsies (PRBs). However, the association between diabetes and major bleeding complications of PRBs remains unclear.

**Methods:** In this retrospective observational study using the Japanese nationwide Diagnosis Procedure Combination inpatient database, we identified patients who underwent an elective PRB between July 2010 and March 2018. The primary outcome was the occurrence of major bleeding complications defined as (i) red blood cell transfusion within 7 days after the PRB or (ii) invasive hemostasis after the PRB. Multiple regression analysis was performed to analyze the association between diabetes and major bleeding complications with adjustment for patient and hospital characteristics.

**Results:** We identified 76,304 patients, including 8,245 patients with diabetes. The proportion of biopsies for patients with diabetes to total biopsies increased year by year (Figure 1). Major bleeding complications occurred in 678 (0.9%) patients, including 622 (0.8%) red blood cell transfusion and 109 (0.1%) invasive hemostasis. Diabetes was significantly associated with major bleeding complications (RR, 2.66; 95% CI, 2.12-3.34).
PO2292

Application of the Renal Chronicity Score on Native Kidney Biopsies: Results from the FCGG Biopsy Registry

Dries Deboersnijder,1 Wim Laerens,2,3 Johan M. De Meester,2 Amelie Deendooven,1 Ben Sprangers,1 'Katholieke Universiteit Leuven Universitaire Ziekenhuizen Leuven, Leuven, Belgium; 2AZ Nikolaas, Sint-Niklaas, Belgium; 3Universiteit Gent, Gent, Belgium; 4Universitair Ziekenhuis Gent, Gent, Belgium.

Background: Chronic changes on kidney biopsy strongly predict renal outcome and have important treatment implications. Sethi et al. recently proposed the renal chronicity score (RCS), a standardized pathology scoring system which uniformly scores chronic changes on kidney biopsies. We report the RCS of the biopsies included in the FCGG registry in 2018 and 2019.

Methods: The RCS is derived from the sum of the degree of glomerulosclerosis, tubular atrophy, interstitial fibrosis and arteriosclerosis, and ranges from 0 (no/minimal chronic changes) to 10 (severe chronic changes). The FCGG registry is a population-based native kidney biopsy registry in Flanders (Northern part of Belgium) that covers a population of approximately 6.5 million inhabitants.

Results: In 2018 and 2019, the RCS was reported in 1106 of 1403 adult biopsies (78.8%), with a median value of 4 (mild chronic changes, Fig. 1A). Minimal change disease (MCD) and lupus nephritis (LN) showed mostly minimal to mild signs of disease chronicity (Fig. 1B). Membranous nephropathy (MN), tubulointerstitial nephritis (TIN), ANCA-associated vasculitis (AAV) and IgA-nephropathy (IgAN) showed an increasing proportion of moderate to severe chronic changes (26%, 35%, 37%, 45%, respectively, Fig. 1B). Finally, in focal segmental glomerulosclerosis (FSGS), nephrosclerosis and diabetic kidney disease (DKD) the proportion of biopsies with moderate to severe chronic changes exceeded 50% (60%, 79%, 80%, respectively, Fig. 1B). The RCS was also higher in biopsies from older patients (Fig. 1C), although this observation is likely confounded by the etiology of kidney disease in the older age categories (i.e., more nephrosclerosis in older patients).

Conclusions: We report on the first large population-based kidney biopsy registry that systematically scores chronic changes on kidney biopsy in a standardized manner, using the RCS. Future research should validate this score by assessing the correlation with prognosis and treatment outcome in individual kidney diseases and determine whether disease-specific modifications in the chronicity classification should be made.

PO2293

Cystatin C and Creatinine as Biomarkers of Pediatric Sarcopenia

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Stanford University School of Medicine, Stanford, CA.

Background: Pediatric sarcopenia defines a state of reduced muscle mass and strength in chronically ill children. Since Creatinine is a byproduct of all skeletal muscle cells and Cystatin C is made by all nucleated cells, we hypothesized that a relationship between the two could estimate muscle mass and muscle strength.

Methods: In 217 recruited healthy children and adolescents, data collected included anthropometric measures, whole body DXA composition, handgrip strength, leg extension and leg flexion. Stored sera were sent for Creatinine and Cystatin C measurements. We developed 4 models to estimate muscle mass and strength. Low lean mass based on an NHANES Z-score of appendicular lean mass index < -1 defined sarcopenia.

Results: Univariate analyses demonstrated the following to be associated with muscle mass and strength: age, sex, weight, height, sexual maturity, serum creatinine, differences in eGFR, and ratio of serum Cystatin C to serum Creatinine (p < 0.01). When compared against a model of only physical exam biomarkers, adding creatinine and cystatin C did not lead to clinically significant improved estimates. Using a definition of sarcopenia defined by low lean mass, there was minimal added predictive ability in identifying sarcopenia in healthy children.

Conclusions: The addition of Cystatin C and Creatinine did not meaningfully improve the estimation of muscle mass or muscle strength in healthy children. Future work remains to evaluate these models in children with chronic kidney disease.

Funding: NIDDK Support, Private Foundation Support

Table 1A. Summary of V values: Model Estimation in Healthy Children

<table>
<thead>
<tr>
<th>Model</th>
<th>Appendicular Lean Mass</th>
<th>Whole Body Total Lean Mass</th>
<th>Handgrip Strength</th>
<th>Leg Strength in Kneee Extension</th>
<th>Leg Strength in Knee Flexion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>0.9333</td>
<td>0.967</td>
<td>0.7673</td>
<td>0.7994</td>
<td>0.6689</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.9166</td>
<td>0.9508</td>
<td>0.7774</td>
<td>0.8054</td>
<td>0.6677</td>
</tr>
<tr>
<td>Model 3</td>
<td>0.918</td>
<td>0.9118</td>
<td>0.7803</td>
<td>0.8054</td>
<td>0.6677</td>
</tr>
<tr>
<td>Model 4</td>
<td>0.9142</td>
<td>0.9418</td>
<td>0.7953</td>
<td>0.8062</td>
<td>0.6618</td>
</tr>
</tbody>
</table>

Funding: Government Support - Non-U.S.

Conclusions:

Diabetes was an independent risk factor for major bleeding complications of PRBs. Moreover, severity of diabetes was associated with increase in major bleeding complications. Nephrologists should carefully judge whether the anticipated benefits counterbalance the relatively high risk of major bleeding complications when considering PRBs for patients with diabetes.

Funding: Government Support - Non-U.S.
PO2294

Behavioral Characteristics and Related Factors Among CKD Patients in South Korea During the COVID-19 Pandemic
Yaeerim Kim,1,2 Jeonghwan Lee,3 Joo Yoon Park,3 Jung Nam An,4 Kyung Don Yoo,5 Yong Chul Kim,6 Woo Yeong Park,3 Kyubok Jin,2 Dong Ki Kim,2 Jung Pyo Lee.1

Background: The recent novel coronavirus disease (COVID-19) pandemic has led to unprecedented changes in behavior. We evaluated the current status of precautionary behavior and physical activity in chronic kidney disease (CKD) patients during the COVID-19 pandemic.

Methods: A population of CKD patients (n=306) registered in a SKETCH (Study on Kidney disease and Environmental Chemicals, Clinical Trial No. NCT04679168) cohort recruited from June 2020 to October 2020 was included in the study. We conducted a questionnaire survey related to (1) risk perception of COVID-19, (2) hygiene behavior, (3) social distancing, and (4) physical activity during the past year (before the pandemic) and during the pandemic. To compare behaviors before and during the COVID-19 pandemic, the Wilcoxon-signed rank test was used. Logistic regression analysis was conducted to identify the relative factors related to risk recognition or behavior changes.

Results: There were 187 (61.1%) patients with eGFR <45 mL/min/1.73 m². This population showed a higher degree of risk perception for COVID-19 than the general population. During the pandemic, social distancing and hygiene-related behavior were significantly increased (P <0.001). The frequency of exercise was decreased only among those with regular exercise, without diabetes, or with a lower Charlson comorbidity index (CCI) (P <0.001), with no change among the other groups. Socioeconomic status and comorbidities significantly affected behavioral characteristics regardless of the category. Age was the most significant determinant of risk perception among CKD patients. More patients showed a higher degree of risk perception for COVID-19 than the general population. Education and income were significantly associated with precautionary behaviors such as staying at home and hand sanitizer use. Also, patients with higher CCI status significantly increased their frequency of exercise (adjusted OR 2.10, 95% CI 1.01-4.38).

Conclusions: CKD patients showed higher risk perception with active precautionary behavioral changes than the general population. Healthcare providers should be aware of the characteristics to comprise precautionary behavior without reducing the physical activity.

PO2295

AKI in Rural Workers: Is Mesoamerican Nephropathy in Fact an Agricultural Nephropathy?
Carlos G. Musso,1,4 Gustavo Atroca Martinez,3,1 Andres Cadena-Bonfanti,2,3 Lil Geraldine Avendaño-Echever,2 Sergio Terrasa,1,3 Maria D. Velez-Verbel,1 William A. Peña-Vargas,4 Rafael Perez,2 Angelica Sierra,2 Research Department. Hospital Italiano de Buenos Aires, Argentina, Buenos Aires, Argentina; 2Universidad Simon Bolivar, Barranquilla, Colombia; 3Clinica de la Costa Ltda, Barranquilla, Colombia; 4Hospital la divina misericordia, Cartagena, Colombia.

Background: Mesoamerican nephropathy (MN) is a chronic tubule-interstitial nephropathy, originally described in Central America, and whose exact etiology is still unknown. Many inducing factors have been proposed such as severe dehydration, rhabdomyolysis, nephrotoxicity, chronic infections, genetic predisposition, etc. However, similar nephropathies to MN have been described in areas geographically far and ethnically diverse from Mesoamerica but which have a common factor: the intensity of hot weather and rural physical labor. For this reason, we suggest the term “agricultural nephropathy” as more appropriate name for this condition. Then, it was decided to study whether this entity could occur among rural workers of non Mesoamerican region but having similar climatic and working conditions, as is the case of the Colombian Caribbean countryside, and to consider how much repeated dehydration could weigh in its pathogenesis.

Methods: A descriptive, observational, cross-sectional study was carried out, based on field work in a farm in Sitio Nuevo (Magdalena, Colombia) in 28 rural worker volunteers (rice fields), who were measured for weight, blood pressure, blood and urine samples to measure electrolytes and osmolality, at 2 times of the day (morning and evening).

Results: Of the 28 young men workers evaluated, 5 (18%) presented a significant increase in serum creatinine during the day (0.8±0.15 vs 1.2±0.17, p = 0.001). The volume of water ingested by the workers was highly variable (2,861 ± 1,591 cL). There was a significant increase in serum sodium (p = 0.001), and urinary osmolality (p = 0.01) values between morning and afternoon values in these 5 patients.

Conclusions: Some rural workers developed parameters compatible with AKI and dehydration during their work day in the Colombian Caribbean countryside
Although Provider Awareness Is High, More Than Half of US Veterans with CKD Being Treated for Hypertension (HTN) Are Not Meeting Blood Pressure (BP) Targets

Jennifer L. Brage-Gresham,1 Diane Steffick,1 Xiaosong Zhang,1 Deidra C. Crews,2 Neil R. Powe,3 Alain Koyama,1 Nilka Rios Burrows,4 Kara Zivin,1 Rajiv Saran,1 University of Michigan Medical School, Ann Arbor, MI;2 Johns Hopkins University, Baltimore, MD;3 University of California San Francisco, San Francisco, CA;4 Centers for Disease Control and Prevention, Atlanta, GA;5 Veterans Health Administration, Ann Arbor, MI.

Background: HTN is a leading cause of kidney failure in the U.S. In people with CKD, BP control is critical to slow progression to kidney failure. We sought to assess HTN awareness among providers and BP control among Veterans with HTN and CKD.

Methods: We estimated both provider awareness (ICD code for HTN) and BP control (s130/80 mmHg, ACC 2017) among ~12 million US Veterans between 2006 and 2018, aged 18+, with CKD and HTN, with 1+ outpatient visit each year. Veterans were determined to have CKD if they had either 1) an ICD diagnosis code, 2) eGFR < 60 ml/min/1.73m², and/or 3) urinary albumin-to-creatinine ratio > 30 mg/g; HTN if they had 1) a diagnosis, 2) were taking BP lowering medication, and/or 3) BP > 130/80. Treatment was defined as a prescription for BP lowering medication.

Results: From 2006 to 2018, ~94% of US veterans with CKD and HTN had a health provider-documented diagnosis code of HTN. The percentage of veterans with diagnosed HTN who were on BP-lowering medications, but did not have their BP under control (BP > 130/80 mmHg) declined from 57.6% to 51.3%. The percentage who had their BP under control increased from 30.2% in 2006 to 32.5% in 2010 but declined to 25.2% in 2018. The percentage with diagnosed HTN who were not receiving BP-lowering medications rose from 5.9% to 17.4%. The percentage of veterans with CKD and high BP who did not have a diagnosis of HTN remained between 5% and 6% throughout.

Conclusions: Provider awareness of HTN in the setting of an integrated health care system is high, as indicated by patients’ recorded diagnosis of HTN. However, despite this high level of provider awareness, more than 50% of patients with diagnosed HTN in 2018 were not achieving the BP target of s130/80 mmHg, reflecting the difficulty in controlling BP in CKD patients. A better understanding of underlying factors, along with designing and implementing quality improvement programs may help improve this practice gap.

Funding: Other U.S. Government Support

References:

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO2301

Shrunken Pore Syndrome Is Associated with a Rise in Mortality in a Community-Based Population of Middle-Aged Individuals

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Background: Chronic kidney disease (CKD) is a risk factor for increased mortality mainly due to cardiovascular disease (CVD). Glomerular filtration rate (GFR) is the best way to estimate kidney function, but it cannot be measured. Creatinine and cystatin C are two molecules that are used in clinical practice to estimate GFR (eGFR). The lower eGFR, the higher is the mortality. CKD staging is therefore a good marker of mortality and development of CVD. However, there are patients who have the same CKD stage and risk factors for development of CVD but different outcome in mortality. Shrunken pore syndrome (SPS) has shown to be a marker of increased mortality in different patient groups regardless of their measured GFR. The theory behind SPS is supposed to be a difference in the renal filtration of small molecules like creatinine compared to middle sized molecules like cystatin C. Little is known about the prevalence of SPS and the effect on mortality in the general population. The aim of our study is to investigate this.

Methods: The study population consisted of 5061 individuals from the Malmö Diet and Cancer Cardiovascular cohort community-based study that was gathered during 1991 and 2000. The individuals were 44-64 years old. Blood samples, anthropometric measurement and a questionnaire about life style etc was available. CAPA was used for eGFR based on cystatin C and LMR was used for eGFR based on creatinine. SPS score was defined as eGFRc ≤ 70% of eGFRc. Generalized linear regression model was used to match individuals with SPS and those without. Kaplan-Meier estimates were used to present survival probabilities in four eGFRc/eGFRc group intervals. To account for within quartet correlation, frailty Cox proportional hazard models with shared frailty were employed. Results are presented as hazard ratios (HR) with 95% confidence intervals (CI).

Results: 405 individuals (8%) fulfilled the criteria for SPS. Median (2.5-97.5% percentiles) eGFRc was 63 (38-97) and median eGFRc was 70 (49-92) mL/min/1.73m2. HR for mortality in individuals with SPS in the matched data was 2.43 (1.15 - 5.14).

Conclusion: SPS has a doubled risk of all-cause mortality. Further studies are needed to explore the mechanisms behind the association between SPS and mortality.

PO2302

Associations Between Serum Biomarkers of Iron Stores and the Progression to Kidney Failure in Patients with Moderate-to-Severe CKD

Viviane Calice-Silva,1 Daniel G. Muenz,2 Murilo H. Guedes,3 Brian Bieber,2 Benedicte Stengel,2 Dominique S. Raj,4 Helmut Reichel,5 Sandra Waechter,6 Tiziana Di Francesco,7 Bruce M. Robinson,8 Roberto Pecotti-Filho,3 Pontificia Universidade Catolica do Parana, Curitiba, Brazil; 2Arbor Research Collaborative for Health, Ann Arbor, MI; 3Centre de Recherche en Epidemiologie et Sante des Populations, Villejuif, France; 4GWU Medical Faculty Associates, Washington, DC; 5Nephrologisches Zentrum Villingen-Schwenningen, Villingen-Schwenningen, Germany; 6Vifor Pharma Ltd, Glattbrugg, Switzerland.

Background: We recently reported that lower levels of biomarkers of iron stores are associated with a higher risk of all-cause mortality and major adverse cardiovascular events in patients with moderate to severe chronic kidney disease (CKD). However, the impact of these parameters on the risk of kidney failure (KF), potentially a competing risk, has not been previously explored.

Methods: Patients from Brazil, France, Germany and the US in CKDnp (eGFR ≤ 60mL/min at enrollment, under nephrology care) and with available TSAT and ferritin levels were included in the analyses. Cox models were used to estimate hazard ratios (HR) for the outcome of KF defined as a composite endpoint including dialysis initiation, transplant, 40% decline of eGFR from baseline, or sustained eGFR ≤ 15 mL/min/1.73m2. Over median follow-up time of 2.0 [0.6-3.0] years, there were 1800 (33%) KF events (15.7/100 pt-years). TSAT had a U-shaped association with KF with highest HR at TSAT<15% in the crude analysis (Model 1 of Table 1). Neither TSAT nor ferritin had a directional association with KF after adjustment for confounders (Model 2).

Conclusions: Levels of biomarkers of iron stores, as captured by TSAT and/or ferritin, are not associated with development of KF in patients with moderate to severe CKD under nephrology care. These findings further the understanding of our previous findings of a higher risk of mortality and cardiovascular events in this population with iron deficiency and high risk of CKD progression.

Funding: Commercial Support - Amgen Inc (since 1996, founding sponsor); Astellas Pharma Inc.; AstraZeneca Pharmaceuticals LP; Baxter Healthcare Corp; Bayer Yakuhin, Ltd; Biogen Idec; BMS; Boehringer Ingelheim; Bristol-Myers Squibb USA Inc.; Italian Society of Nephrology (SIN); Japanese Society for Perioperative Dialysis (JSPD); JMS Co., Ltd.; Kidney Research UK; Kidney Foundation Japan (KFJ); Kissie Pharmaceutical Co., Ltd.; Kyowa Kirin Co., Ltd. (since 1999 for Japan DOPPS); Merck Serono & Co. Inc.; Nicolai Co., Ltd.; NOO Pharmaceutical Co., Ltd.; Terumo Corporation; Torii Pharmaceutical Co., Ltd.; Vifor Fresenius Medical Care Renal Pharma Ltd, Government Support - Non-U.S.

PO2303

Association Between the Triglyceride-Glucose (TyG) Index and Coronary Artery Calcification Progression in Non-Diabetic CKD

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Background: Patients with chronic kidney disease (CKD), the likelihood of complications of cardiovascular disease(CVD) may increase compared to general population. TyG (fasting triglycerides [mg/dL] X fasting glucose [mg/dL]/2). Mean arterial pressure (MAP) was calculated as DBP + (SBP – DBP)/3. Mean arterial pressure (MAP) was calculated as DBP + (SBP – DBP)/3. Mild ischemic CKD was defined as 80eGFR ≥ 90 mL/min/1.73m2 by the Chronic Kidney Disease Epidemiology Collaboration equation (mild-CKD group). CAC aggravation was defined as an increased coronary artery calcification score (CACS) in the in the follow-up period. To calculate the odds ratio for incident CKD, logistic regression analyses were performed.

Results: 1,516 patients were enrolled, of which 746 were in the mild-CKD group without diabetes. The CACS aggravation was significantly higher in participants with a tyG index of 8.9 or higher [OR 1.705 (1.351-2.152), P-value <0.001]. After adjusting for age, sex, MAP, Hemoglobin, Ca X P, potassium associated with increased risk of CAC in participants with mild renal insufficiency [OR 1.534 (1.058-2.224), P=0.027].

Conclusions: Among non-diabetic CKD, tyG index of 8.9 or higher had a positive correlation with CAC progression.

PO2304

Plasma Proenkephalin and Incident CKD in REGARDS

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Background: Plasma proenkephalin (PENK) is a precursor of active enkephalins. High plasma concentrations have been previously associated with eGFR decline. Whether PENK concentrations vary by race and whether the association of PENK with incident CKD differs by race is uncertain.

Methods: In a nested cohort of 3,986 community-living participants within the REGARDS cohort, we measured PENK by ELISA. Primary outcomes were incident CKD (new eGFR <60 mL/min/1.73m2 plus 40% decline), significant eGFR decline (30% decline) and incident albuminuria (new UACR > 30mg/g) at a follow-up visit 9.4 years after baseline.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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PO2305

Novel Approach to the Relation of Environmental Exposure and Kidney Dysfunction: Data Analysis from Korean National Environmental Health Survey (KoNEHS), 2015-2017

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Background: Forecasting patient outcomes with kidney disease using standard statistical techniques is complex to estimate effects of the environmental chemicals. Herein, we aim to assess risk prediction for kidney disease in the general population using novel methods.

Methods: Serum POPs, serum creatinine or urinary albumin were measured in subpopulation (n=1,266) among the general adult participants from the 3rd Korean National Environmental Health Survey (KoNEHS) (n=3,787). Classification algorithms were used for the prediction of chronic kidney disease (CKD), defined by estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (UACR). In addition, weight quantile sum (WQS), which provides weights to the components of the mixture, was used to assess multi-pollutant effects.

Results: Of 1,266 adult subjects and 44 variables, including baseline characteristics and laboratory findings, were analyzed for the CKD prediction. A decision-tree algorithm was applied that performed a conventional method such as logistic regression (AUC 0.635 vs. 0.621). Among various decision-tree models, the lipid-corrected polychlorinated biphenyl congener 153 (PCB 153) was selected as the best predictor of CKD. Because persistent organic pollutants (POPs) accumulate with age, stratification analysis was conducted based on age. In the WQS model, PCB 153 showed the highest weight in its contribution to lower eGFR after adjusting covariates in the middle-aged group (under 50 years) (p=0.0135). If subjects with young age (under 50 years) were hemoglobin level > 13.25 g/dl, the CKD was predicted as 71.4% in the high serum PCB153 group.

Conclusions: We propose a machine learning-based prediction model. POPs and age were interrelated as notable risk factors for healthy kidney volunteers.

PO2306

Prevalence and Associated Factors for CKD in Rural and Peri-Urban Bangladesh

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Background: Chronic Kidney Disease (CKD) is an increasing public health threat worldwide. Studies have documented CKD among adult population in urban Bangladesh, however, in rural and peri-urban settings still lagging behind. We aimed to generate data in understanding the prevalence and CKD-related factors.

Methods: We recruited participants randomly from the Demographic Surveillance System of Mirzapur, Bangladesh in two phases. In phase 1, we screened participants using a laboratory-based creatinine and albumin to creatinine ratio (ACR) and collected information on socio-demographic, lifestyles, and health histories. We evaluated the participants’ CKD status following the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and their estimated glomerular filtration rate (eGFR). Those participants who had eGFR below 60 ml/min/1.73 m2 and/or ACR a30 mg/g were considered for phase 2. After three months, in phase 2, we repeated the blood and urine test for GFR and ACR. A participant was diagnosed as a case of CKD if (s)he had eGFR below 60 ml/min/1.73 m2 or had ACR a30 mg/g for more than three months as suggested by the Kidney Disease Outcomes Quality Initiative guidelines.

Results: We enrolled 928 participants; of them 872 completed the study procedure and included in the analysis. The mean ± standard deviation (SD) of age was 48.2 ± 16.4. In phase 1, probable CKD cases were 281 (32%), however, in phase 2, confirmed cases were 192 (22%) [stage-1, 4.0%; stage-2, 11.8%; stage-3, 5.5%; stage-4, 6.6%; stage-5, 0.11%]. In the multivariate logistic regression analysis, associated factors for prevalent CKD included aged ≥60 years (adjusted odds ratio [aOR], 3.02; 95% confidence interval [95% CI], 1.85 to 13.63), hypertension (aOR, 3.08; 95% CI, 2.17 to 4.59), diabetes (aOR, 2.52; 95% CI, 1.60 to 3.96), anemia (aOR, 2.50; 95% CI, 1.63 to 3.84) and presence of RBC in urine (aOR, 3.20; 95% CI, 1.71 to 5.98).

Conclusions: In rural and peri-urban Bangladesh, this is the first study of CKD prevalence, and repeated confirmatory testing revealed a prevalence of approximately 22%, which is higher than in urban setting. Findings suggested that CKD monitoring systems are required to assess the overall burden and effective steps should be taken to mitigate these major risk factors.

PO2307

Association of XOR Activity and NLRP3 Inflammasome Among CKD Patients

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Background: Previous studies have shown few result on the relationship between XOR activity and NLRP3 inflammasome in non-hemodialysis patients.

Methods: CKD patients in nephrology department with normal uric acid were recruited. Urine chemical and biochemistry and clinical data were collected. XOR activity was detected by fluorescence colorimetry, XO activity was detected by double antibody sandwich ELISA, and NLRP3 Inflammasome were detected by competitive binding method. After correlation analysis, multiple (stepwise) regression analysis was performed to explore the correlation between XOR and NLRP3 inflammasome and the relationship with clinical data of patients.

Results: The correlation analysis of XOR activity, XO activity, XOR/XO ratio and NLRP3 Inflammasome with biochemical indicators showed that XOR activity significantly correlated with eGFR, DBP, FBG, and age, while XOR/XO ratio was negatively correlated with age, serum total protein, serum creatinine, and serum chloride concentration; Log(XO) was positively correlated with eGFR and FBG, and negatively correlated with serum chloride concentration; The ratio of X/XOR was positively correlated with total protein and UA, and negatively correlated with eGFR, creatinine and alanine transferase; NLRP3 Inflammasome were positively correlated with XOR, Log(XO) and serum sodium concentration, and negatively correlated with sex; Multiple linear (stepwise) regression results showed that eGFR, FBG and DBP were independent influencing factors of XOR/eGFR, FBG and UA and total cholesterol were independent influencing factors of Log(XO); Serum creatinine, serum sodium concentration and XOR activity were independent influencing factors of NLRP3 Inflammasome, and there was no collinearity in statistical analysis. According to the value of eGFR, the patients were divided into two groups. The XOR activity, Log(XO), XOR/XO ratio, serum creatinine, total protein and alanine transferase were compared between the two groups, and the differences were statistically significant.

Conclusions: In CKD patients, elevated fasting blood glucose and diastolic blood pressure are independent risk factors for XOR activity, while elevated XOR activity is an independent risk factor for NLRP3 Inflammasome. Therefore, controlling FBG and DBP in CKD patients has certain clinical reference significance for reducing XOR activity and further reducing NLRP3 Inflammasome.

PO2308

Trends in Volume, Appropriateness, and Outcomes of Referrals to Nephrology over the Last Two Decades: A Retrospective Analysis Using the Alberta Kidney Disease Network Database

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Background: It is well-established that guideline-concordant referrals to nephrology are associated with improved patient outcomes. However, some referrals are unnecessary (guideline-discordant) leading to high volumes and delays for referrals that are guideline concordant. We investigated the trends in the number of referrals to nephrology, and relationships in Alberta.

Methods: Retrospective cohort analysis of patients with at least one visit to a nephrologist from primary care between 2006 and 2019. A referral was considered appropriate based on the KDIGO defined criteria (estimated glomerular filtration rate
Microscopic Hematuria and Leukocyturia Are Highly Prevalent in East Africa and Associated with CKD

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Background: Microscopic hematuria and leukocyturia may reflect parenchymal kidney disease; there have been few population-based studies of these urinary abnormalities in Africa.

Methods: We included a population-based sample of 3,686 East Africans. We defined hematuria and leukocyturia as heme and leukocyte esterase dipstick positive (+1), respectively. We used sampling weights to estimate the community-based prevalence of hematuria and leukocyturia and used weighted multivariable log-link Poisson models to assess the association of potential risk factors with these abnormalities, and separately, the association of urine abnormalities with CKD (eGFR < 60 mL/min/1.73m² or dipstick proteinuria ≥1+).

Results: Most participants with leukocyturia did not have hematuria or proteinuria; there was minimal overlap between hematuria and proteinuria (Figure). With sample weighting, the mean age was 38 years; 52% were female. The prevalence of hematuria was 3.7% in eastern Uganda, 2.8% in southwestern Uganda and 2.8% in Kenya. The prevalence of leukocyturia was 11.2% in eastern Uganda, 8.7% in southwestern Uganda was 3.7% in eastern Uganda, 2.8% in southwestern Uganda and 2.8% in Kenya. The prevalence of hematuria and leukocyturia was >60 mL/min/1.73m² or dipstick proteinuria ≥1+).

Conclusions: Hematuria and leukocyturia are common in rural East Africa, with considerable regional difference. These urinary abnormalities may represent a unique pattern of kidney disease in this region.

Funding: NIDDK Support

PO2309

The Effect of Cardiometabolic Comorbidities on Risk of CKD Incidence: A Longitudinal Cohort Study

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Background: Chronic kidney disease (CKD) and cardiometabolic conditions are closely inter-related. We studied the risk of incident CKD among patients who had or developed type 2 diabetes (T2D), atherosclerotic cardiovascular disease (ASCVD), or heart failure (HF).

Methods: We conducted a longitudinal cohort study using the electronic medical records of Kaiser Permanente Northwest to identify 371,109 adult patients without CKD at baseline (first known eGFR ≥60 mL/min/1.73m² between 2005-2017) and followed them through 2019 for incident CKD (two eGFR measurements <60 mL/min/1.73m²). We assessed T2D, ASCVD and HF at baseline and prior to CKD incidence. We used generalized estimating equation (GEE) models to calculate age/sex-adjusted CKD incidence per 1,000 person-years independently for baseline T2D, HF, and ASCVD. Time-dependent Cox regression models were used to determine the effect of baseline or development of T2D, ASCVD and HF on CKD incidence adjusting for age, sex, race/ethnicity, renal angiotensin aldosterone system (RAAS) inhibitor and statin use, smoking, and blood pressure ≥140/90 mmHg.

Results: Study subjects were 49.7±14.9 years old and 56% were women. CKD incidence among patients with T2D or HF was more than double vs. patients without T2D or HF, and 55% higher among patients with vs. without ASCVD (Figure). We used the time-dependent model, risk of CKD incidence was increased by more than 2-fold by HF (hazard ratio 2.12, 95% CI 2.05-2.19), 71% by T2D (1.71, 1.66-1.75), and 26% by ASCVD (1.26, 1.23-1.30).

Conclusions: Cardiometabolic conditions, particularly HF and T2D are independent risk factors of incident CKD. Treating the cardiometabolic-renal syndrome as a single clinical entity may benefit these patients.

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PO2311

Determining the Association Between Continuity of Primary Care and Acute Care Use Among Adults with CKD in Alberta, Canada

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Background: Acute care use is high among individuals with chronic kidney disease (CKD). It is unclear how relational continuity of primary care influences downstream acute care use. We aimed to determine if poor relational continuity of primary care is associated with higher rates of all-cause and potentially preventable acute care use among adults with CKD.

Methods: We conducted a population-based retrospective cohort study of adults with stages 3 and 4 CKD and at least three visits to a primary care provider between April 1, 2011 to March 31, 2014 in Alberta, Canada. Relational continuity was calculated using the Usual Provider Continuity index and descriptive statistics were used to summarize patient and acute care encounter characteristics. Adjusted rates (per 1,000 person-years) and incidence rate ratios for all-cause and CKD-related ambulatory care-sensitive condition (ACSC) hospitalizations and emergency department (ED) visits were estimated using negative binomial regression models.

Results: Among 86,475 individuals with CKD, 51.3%, 30.0%, and 18.7% of patients had high, moderate, and poor continuity of primary care, respectively. There were 77,988 all-cause hospitalizations, 204,615 all-cause ED visits, 6,489 (8.3% of all hospitalizations) CKD-related ACSC hospitalizations, and 5,461 (4.1% of all ED visits) CKD-related ACSC ED visits during a median follow-up of 2.3 years. Rates of all-cause hospitalization and ED use increased with poorer continuity of primary care in a stepwise fashion across CKD stages. Poor continuity of primary care was also associated with higher rates of CKD-related ACSC hospitalization and ED visits, particularly among individuals with stage 3 CKD.

Conclusions: Poor continuity of care is associated with increased acute care use and targeted strategies are needed to strengthen patient-provider relationships within primary care among those with CKD.

Funding: Other NIH Support - Canadian Institutes of Health Research (CIHR); Alberta Strategy for Patient-Oriented Research SUPPORT Unit (AiSPORU)

PO2313

Submaximal Dose of Angiotensin Converting Enzyme Inhibitor and Angiotensin II Receptor Blockers Among Persons with Proteinuria


Background: Underutilization of angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB) for treatment of albuminuria is a known quality of care gap. Among those treated with ACEi/ARB, submaximal doses represent an opportunity to improve CKD management.

Methods: Using the OptumLabs Data Warehouse, a longitudinal, real-world dataset with deidentified claims and electronic health record data, we identified adults with proteinuria, defined as either urine albumin/creatinine ≥30 mg/g or protein/creatinine ≥150 mg/g, who were prescribed an ACEi/ARB between 1/1/2015 and 12/31/2016. Among patients without apparent contraindication to ACEi/ARB dose escalation (blood pressure <130/80 mmHg, eGFR >15 ml/min/1.73m², or prior diagnosis of acute kidney injury or hyperkalemia), we examined the proportion taking the maximal recommended dose of their ACEi/ARB, overall and by demographic and clinical factors. We used multivariable logistic regression to assess factors associated with submaximal dosing.

Results: Of 79,413 patients with proteinuria receiving ACEi/ARB therapy, 50% (n=39,731) had no apparent contraindication to dose escalation. 34% (n=13,566) of these patients were on maximal ACEi/ARB doses. In multivariable analyses, younger age, Asian race, Hispanic ethnicity, higher serum potassium, and non-diabetes status were associated with submaximal dosing (Figure).

Conclusions: Among persons with proteinuria and no apparent contraindication for ACEi/ARB dose escalation, over half were on submaximal doses. Concerns over hyperkalemia may drive underdosing. However, greater attention toward maximizing ACEi/ARB dose as tolerated, especially among patients without diabetes, could optimize cardiovascular and kidney health.

Funding: NIDDK Support

PO2314

Genetic Variant rs671 of ALDH2 Gene Is Associated with Reduced Renal Function in Chinese Population

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Background: ALDH2 is a mitochondrial aldehyde dehydrogenase and ALDH2 rs671 genetic polymorphism was associated with hypertension and diabetes. Genome-wide association analysis of East Asians revealed ALDH2 rs671 variant associated with kidney function traits, but comprehensive epidemiological studies are lacking. We conducted this study to explore the associations between ALDH2 rs671 and kidney function traits in Chinese population.

Methods: A total of 15,856 individuals completed medical check-up in a single center were enrolled. ALDH2 gene mutation detection kit was used to genotype the rs671 polymorphism. Clinical laboratory data were collected from the records of medical check-up. Urine albumin to creatinine ratio (UACR) was tested in 5,168 individuals and the data was log-transformed for further analysis. Linear and logistic regression analysis were used to estimate the association between rs671 SNP and renal function traits.

Results: The average age was 48±9.7 years and the individuals were mainly males (67.0%). 17.7%, 13.0% and 30.6% individuals were obese, diabetic, and hypertensive, respectively. Frequencies of GG, GA, and AA genotypes were 68.0%, 29.4% and 2.6%. Male individuals with A allele were associated with a significant increased level of all-cause proteinuria (β = 1.664, 95% CI: 1.141, 2.186) and blood urea nitrogen (β = 0.156, 95% CI: 0.107, 0.205), and reduced estimated glomerular filtration rate (eGFR, β = 1.057, 95% CI: -1.347, -0.767), uric acid (β = -8.893, 95% CI: -11.908, -5.877), logUACR (β = -0.066, 95% CI: -0.122, -0.011). Similar associations were not observed in female individuals. Besides, we did not observe association between ALDH2 genotype and chronic kidney disease (CKD), albuminuria, or proximal tubular injury.

Conclusions: ALDH2 rs671 polymorphisms were associated with decreased renal function in male individuals other than the females. Further analyses were needed for further explore the direct and indirect effects of ALDH2 SNP on CKD, albuminuria, and proximal tubular injury.

Funding: Government Support - Non-U.S.
Impact of Dietary Fatty Acid on All-Cause Mortality According to Kidney Function Based on a Nationwide Population Study

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Background: Although the relationship between fatty acids and the risk of mortality has been long-lasting discussed, there is little evidence to support that the effect of saturated fatty acids (SFA) and polyunsaturated fatty acids (PUFA) this study aims to investigate the association between dietary fatty acids and all-cause mortality among the general population.

Methods: We used data from the 92,062 participants of US National Health and Nutrition Examination Survey 1999-2015. The intake of fatty acids was adjusted with the total energy intake and divided by the quartile, the first quartile group was regarded as the reference. We used a multivariate Cox-proportional hazard model to identify the impact of fatty acids on all-cause mortality.

Results: A total of 36,747 subjects were finally included in the study. During 97.9 ± 53.9 months, there were 922 (4.4%) and 3,544 (22.4%) death cases in eGFR <60 mL/min/1.73 m² and <90 mL/min/1.73m² groups, respectively. Among 8 different SFA, hexadecanoic acid (adjusted hazard ratio [aHR] 1.13, 95% confidence interval [CI] 1.05-1.21 in 4th quartile [Q4]) and octadecanoic acid (aHR 1.13, 95% CI 1.15-1.25 in Q4) showed that greater intake was associated with the increased risk for all-cause mortality. In addition, most PUFA except eicosatetraenoic acid showed a beneficial effect on all-cause mortality. Among subjects with eGFR >90, the harmful effect of saturated fatty acid was attenuated and the beneficial effect of PUFA remained in only octadecanoic acid. On the contrary, for the subjects with eGFR <90, the harmful effect of hexadecanoic acid (aHR 1.17, 95% CI 1.05-1.32 in Q4) and octadecanoic acid (aHR 1.16, 95% CI 1.04-1.30 in Q4) was exacerbated. The beneficial effect of PUFA was also prominent in this group; octadecatetraenoic acid (aHR 0.67, 95% CI 0.57-0.77 in Q4), eicosapentaenoic acid (aHR 0.86, 95% CI 0.79-0.98 in Q4), docosapentaenoic acid (aHR 0.88, 95% CI 0.79-0.94 in Q4), and docosahexaenoic acid (aHR 0.88, 95% CI 0.79-0.94 in Q4).

Conclusions: The impact of dietary fatty acid on all-cause mortality was different in according to the kidney function. More specified and targeted counseling for restricting SFA and encouraging PUFA needs to be considered especially for subjects with lower eGFR.

Impact of Dietary Beta-Carotene on All-Cause Mortality According to Different Clinical Conditions, Including Decreased Kidney Function

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Methods: We used a multivariate Cox-proportional hazard model to identify the impact of dietary beta-carotene on all-cause mortality. The intake of beta-carotene was divided by total energy intake and divided by the quartile, the first quartile group was regarded as the reference. The subgroup was made by 1) the presence of hypertension, 2) diabetes, 3) the status of alcohol consumption, and 4) smoking status, and 5) estimated glomerular filtration rate (eGFR) 90 mL/min/1.73m², respectively. We used a multivariate Cox-proportional hazard model to identify the impact of dietary beta-carotene on all-cause mortality.

Results: A total of 36,747 subjects were finally included in the study. There were 14,469 (39.4%), 4,704 (12.8%), and 15,804 (43.0%) subjects with hypertension, diabetes, and eGFR <90 mL/min/1.73 m², respectively. There were 8,774 (23.9%) of ex-smokers and 13,694 (37.3%) of current smokers, respectively. During 97.9 ± 53.9 months, there were 4,465 (12.2%) death detected. After adjusted with multivariable, greater intake of beta-carotene significantly reduced the risk for all-cause mortality in subjects without hypertension (adjusted hazard ratio [aHR] 0.81, 95% confidence interval [CI] 0.76-0.86 in 4th quartile group) and with diabetes (aHR 0.85, 95% CI 0.75-0.96 in Q4), non-alcoholics (aHR 0.86, 95% CI 0.74-0.99 in Q4), and ex-smokers (aHR 0.79, 95% CI 0.66-0.93 in Q4), respectively. On the contrary, according to the eGFR, participants with eGFR <90 mL/min/1.73 m² had a beneficial effect of dietary beta-carotene (aHR 0.82, 95% CI 0.76-0.89 in Q4) compared to the participants with eGFR ≥90 mL/min/1.73 m² (aHR 1.00, 95% CI, 0.78-1.27).

Conclusions: Among the various medical conditions, decreased kidney function status was the only condition to predict the beneficial effect of dietary beta-carotene. More specified and targeted counseling for encouraging intake of beta-carotene needs to be considered especially for subjects with lower eGFR.
Results: After the change in eGFR reporting, rates of metformin initiation increased (4/27 in 2020 vs. 0.219 in 2019), while discontinuation rates were stable (18% in 2019 vs. 15% in 2020) among Black patients with CKD. Rates of dialysis initiation were comparable (2.7% in 2020 vs. 1.4% in 2019, mean eGFR 8 vs. 13 ml/min/1.73m²) in Black patients with CKD, with the primary indication of uremic symptoms remaining unchanged. Comparing Black vs. non-Black patients, subcategory referral rates for nephrology and transplant nephropathy were higher for Blacks after the change in eGFR reporting (Figure 1).

Conclusions: After removing the race coefficient from eGFR reporting, patterns of medication prescription rates and dialysis initiation did not substantially change, however subcategory referral rates increased for Black patients with CKD. We acknowledge that the COVID-19 pandemic may have impacted these trends, but the trends overall are encouraging for improving health outcomes and nephrology access to care for Black patients with CKD.

Background: Elimination of the race coefficient from the CKD-EPI equation has variable impact on clinical care and CKD research across V A locations nationally. Ideally having CKD when eliminating the race coefficient. Median (IQR) number of reclassified persons with chronic kidney disease (CKD).

Methods: We identified U.S. Veterans with incident non-dialysis CKD stages 3-4 based on laboratory data from 2005-2019 from the Veterans Affairs (VA) Corporate Data Warehouse. Demographic characteristics and laboratory values were used to calculate estimated glomerular filtration rate (eGFR) by the CKD-EPI equation with and without the race coefficient. We identified Black patients who were reclassified from non-CKD to CKD status or to a different CKD stage, as well as individuals whose race was not reported and eGFR could not be calculated using a race-based equation. The number of additional persons with CKD identified without the race coefficient was evaluated by V A station.

Results: There were 1,765,410 individuals with CKD stages 3-4 by race-based eGFR. Eliminating the race coefficient resulted in reclassification of 119,142 (35.2%) Black individuals as having CKD when eliminating the race coefficient. Median (IQR) number of reclassified individuals per VA station was 470 (110.5-1,393) reclassified Black persons and 1,550 (584-2,665.75) individuals of unidentified race (Figure). Conclusion: Eliminating the eGFR race coefficient will lead to substantial but variable impact on clinical care and CKD research across VA locations nationally. Ideally this shift will achieve more equitable clinical outcomes for Black persons and expand inclusion in CKD clinical trials and observational research to advance CKD care.

Funding: Other U.S. Government Support

PO2319
Comparing Estimated Glomerular Filtration Rates (eGFR) for US Black Veterans with and Without the Black-Race Coefficient and Normalization to a Fixed Body Surface Area (BSA)
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Background: The CKD-EPI estimation of GFR includes two corrections: 1) increasing eGFR for Blacks by 15.9% to more accurately reflect measured GFR; 2) normalizing eGFR in all races to a fixed value (1.73 m²) of BSA to compare across populations. We aimed to assess the impact of removing both corrections—separately and together—on the prevalence of CKD in Black US Veterans.

Methods: Among 7 million Black US Veterans, aged 18+ with at least one serum creatinine lab measurement (2006-2018), we estimated the prevalence of eGFR < 60, using four GFR-correction methods: 1) eGFR using the CKD-EPI equation with the Black-race coefficient and normalized to a BSA of 1.73 m²; 2) #1, without the Black-race coefficient; 3) #1, without normalization for BSA; and 4) #1, without the Black-race coefficient or normalization for BSA.

Results: Among Black Veterans, the average age was 57 years, 87% males, and average BSA was 2.11 m². The prevalence of CKD varied appreciably by the method of GFR estimation. CKD prevalence was highest (15-20%) throughout the 13-year study period without use of the Black-race coefficient (#2) and lowest (6-8%) without normalization for BSA (#3). The method with neither the Black-race multiplier nor BSA normalization (#4) yielded similar estimates of CKD prevalence as the CKD-EPI method of eGFR estimation (#1), differing by <2% throughout the study period. Patient-level agreement between the latter two methods was nearly 90%.

Conclusion: Our results show good agreement between Black Veterans classified as having CKD using the CKD-EPI equation with both corrections and those same veterans classified with CKD without either correction. Pending recommendations from the NKF-ASN Task Force, the latter method (#4) offers a simplified procedure to provide individualized GFR estimates on the original scale (mL/min) for all individuals.

Funding: Other U.S. Government Support

PO2320
Social Determinants of Health (SDOH), Environmental Inequities and ESRD Among US Veterans: An Integration of Ecological and Spatial Approaches
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Background: Disparities in kidney health are often due to underlying environmental and social determinants of health (SDOH). We assessed geographic variation and the association between air pollution, SDOH, and ESRD among US veterans.

Methods: We used data from about 3 million Veterans with CKD between the years of 2006-2016 (prevalent and incident CKD cases). Environmental and SDOH were obtained from various data sets, including the American Community Survey (2009), the National Neighborhood Data Archive (2006) and others. County prevalence of ESRD was calculated as # ESRD cases/1000 person-years. County-level environmental factors and SDOH included average daily PM2.5, neighborhood disadvantage index, etc. A geographically weighted regression model (GWR) was applied to explore the relationship between SDOH, air pollution and prevalence of ESRD.

Results: Average of county-level prevalence of ESRD was 3.1/1000 person-years (SD=0.21, n=3,231). The prevalence of ESRD was higher in the rust-belt area of the Midwest and the Southeast region (Fig 1a). Neighborhood disadvantage index was

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associated with higher ESRD prevalence in the West and parts of the Midwest (Fig 1b). PM2.5 was associated with higher prevalence in the East North Central and South West Central regions (Fig 1c).

Conclusions: Variation exists in the association between environmental factors, SDOH and the presence of ESRD geographically. It highlights the importance of attention to the environment and community-based SDOH, toward preventing and managing ESRD based on residence and individualized patient care.

Funding: Veterans Affairs Support

PO2321
Facility-Level Variation and Racial Disparities in Albuminuria and Serum Creatinine Dual Testing in the US Veterans Health Administration (VHA) Health Care System
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Background: Simultaneous urine testing for albumin (UAlb) and serum creatinine (SCr), i.e., 'dual testing', is now an accepted quality measure in the management of diabetes. As kidney disease is defined by both UAlb and SCr testing, this approach could be more widely adopted in kidney care. We therefore sought to assess facility-level variation and racial differences in performance of dual testing in the integrated VHA health care system.

Methods: We included patients with any inpatient or outpatient visit to the VHA during the period 2009-2018. Dual testing was defined as UAlb and SCr testing in the outpatient setting within a fiscal year. A generalized linear mixed-effects model was applied to explore individual level (demographics and comorbidities) and facility level predictors of receiving dual testing.

Results: We analyzed data from approximately 6 million veterans per year (total n=69,102,389; 91.1% male). Dual testing increased on average from 17% to 21%, but varied substantially among VHA centers (0.3% to 43.7% in 2018) (Figure). Dual testing was strongly associated with diabetes (odds ratio [OR]: 10.4, 95% CI 10.3-10.5, p<0.0001) and not associated with VHA center complexity level. Despite a higher proportion of Black veterans receiving dual testing compared to White veterans (28.0% vs 21.7% in 2018), they were less likely to be tested after adjusting for other individual and facility characteristics (OR: 0.93, 95% CI 0.92-0.93, p=0.0001).

Conclusions: Performance of dual testing varied among VHA centers and is low in both White and Black veterans. Simultaneously incorporating UAlb and SCr for kidney care may help improve both risk stratification and management of individuals with or at risk of kidney disease.

Funding: Other U.S. Government Support

PO2322
Three New Race-Free, Community-Based Equations to Estimate GFR: The Machine Learning Estimation of Renal Function (MLERF) Equations
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Background: As inclusion of race in glomerular filtration rate (GFR) estimation has become an increasingly controversial issue, it is of vital importance to propose race-free equations and evaluate their performance.

Methods: Using Multivariable Fractional Polynomials (MFP), Generalized Additive Models (GAM), and Random Forests (RF), we developed three new GFR estimating equations from the community-based Genetic Epidemiology Network of Arteriopathy Study (GENOA) study (N=1010). We then compared performance of the new equations to the CKD-EPI creatinine equation using the Epidemiology of Coronary Artery Calcification (ECAC) cohort study and the Assessing Long Term Outcomes in Living Kidney Donors (ALTOLD) (N=792). Due to lack of black participants in external data, we also evaluate performance of equations in Black participants internally using development data. A rigorous bootstrapping method, allowing equation coefficients to change for each bootstrap sample, was used to evaluate performance of our new equations to address the issue of overfitting.

Results: Our final equations were based on creatinine, age and sex. The addition of race yielded only minor nonsignificant improvements in RMSE and thus race was not included in the final equations. In external data (Figure), our new equations showed similar P30, RMSE, bias and precision compared to the CKD-EPI creatinine equation which included race as a predictor. Our equations also showed marked improvements in terms of bias and accuracy for Black participants over the CKD-EPI creatinine equation in the development data.

Conclusions: Performance of our new race-free equations using community-based cohorts were comparable to CKD-EPI creatinine equation in external validation and superior in Black participants in internal validation. Our study indicated that race can be removed from equations to estimate GFR in Black and White participants without significantly sacrificing equation performance.
Effect of Removing Race Coefficient (RC) from Estimated Glomerular Filtration Rate (eGFR) Among Black Adults in the US Military Health System (MHS)

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Background: The use of race in calculating eGFR is under scrutiny as a possible contributor to healthcare disparities in the US. Using the MHS electronic medical record, we evaluated the effect in Black adults of removing eGFR race adjustment on the overall prevalence of chronic kidney disease (CKD) and on the prevalence at specific levels of GFR important in clinical decision-making.

Methods: Fiscal Year (FY) 2015 data were extracted from the MHS Data Repository for individuals of Black race aged ≥18 without end-stage kidney disease. eGFR was calculated from serum creatinine using the CKD-EPI equation both with and without adjustment for race. CKD was defined as having the most recent eGFRs in the FY persistently ≤60 mL/min/1.73m2 for more than 3 months (KDIGO criteria).

Results: 136,934 Black individuals (age=43±14 years, 38% female, 40% active duty) had serum creatinine measured a total of 259,930 times. With RC, mean eGFR was 98.1±25.7, 4.5% had at least one eGFR ≤60, and 1.3% met CKD by KDIGO criteria (Table). Removal of RC decreased mean eGFR to 84.7±22.2 (Δ=−13.3±6.3) and increased CKD prevalence to 2.1% (Δ=68%). Without RC, 0.9% of those with GFR<60 were reclassified as having CKD stage 3 and 5.6% of those with CKD stage 3 reclassified into CKD stages 4-5. Without the RC the prevalence of CKD stages 3b-5 increased by 75%, of CKD stages 4-5 by 65%, and of eGFR<20 (eligible for transplant listing) by 71%. Among active duty, removal of RC increased prevalence of CKD by 102% and of CKD stages 3b-5 by 68%.

Conclusions: Removal of the RC resulted in significant reclassification from non-CKD to CKD and from lower to higher stages of CKD. Consequences for patient education, treatment decisions, resource utilization, and clinical outcomes may benefit from a study. The views expressed in this abstract are those of the authors and do not reflect official policy of the Departments of Army/Navy/Air Force, Department of Defense, Department of Health and Human Services, or the US Government.

Funding: Other U.S. Government Support

PO2324

Social Determinants of Health and Estimated GFR in the MDRD Study

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Background: Use of race in medical algorithms is facing increasing scrutiny. One concern is that race differences do not reflect biological differences, but rather differences in social determinants of health (SDH). The MDRD Study equation was the first eGFR equation to include race [self-identified and categorized as Black vs non-Black] in addition to age, sex and serum creatinine (Scr), due to observed differences between Black and non-Black individuals in mean measured GFR (mGFR) (1.21 times higher with the same age, sex and Scr) and mean Scr (17.1% higher for the same age, sex and mGFR, accounting for mGFR measurement error). Subsequent analysis suggested higher mean creatinine excretion and lower mean creatinine secretion in Black individuals. Here we explore the impact of SDH on the Black race coefficient in the MDRD Study equation and on the racial difference in observed Scr in the MDRD Study.

Methods: SDH and related variables included income, household size, education, employment, marital status, dietary protein and creatinine excretion. We examined the magnitude of the Black race coefficient and the observed race difference in Scr without and with adjustment for SDH variables.

Results: Among the 1628 participants at baseline visit 3, mean mGFR was 40 (range 5-168) and 12% were Black individuals. There were significant differences between Black and non-Black individuals for all SDH except dietary protein. Addition of SDH (Figure) did not substantially alter the Black race coefficient in eGFR (left) or the race difference in mean Scr (right).

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Conclusions: We were not able to show that these SDH account for the observed race and gender gap between estimated and measured eGFR or Scr in the MDRD Study. Key limitations include availability of SDH variables, residual confounding between race and SDH, and a single study of patients with CKD from 30+ years ago which may not reflect a more contemporary diverse population. These results do not detract from concerns for use of race in GFR estimation.

PO2326
Impact of Race/Ethnicity on the Current Screening Approach for CKD

Background: KDIGO recommends screening for chronic kidney disease (CKD) with both estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (ACR). Screening is advised for people with diabetes mellitus, hypertension and/or cardiovascular disease (CVD). People of African descent are at increased risk for CKD, while several reports indicate that the screening approach insufficiently capture CKD in this group. eGFR correction for African race/ethnicity may contribute to this discrepancy, but age and socioeconomic status (SES) may be involved. We assessed whether CKD detection is influenced by race/ethnicity correction and we defined how age >50 yr or lower SES influence CKD detection.

Methods: Baseline data of 21,617 participants (mean age 44 yr, 43% male) of Dutch (4,564), South-Asian Surinamese (3,043), African Surinamese (4,151), Ghanaian (2,339), Moroccan (3,614) and Turkish (3,096) ethnicity included in the multi-ethnic HELLUS cohort study (Amsterdam, The Netherlands) were analysed. We defined CKD as eGFR (CKD-EPI formula, <60 ml/min/1.73 m²) and/or ACR (≥3 mg/mmol). Detection rate was characterised by the c-statistic for three screening approaches in each ethnic group; I) the traditional approach (i.e. screening when having diabetes mellitus, hypertension, or CVD); II) the traditional approach plus age >50yr; and III) the traditional approach plus low SES (i.e. none or elementary schooling). C-statistic with and without correction for race/ethnicity were compared.

Results: Of participants, 2,335 (11%) had CKD. Estimated CKD was slightly more prevalent in participants of African Surinamese (11 vs 13%) and Ghanaian (12 vs 14%) descent, when the correction for race/ethnicity was discontinued. Compared to approach I, approach II and approach III did not have a higher c-statistic, overall and within African origin subgroups. Race/ethnicity and SES were involved in the screening decision.

Conclusions: Our study shows that discontinuation of the race/ethnicity correction, or addition of age >50 yr and low SES as criteria for CKD screening have little impact on the detection rate of the currently advised screening approach.

PO2327
Impact of Race/Ethnicity and Age on Survival in Advanced CKD Patients Treated with Conservative Management vs. Dialysis
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Background: Given evidence that dialysis may not offer survival benefit nor improve quality of life in certain groups (elderly, multi-morbid), there is growing interest in conservative management (CM) as an alternative treatment strategy for advanced CKD. Yet little is known about the impact of CM vs. dialysis on CKD outcomes, including mortality, across different racial/ethnic and age groups.

Methods: In a national cohort of 309,188 advanced CKD patients (a2 eGFRs <25 separated by ≥90 days), we compared mortality rates in patients treated with CM vs. dialysis from 1/1/07-6/30/20 from the Optum Labs® Data Warehouse (OLDW), which contains de-identified administrative claims, including medical and pharmacy claims and enrollment records for commercial and Medicare Advantage enrollees as well as electronic health record data. Patients were categorized according to receipt of dialysis vs. CM, defined as those who did vs. did not receive dialysis within 2-3ys of the index eGFR (1st eGFR <25, with the former group parsed according to timing of dialysis initiation, defined as late, intermediate, vs. early dialysis (eGFRs <5, 5<10, vs. ≥10 at dialysis transition). We used Poisson regression to compare mortality rates in CM vs. dialysis patients across race/ethnicity and age.

Results: Whereas late, intermediate, and early dialysis had higher mortality rates than CM in Non-Hispanic Whites across all age groups, in Hispanic patients CM and dialysis had similar mortality rates across all ages. In Non-Hispanic Blacks, Asians, and Other races/ethnicities, CM vs. late dialysis had similar mortality rates among those ≥75 yrs old, whereas CM demonstrated survival benefit vs. all dialysis groups in younger ages.

Conclusions: In a diverse and nationally representative cohort of CKD patients, we observed differential relationships between CM vs. dialysis on mortality rates across race/ethnicity and age. Further research is needed to determine which patient characteristics and health services optimize candidacy and choice of CM vs. dialysis to enable a personalized approach.

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PO2328
Evaluation of the Cambridge GFR Estimating Equation in a Diverse Population
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Background: Evaluation of GFR is not standardized in oncology; serum creatinine (Scr) estimated creatinine clearance (cClcr) using the Cockcroft Gault equation, and estimated GFR (eGFR) using Scr (eGFR) using the MDRD Study or CKD-EPI equation are often used interchangeably. KDIGO guidelines recommend eGFR, using standardized Scr and the CKD-EPI equation as the initial test in adults, and confirmatory tests using serum cystatin C (eGFRcys or eGFRcys-cys), measured creatinine clearance (mClcr) or measured GFR (mGFR) using exogenous filtration markers.

Methods: Janowitz and colleagues recently reported a new equation developed in patients with cancer that can be used with or without IDMS-traceable assays, CamGFR2 (Williams et al. Clin Cancer Res 2021), which performed better than CKD-EPI eGFR in the development population, but which has not been evaluated in an external validation population. To determine if CamGFR2 could be used in other settings, we evaluated CamGFR2 and other commonly used equations in two large, diverse study populations.

Results: Study populations included the CKD-EPI 2009 external validation population [n=3771, mean (SD) age 49.2 (14.6), mGFR 69.2 (35.5) ml/min/1.73 m²], men 54.1%, African American 10%, diabetes 28.2%, and CKD-EPI 2012 external validation population [n=1119, mean (SD) age 49.9 (16.6) years, mGFR 69.8 (41.0) ml/min/1.73 m²], men 59.3%, African American 3%, diabetes 53.1%. (Note: study participants were not included in the development of the CKD-EPI equation.) No eGFRcys equation, including CamGFR2, performed better than the CKD-EPI equation. As previously reported, CKD-EPI eGFRcys-cys performed better than CKD-EPI eGFR or eGFRcys (both r<0.85, NEJM 2012).

Conclusions: In conclusion, eGFRcys using CamGFR2 is not more accurate than using CKD-EPI in a diverse population. Studies comparing CamGFR2 vs. CKD-EPI equations in patients with cancer are needed

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PO2329

Racial and Ethnic Predictors of Hyperkalemia Recurrence
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Background: Understanding predictors of recurrent HK may help healthcare providers provide a more individualized approach to HK management. This study aims to explore if race and ethnicity are independently associated with recurrent HK.

Methods: The cohort consisted of 2,457,498 US veterans who had a HK event (sK >5.0 mEq/L) between 2004 and 2018. We evaluated possible demographic predictors of 1-year HK recurrence using Fine and Gray competing risk regression model, where the competing event was all-cause mortality within 1 year after index HK event. We defined HK recurrence as the third or later potassium measurement after the index HK measurement, and patients need to have at least one or more normal potassium measurements (≤5 mEq/L) between the HK events.

Results: Cohort mean age was 63±13yrs, mean index potassium level was 5.31±0.29 mEq/L, and median (IQR) index eGFR was 68 (49.86) ml/min/1.73m²; 96% were male, 13% were Blacks, and 6% were Hispanic. Overall, 17% of patients had a HK recurrence within 1 year after index HK occurrence. Black patients had a 19% higher risk of 1-year HK recurrence (hazard ratio [HR] [95% CI]: 1.19 [1.18, 1.20]) compared to White patients. Hispanic patients had a 34% higher risk of 1-year HK recurrence (hazard ratio [HR] [95% CI]: 1.34 [1.32, 1.36]) compared to non-Hispanic patients. Other predictors for high risk of 1-year HK recurrence include older age (15% higher for each 15 year increment of age) and male (22% higher compared to females) (Table).

Conclusions: Being Hispanic, Black, male, or older age, was associated with a higher risk of HK recurrence within 1 year after index HK event. Further studies are needed to understand the reasons for these disparities and their potential associations with clinical management of HK.

Funding: Commercial Support - AstraZeneca

PO2330

Ethnic Differences for Incident CKD in Asians
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In Asia, there is sparse data on incident CKD among different ethnic groups. We aimed to describe the incidence and risk factors associated with incident CKD in the major ethnic groups in Asia.

Methods:
Prospective cohort study of 5580 general population participants age 40-80 years (2234 Chinese, 1474 Malays and 1872 Indians) in Singapore who completed both baseline and 6-year follow up visits. Incident CKD was defined as an estimated glomerular filtration rate <60 ml/min/1.73 m² in those free of CKD at baseline.

Results: The 6-year incidence of CKD was highest among Malays (10.0%), followed by Chinese (6.1%) and Indians (5.8%). Logistic regression showed that older age, diabetes, higher systolic blood pressure and lower eGFR were independently associated with incident CKD in all 3 ethnic groups, while hypertension and cardiovascular disease were independently associated with incident CKD only in Malays. The same factors were identified by machine learning approaches gradient boosted machine (GBM) and random forest (RF) to be the most important for incident CKD (Figure 1). Adjustment for clinical and socioeconomic factors reduced the excess risk in Malays by 60% compared to Chinese but only 13% compared to Indians.

Conclusions: Incidence of CKD is high among the main Asian ethnic groups in Singapore, ranging between 6-10% over 6 years. Differences between ethnic groups were partially explained by clinical and socioeconomic factors. These findings may inform policy development and resource allocation to target risks factors to reduce incident CKD.

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PO2331

Muscle Mass and Estimates of Renal Function: A Longitudinal Cohort Study
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Background: Current guidelines suggest using creatinine-based estimated glomerular filtration rate (eGFRcr) as measurement of renal function, but muscle mass as key determinant of creatinine after renal function may lead to imprecise estimates. We explored effects of 24-hour height-indexed creatinine excretion rate (CER index) – an accurate marker of muscle mass – on eGFRcr and muscle mass-independent cystatin C-based eGFR (eGFRcc) and predicted probabilities of misclassification given age, sex, and CER index.

Methods: We included 8,076 community-dwelling individuals enrolled in the PREVEND study. Misclassification was defined as eGFRcr <60 ml/min/1.73 m² when eGFRcc was ≥60 ml/min/1.73 m², as accurately marker of muscle mass – on eGFRcr and muscle mass-independent cystatin C-based eGFR (eGFRcc) and predicted probabilities of misclassification given age, sex, and CER index.

Results: In a simulated 70-year-old male with low muscle mass (CER index of 4 mmol/24 hour), predicted baseline eGFRcr and eGFRcc were 87.5 and 60.5 (difference: 27.0) ml/min/1.73 m², respectively (Figure). Percentages (95% CI) of misclassification in males and females older than 60 years with low muscle mass were 18.5% (14.8% to 22.1%) and 15.2% (11.6% to 18.8%), respectively. Over time, for that same 70-year-old male, eGFRcc and eGFRcr disagreed with 2.3, 4.9, 7.7, and 10.7 ml/min/1.73 m² at baseline, 5 years, 10 years, and 15 years of follow-up, respectively.

Conclusions: Low muscle mass may cause considerable overestimation of single measurements of eGFRcr. Muscle wasting may cause spurious overestimation of repeatedly measured eGFRcc. Implementing muscle mass-independent markers for estimating renal function, like cystatin C as superior alternative to creatinine, is crucial to accurately assess renal function in settings of low muscle mass or muscle wasting.
Muscle Is a Non-GFR Determinant of Serum Filtration Marker Levels and Is Associated with Differential Accuracy of GFR Estimating Equations in Older Adults

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Background: Current GFR estimating equations use creatinine are limited by association with muscle. It is not known whether this is true for recently developed equations using novel filtration markers. These associations are relevant for older adults in whom reduced muscle mass is common.

Methods: In a cross-sectional analysis of 540 community dwelling older adults in Reykjavik, Iceland, serum levels of creatinine (Cr), cystatin-C (Cys), and novel filtration markers (beta-trace protein [BTP], beta-2-microglobulin [B2M], N-acetylthreoline, pseudouridine, phenylacetylglutamine, and tryptophan) were measured, and GFR was measured using clearance of iohexol (mGFR). GFR was estimated from Cr, Cys, or panels of novel filtration markers using CKD-EPI equations. Thigh muscle area (TMA) was assessed using computed tomography. The association of each filtration marker with TMA was determined using linear regression with adjustment for mGFR, GFR measurement error, age, and sex. The performance of the estimating equations was assessed using bias and percent of large (≥30%) errors (1-P30) among those in the lowest sex-specific quintile of TMA compared to the upper four quintiles.

Results: Mean age was 80 (SD 3.8) years, with a mean mGFR of 63 (SD 16) mL/min/1.73m². After adjusting for mGFR, all filtration markers had a residual association with TMA, but Cr had a substantially greater association even after adjustment for age and sex. Both bias and 1-P30 were greater in the subgroup with low TMA for eGFR from Cr and/or Cys but not for panel eGFR equations (see figure).

Conclusions: Panel eGFR may be preferable in older adults with low muscle mass. Practical tests are needed to identify individuals with low muscle mass for whom eGFR from Cr and Cys may be less accurate.

PO2333

Gender-Specific Glomerular Filtration Rate Reference Values for Healthy Individuals Aged 18 to 90 Years

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Background: Normal glomerular filtration rate (GFR) values based on a reference method are lacking in the elderly. We measured GFR (mGFR) in healthy individuals aged 18 to 90 years of age to describe normal mGFR decline with age, by gender, and evaluated the performances of GFR-estimating equations in this population.

Methods: We measured GFR with renal clearance of 125-I-Cr-EDTA in 630 healthy men and women, aged 18-90 years. GAMLLSS were used to reference values of GFR, and a piecewise linear regression model, to assess the relationship between GFR, age and gender. Bias, precision and accuracy of the CKD-EPI and FAS equations were evaluated.

Results: Participants (43% men) had a mean mGFR of 90.5±15.9 mL/min/1.73m². The 5th percentile stayed above 60 mL/min/1.73m² up to 80 years in men, but reached this threshold at age 63 in women, 25% of them getting below at age 76. In both genders, mGFR distribution physiologically declined as from 40 years (Figure), significantly faster in women than in men, 0.83±0.07 vs 0.67±0.07 mL/min/1.73 m² per year, p<0.001. Overall, median bias was significantly lower for the FAS than the CKD-EPI equation (-1.6 [95%CI: -2.9 ; -0.1] vs 3.4 [1.8 ; 4.9] mL/min/1.73 m², p < 0.001), whereas precision and P30 accuracy, 6.6 [4.9 ; 8.8] for FAS vs 8.5 [6.6 ; 10.9] for CKD-EPI, did not significantly differ between them. Performance metrics were similar in men and women, but differed across age classes. Above 65 years, CKD-EPI appeared to overestimate and FAS to substantially underestimate mGFR.

Conclusions: Ageing appears to be associated with faster GFR decline in women than in men, which may explain the paradoxical association of high CKD prevalence and low kidney failure incidence in women. Age- and gender-specific reference values should be considered for CKD diagnosis and drug dosing guidelines, particularly in the elderly.

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PO2334
Epidemiology of CKD Based on Age-Adapted GFR Thresholds
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Background: Age-adapted GFR criteria for definition of chronic kidney disease (CKD) have been proposed to account for normal age-related decline in kidney function. The aim of this study was to determine the prevalence and incidence of CKD stages 1-5 based on age-adapted GFR thresholds compared with current KDIGO criteria.

Methods: In this retrospective study, we obtained all serum creatinine (SCi) values and urine protein measurements from every clinical laboratory in Iceland in 2008-2016. Clinical data, including ICD-10 diagnosis codes, were retrieved from nationwide electronic medical records. Estimated GFR was calculated from SCi using the CKD-EPI equation. CKD was defined as presence of kidney damage, either proteinuria or ICD-10 diagnosis codes indicative of kidney disease, or reduced eGFR for ≥3 months. Reduced eGFR was defined as <60 mL/min/1.73 m² according to the standard KDIGO criteria or based on the following age-adapted thresholds: <75 mL/min/1.73 m² for age <40 years, <60 mL/min/1.73 m² for age 40-65 years, <55 mL/min/1.73 m² for age ≥65 years.

Incidence of CKD was calculated in individuals without evidence of CKD at study entry. Prevalence and incidence were standardized to the EU-27 population.

Results: We obtained 2,120,147 SCi values for 218,437 individuals. The median age was 46 (range, 18-107) years; 47% were men. A total of 25,596 individuals met the KDIGO criteria for CKD compared with 17,593 when the age-adapted criteria were applied. The mean annual age-standardized prevalence per 100,000 overall and for men and women was 5940, 5130 and 6750, respectively, using the KDIGO criteria, and 3640, 3270 and 4010, respectively, applying the age-adapted GFR thresholds.

Conclusions: This nationwide Icelandic study comprising SCi values and other markers of kidney damage for the majority of the Icelandic population demonstrates a markedly lower CKD prevalence and incidence with use of age-adapted GFR thresholds as compared with the standard KDIGO criteria.

Funding: Government Support - Non-U.S.

PO2335
Estimated Glomerular Filtration Rate Equations Based on Cystatin C Are Determined by Bioimpedance-Retrieved Fat Mass Index in Swedish Adults
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Background: The growing burden of obesity and its associations with chronic kidney disease (CKD) is becoming a hot topic for nephrologists. CystatinC, a marker of kidney function, tends to be increased in obesity. We hypothesize that bioimpedance acquired fat mass index acquired is associated with estimated glomerular filtration rate (eGFR) based on cystatinC.

Methods: 5061 subjects, born 1926-45, were selected from the population based Malmö Diet and Cancer cohort (MDC CC). They underwent body composition analysis on BIA-103 RJL system and biochemistry during the year 1991-95. Men and women were divided into 3 groups according calculated fat mass index z-score (FMIZ): low(>1), middle(-1<1,1), high(-1). eGFR calculated using 4 equations: Chronic Kidney Disease Epidemiology Collaboration 2012 (CKD-EPI creatinine, CKD-EPI cystatinC), cystatinC eGFR based on Caucasian, Asian, pediatric, and adult cohorts (CAPA), the Lund-Malmö revised creatinine equation (LMC). The mean slope was -1.70 ± 2.63 ml/min per 1.73 m² per year when estimated by the mixed-effects model and -1.69 ± 3.18 ml/min per 1.73 m² per year when estimated by Nelder-Mead algorithm.

Results: CystatinC correlated with fat weight (kg), FMI and FMIZ in both sexes, meanwhile creatinine was not associated with muscle mass. Significant sex difference observed in high FMZ group revealing lower CAPA and lower CKD-EPI cystatin C values in women and no differences in creatinine based eGFR both in men and women (Fig. 1). Women with high FMZ tended to have higher body mass index compared to men (p<0.001) and no age difference. Muscle mass remained almost unchanged in FMI groups in both sexes.

Conclusions: The correlation between cystatinC and fat weight may be due to several reasons. Obesity induced CKD is one. Further studies are warranted to exclude that cystatinC originates from adipose tissue. The use of cystatinC eGFR equations should be used with caution in obese individuals, especially in women.

Fig.1 Kidney function calculated by different estimated glomerular filtration rate equations with regards to sex and fat mass index z-score group

PO2336
Estimated GFR Slope and Risk of Subsequent ESKD in Japanese Patients with CKD: The CKD-JAC Study
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Background: Slope of estimated glomerular filtration rate (eGFR), or rate of eGFR change, is a well-accepted measure of kidney disease progression. Previous studies have shown strong associations between eGFR slope and subsequent ESKD, but there is a dearth of evidence in Asian populations. We aimed to investigate the association between eGFR slope and subsequent ESKD in Japanese patients with CKD using data from the Chronic Kidney Disease Japan cohort (CKD-JAC study).

Methods: We investigated the association of 2-year change in eGFR slope with ESKD over the long term. Slopes were estimated with the linear mixed models with an unstructured variance-covariance matrix, random intercept, and random slope for each individual to estimate slope (mixed model slope) or the least-squares linear regression (least-squares slope). We also conducted sensitivity analyses to investigate the association of 1- and 3-year changes in eGFR with ESKD.

Results: Of the total 2966 participants, we included 2381 individuals after excluding those who were censored within the 2-year baseline period (n=509) and those with eGFR measured less than twice each year (n=76). The mean slope was -1.70 ± 2.63 ml/min per 1.73 m² per year when estimated by the mixed-effects model and -1.69 ± 3.18 ml/min per 1.73 m² per year when estimated by Nelder-Mead algorithm.

Conclusions: The association between eGFR slope and ESKD was pronounced when the slope was estimated over a longer baseline period.

Funding: Commercial Support - Kyowa kinen Co.,Ltd.

PO2337
REVEAL-CKD: Prevalence of Undiagnosed Early CKD in France and Japan
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Background: Screening and monitoring of at-risk populations, such as those with type 2 diabetes (T2D), is necessary for early detection and management of chronic kidney disease (CKD). Global prevalence of undiagnosed early CKD and associated factors have not been recently studied. The objective of the REVEAL-CKD study is to assess the prevalence of undiagnosed stage 3 (S3) CKD.

Methods: REVEAL-CKD is a multi-national, multi-region secondary data study. Data for the French study cohort was extracted from THIN Cegedim (Cegedim Health Data, Boulogne-Billancourt, France) an electronic medical record (EMR) database from outpatient primary care practices. Data from the Japanese cohort was collected from THIN Japan (linking hospital systems) EMR with reimbursement claims, was used for the

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Japanese cohort. The study population included patients aged 18 years between 2015-2020 with two consecutive estimated glomerular filtration rate (eGFR) readings ≥30 and <60 mL/min/1.73 m² recorded >90 and ≤730 days apart. Undiagnosed CKD was defined as the absence of an associated CKD diagnosis code any time before 12 months prior to the first eGFR measurement and up to 6 months after the second eGFR. Presence of recorded urine albumin-to-creatinine ratio (UACR) was also assessed.

Results: After applying the eligibility criteria the study cohorts included 23,160 patients in France and 90,902 in Japan, and the proportions of patients with undiagnosed stage 3 CKD were 95.4% (95% CI 95.1, 95.7) and 92.1% (91.9, 92.3), respectively. Prevalence in both cohorts was consistent across subgroups stratified by age (45-65, and >65 y), sex, and presence of comorbidities (T2D, HTN, and heart failure) with the exception of T2D in Japan, where undiagnosed prevalence was 82% (95% CI 81.9, 83.0). Only 2.4% of patients in the cohort in France and 5.5% in Japan had a record of a UACR value.

Conclusions: The results presented here indicate that a high proportion of early CKD patients in France and Japan are undiagnosed, with a very low frequency of UACR testing. With the advent of promising novel therapies to mitigate disease progression in patients at risk and the potential to improve patient outcomes, a clear imperative exists to highlight the importance of early CKD detection, diagnosis, and intervention.

Funding: Commercial Support - AstraZeneca

PO2338
Trends in CKD Awareness and Related Clinical and Demographic Characteristics in Korea from 1998 to 2018

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Background: Chronic kidney disease (CKD) is a common and growing problem in Korea. Although CKD awareness is the first step of CKD management, evidence indicates that the rate of CKD awareness is unsatisfactory worldwide. Thus, we investigated the trend of CKD awareness for CKD patients in Korea.

Methods: Through analyzing data of Korea National Health and Nutrition Examination Survey (KNHANES) in 1998 (phase I), 2005 (phase II), 2010-2012 (phase V), and 2016-2018 (phase VII), we evaluated the rate of CKD awareness according to CKD stage in each phase of KNHANES. CKD was defined when estimated glomerular filtration rate was below 59 ml/min/1.73 m². Clinical and sociodemographic characteristics were compared between CKD awareness and unawareness groups. Multivariate regression analysis was used to calculate adjusted odds ratio (OR) and 95% confidence interval (CI) for CKD awareness (adjusted OR [95% CI]) in given socioeconomic and clinical factors.

Results: The overall rate of CKD awareness remained at low levels less than 4.1% across all phases of KNHANES. In particular, the rate of CKD awareness was remarkably low in stage 3 CKD. Compared to CKD unawareness group, CKD awareness group was of young age, higher income, higher education, more medical aid, higher prevalence of comorbidities, and more advanced CKD. In multivariate analysis, CKD awareness was significantly associated with younger age (0.95 [0.93-0.98]), medical aid (4.35 [1.95-9.73]) and renal function (0.90 [0.88-0.92]).

Conclusions: The rate of CKD awareness has been consistently low in Korea. This trend warrants the special endeavor to promote CKD awareness in Korea.

PO2339
Usefulness of Machine-Learning-Predicted Probability as a New Risk Index for Prediction of Renal and Life Prognoses of CKD

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Background: Personalized and accurate prediction is useful for chronic kidney disease (CKD) therapy. Predialysis death is a competitive risk of dialysis in CKD patients and lowers the accuracies of the prediction of their renal and life prognoses. Thus, we determined whether machine-learning-predicted probability works as an index for the risks of predialysis death and dialysis in CKD patients and attempted its application.

Methods: We constructed a database of electronic-medical-record data of CKD patients in Japan, and developed risk prediction machine-learning models using random forest (RF), Gradient Boosting Decision Tree, and eXtreme Gradient Boosting for the prediction of dialysis and death over 1 year. The performances of the probabilities estimated using the models were compared by the bootstrap method with those of clinical indices in a prospective cohort study of CKD patients (n=67,957).

Results: Sixteen models were developed and showed statistically significantly higher C-statistics than clinical indices. Two RF models including 22 or 8 variables showed high C-statistics: 0.932 (95% CI 0.916, 0.948) and 0.95 (0.915, 0.945), respectively, which were higher than estimated glomerular filtration rate and urinary protein levels (p=0.0001). Cox proportional hazards models with the spline term showed the relationship between the high probabilities and the high outcome risks (p<0.0001). We also developed a Web-based risk prediction system using those two models.

Conclusions: This study showed that the machine-learning-based probability is useful as a new risk index for dialysis and death and applicable to clinical practice.

PO2340
A Machine Learning Algorithm to Identify Patients with Possible Non-Dialysis-Dependent CKD

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Background: The DAKOTAH study is a retrospective study of patients with non-dialysis-dependent chronic kidney disease (NDD CKD) in France based on data from the Echantillon Généraliste des Bénéficiaires database. A stepwise machine learning approach was used to identify patients with possible NDD CKD who could not be captured using the NDD CKD case definition (Figure). The potential ‘CKD’ population was designated as patients with a diagnosis of diabetes, cardiovascular disease or hypertension, or with ≥2 prescriptions for antidiabetic and/or antihypertensive drugs, during 2012–2017. Second, an unsupervised algorithm was trained to identify patients very likely to have CKD (‘possible CKD’) in the potential CKD population. Similarity between patients was based on CKD-related variables: sex; number and duration of hospitalizations for renal failure; number of GP visits.

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PO2341

Developing an Electronic Health Record (EHR)-Based Model for Delineating Advanced CKD Cohort in Veterans Affairs (VA) System

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Background: Late diagnosis of chronic kidney disease (CKD) and non-referral to nephrology are important limiting concerns for pre-end stage kidney disease (ESKD) nephrology care, including dialysis modality education. Querying existing electronic database with longitudinal patient-level data can improve recognition of advanced stage 4–5 CKD and facilitate evidence-based pre-ESKD care. Using a mixed approach of electronic query followed by manual chart review, we report the development of an Electronic Health Records (EHR)-based model that allows identification and quantification of advanced CKD burden in a regional Veterans Healthcare System (VHS).

Methods: We identified all Veteran enrollees at a large regional VHS using VA Informatics & Computing Infrastructure data set. Among these, we identified all Veterans with an eGFR below 30 ml/min or an existing ICD-10 diagnostic code for stage 4–5 CKD within last 12 months. We applied diagnostic and procedure codes for dialysis, ESKD, and acute kidney injury (AKI) in an iterative approach to improve the accuracy of identifying non-dialysis advanced CKD cohort.

Results: Of 148,164 active enrollees within VHS, our initial model of using a single eGFR <30 ml/min identified 3,813 (2.57%) Veteran enrollees with advanced CKD. Manual review of a select cohort (n=787) showed 63.3% error rate, with high rates of ESKD and AKI being major confounders. Successive iterations involved exclusions of ESKD and AKI codes and incorporation of a second latest eGFR >90 days before latest eGFR (n=1,329) Veteran with the residual error of 14.4% on manual chart review without the possibility of further automated exclusions. Of these, 872 were found to have definitive advanced CKD and 457 were classified as probable advanced CKD based on whether both or only one of the latest two eGFRs more than 90 days apart were below 30 ml/min with CKD.

Conclusions: An EHR-based model to identify advanced CKD can be successfully developed for a regional VHS with over 85% accuracy. Further testing is needed to determine its wider applicability across additional VHA sites, and if validated, this model can be applied across the VHA electronic data to identify the burden of advanced CKD for needs assessment and clinical care among Veterans.

Funding: Veterans Affairs Support

PO2342

Developing a Prediction Model for Incidence of Newly Detected CKD Among US Veterans, 2009-2018

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Background: Both screening and awareness of CKD remain low in the US. We sought to develop a tool to aid physicians and health systems in identifying patients most likely to develop CKD, using a large national sample of patients in the Veterans Health Administration (VHA).

Methods: Using 29,524,195 observations from Veterans, aged 18+ with outpatient s. creatinine data (2006-2018), we modeled the probability of newly detected CKD using discrete survival methods. Veterans were screened for 2–3 years to ensure no pre-existing CKD. Newly detected CKD was defined as a diagnosis or by laboratory measurement (eGFR <60 ml/min/1.73m2 or UACR 30+ mg/g). Predictors included demographics, comorbidities, nephrotoxic medications, and laboratory values updated each year. Model fit assessed by the c-statistic.

Results: The cohort had a mean age of 59 years with 89% males and 15% Black race. The average eGFR was 87 ml/min/1.73m2 and median UACR was 8 mg/g, with an average of 3.9 years follow-up. The largest predictors of incident CKD were diabetes, kidney stones, urinary tract infections, sickle cell anemia, and an eGFR between 60-69 ml/min/1.73m2. Concordance was high (c-statistic=0.84, Fig: ROC curve). Using a threshold of 3% for screening would require testing ~1/3 of Veterans (~1 million per year), yielding an 83% true positive and a 17% false negative rate.

Conclusions: We are able to accurately predict the probability of incident CKD in the VHA. This predictive model has the potential for improving targeted screening efforts for CKD, facilitating its earlier detection, raising awareness, and reducing disparities. If externally validated, the impact of these findings would be generalizable to populations/ health systems beyond the VHA.

Funding: Veterans Affairs Support

PO2343

A Population Health Survey-Based Prediction Equation for Incident CKD: The CKD Population Risk Tool CKDPort/PREDICT-CKD LIFESTYLE

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Background: Chronic kidney disease awareness among the general public is less than 10%. Patients’ health behaviours are known to be associated with CKD development and disease progression. Prediction tools that engage the general public with their self-reported health information could increase awareness, identify modifiable lifestyle risk factors, empower patients, and prevent disease. The study objective was to develop and validate a population health survey-based prediction equation to determine the risk of incident CKD in the general public.

Methods: Participants: Participants completed the Canadian Community Health Survey (CCHS) were linked to laboratory and hospital admission data between 2000 and 2015 in Ontario, Canada. The primary outcome was incident CKD (eGFR < 60 ml/min/1.73m2) within up to 8 years of follow-up. Models accounted for the competing risk of all-cause mortality. The CCHS is a random, comprehensive, prospective, general population survey that captures information on demographics, co-morbid illnesses, lifestyle and behaviours, diet, body mass index and mood. External validation was performed using data from the UK Biobank.

Results: From 22,200 eligible adults, 1,981 (8.9%) developed incident CKD during a mean follow-up time of 8 years. Domains included in the final reduced model were baseline eGFR, smoking, alcohol, physical activity, education, mood, fruit and vegetable intake, diabetes, hypertension, heart and lung disease, urinary incontinence, cancer, and BMI. The model demonstrated excellent discrimination in individuals with and without a baseline eGFR measure (5-year c-statistic with baseline eGFR: 0.84 95%CI 0.82-0.85, without 0.81 95%CI 0.80-0.82), was well calibrated (Brier score at 5-years with baseline eGFR: 0.07 95%CI 0.007-0.08, without 0.08 95%CI 0.07-0.08), and was consistent in a sensitivity analysis using 2 measures of eGFR > 90 days apart to define the outcome. The model was consistent with external validation.
Conclusions: Lifestyle and health behaviour information from population-based health surveys can predict incident CKD in the population with excellent discrimination and can be used to improve public engagement in CKD awareness.

**PO2344**

**Predicting ESKD Risk and Time to RRT Initiation Based on Past Slope and Current Value of eGFR: The CKD-JAC Study**

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**Background:** Past slope and current estimated glomerular filtration rate (eGFR) are used to predict future risk of end-stage kidney disease (ESKD) and time to renal replacement therapy (RRT) initiation in clinical practice, but there is limited quantitative evidence supporting this practice. To address this, we analyzed data from the Chronic Kidney Disease Japan Cohort (CKD-JAC) Study.

**Methods:** We investigated the association of 2-year slope eGFR, estimated using linear mixed models, with subsequent risk of ESKD using Cox regression models adjusting for eGFR and other potential confounders collected 2 years after cohort entry. We calculated the net reclassification improvement (NRI) to assess whether adding past slope to age, sex, eGFR, and urine albumin-to-creatinine ratio (UACR) improves ESKD risk prediction. We predicted time to RRT initiation based on the past slope and current eGFR, assuming eGFR of 6 mL/min/1.73m² to be the timing of RRT initiation, and compared it with actual time to RRT initiation.

**Results:** We included 2381 participants who had survived free of ESKD for 2 years and with eGFR measurements at least twice each year. The mean 2-year eGFR slope was -1.70 ± 2.63 mL/min per 1.73 m² per year. During a median follow-up of 4.7 years after the 2-year slope evaluation period, 175 participants died and 810 reached ESKD requiring RRT. In adjusted analysis, lesser slope of eGFR decline was associated with lower risk of ESKD (hazard ratio per 1 mL/min per 1.73 m² per year, 0.89; 95% CI, 0.87 to 0.90). Adding past eGFR slope to age, sex, eGFR, and UACR substantially improved classification accuracy in 2-year risk prediction of ESKD, with an NRI of 0.343 (95% CI, 0.036 to 0.662). Among 560 individuals who were predicted to initiate RRT during the study period and actually reached ESKD, the median predicted time to RRT was 30.6 months (IQR, 12.3 to 47.0), and the median of these differences was -1.5 months (IQR, -14.3 to 7.3). The prediction became more accurate as RRT initiation was predicted to occur in the closer future.

**Conclusions:** Our results indicate that past eGFR slope adds information to ESKD risk assessment beyond current eGFR and that combination of these informs prediction of time to RRT initiation.

**Funding:** Commercial Support - Kyowa Kirin Co., Ltd.

**PO2345**

**Need and Preference Assessments for Renal Care and Comprehensive Pre-ESKD Education Services for Advanced CKD Veterans**

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**Background:** Current guidelines suggest Specialty Renal Care (SRC) and comprehensive pre-end-stage kidney disease (ESKD) education (CPE) Services for all patients with advanced, stage 4/5 chronic kidney disease (CKD). Despite this, half of incident ESKD patients receive none or <6-months pre-ESKD renal care. Estimating outstanding needs and understanding Veterans preferences for receiving such care can improve renal care allocations and quality. Veterans Health Administration (VHA). We conducted a community-based evaluation of advanced CKD Veterans to assess their current state of and outstanding needs and preferences for SRC and CPE at North Florida/South Georgia VA system (VHS).

**Methods:** Through an iterative approach of electronic health records (EHR) query followed by manual review of randomly selected EHRs, we created a model for isolating advanced CKD cohort at NF/SG VHS. We then sorted the cohort in a random order, and mail-invited Veterans with up to three attempted calls for those who do not call back to actively opt-out of participation. Surveys were conducted for those agreeable for participation.

**Results:** Of the 148,164 active enrollees, we identified 1329 (0.9%) Veterans with advanced CKD. Of the 226 Veterans randomly selected mail-invites, 166 made final contact; 94 completed, 50 asked for more time, and 22 refused to participate in the surveys. Awareness of CKD (91%) and prevalence of renal care (86%) were high among respondents albeit, 40% received renal care from non-VAMC providers. Aggregate outstanding need for VA-preferred SRC and CPE were 14(15%) and 69(73%) respectively. Among those with preferences for receiving SRC were 64(83%) & 80(97%), and receiving CPE were 21(30%) & 34(50%) through in-person and telemedicine-based care respectively. There were significant differences in needs and preferences across the socio-demographics and rural-urban spectrum.

**Conclusions:** Despite high awareness of CKD diagnosis and prevalence of SRC, there is significant outstanding need for targeted CPE services in advanced CKD Veterans. Further validation of this model at additional VHSs and its application across the system can allow projection of outstanding needs for SRC and CPE across the VHA and guide appropriate allocation of resources to improve Veteran outcomes.

**Funding:** Veterans Affairs Support

**PO2346**

**Artificial Intelligence-Based Prediction Model for Screening Veteran Patients at Risk of Developing CKD**

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**Background:** Developing effective screening tool for Chronic kidney disease (CKD) helps in reducing morbidity, mortality as well as cost and burden to the health system. Here we present preliminary result on feasibility and performance of employing Convolutional Neural Network (CNN) prediction model in detecting patients who are at risk of CKD based on longitudinal data from Electronic Health Records (EHR).

**Methods:** A synthetic dataset containing a total of 100,000 synthetic patient records, derived from cross-sectional cohort of Veteran from the general population, was used to train and validate the prediction model. The dataset was generated by using Synthea™, a patient generator tool, and contains standard data elements that are commonly used in major Electronic Health Record systems. A total of 12,503 patients with CKD and 18,212 patients without CKD matched by propensity score along with 290 other features including anthropometrics, medication, comorbidities, and laboratory data were used to train and validate the prediction model.

**Results:** The CNN algorithm has been designed, implemented and tested using the synthetic dataset, achieving precision of 0.918, recall of 0.739, specificity of 0.983, accuracy of 0.932, and AUROC of 0.937 as depicted in Figure 1. Additionally, based on the dataset, age, diabetes, elevated BMI and medication taken, specifically 24 HR Metformin Hydrochloride, represent the topmost important features to predict the onset of CKD.

**Conclusions:** Using CNN and synthetic veteran patient dataset, we have demonstrated a viable prediction model for CKD detection in healthy patients at-risk of CKD using longitudinal data from EHR system. The prediction model can be easily deployed in a CKD screening program in healthcare institutions with existing EHR systems.

**Funding:** Veterans Affairs Support

**Figure 1: Onset of CKD Prediction Metrics**

**PO2347**

**Identifying Hotspots of CKD in the United States with Data from a Large National Clinical Laboratory Network**

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**Background:** CKD is typically detected through routine laboratory testing. We sought to assess the feasibility of analyzing data from one of the largest clinical laboratory networks in the US to map CKD hotspots across the nation.

**Methods:** Laboratory results for serum creatinine were analyzed from a nationally standardized laboratory platform with the Laboratory Corporation of America (Labcorp) across a 6-month period (July to December 2019, n=21,884,579). We assessed the percent of results with eGFR <60 ml/min/1.73m² (CKD stages 3-5) at US county-level (n=2,972 counties, <11 results supressed). Due to lack of race information, the CKD-Epi equation without the race coefficient was employed for the entire population. Hotspot analyses were performed using the GeoDa software.

**Results:** The total population was 44% male with mean age of 56 years. eGFR results < 60 ml/min/1.73m² totalled 4,165,540 (19%) and county-level distribution ranged from 0% to 75% (Fig. A) with an overall mean age of 72 and 44% male. Results of the hotspot analysis (Fig. B) shows the percent of decreased kidney function varies markedly across

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the US, with clear hot spots in the south and southeast, far northeastern Pacific West, Missouri, Colorado, and Utah. The upper midwest and most of the northeast appeared as cold spots, with the southwest being neither a hot nor cold spot.

Conclusions: We demonstrate the feasibility of leveraging a large national laboratory network database for mapping the distribution of county prevalence of CKD and identification of CKD hotspots. On-going work is focusing on understanding factors underlying these hotspots and will help guide population health improvement, raise awareness, guide health policy and direct public health action and quality improvement efforts related to kidney disease.

**Funding:** Commercial Support - Laboratory Corporation of America Holdings

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**PO2348**

**Healthy People 2020 Final Review of National CKD Objectives**

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**Background:** Chronic Kidney Disease (CKD) is a significant public health problem in the United States (US) and a major source of disability and poor quality of life for those afflicted. An estimated 14.9% of adults ages 20 or older had physiological evidence of CKD determined from data collected through the 2015-18 National Health and Nutrition Examination Survey (NHANES). In 2018, more than 130,000 people in the US began treatment for end-stage kidney disease (ESKD), the final stage of CKD. Kidney diseases are one of the leading causes of death in the US, and CKD exacts a high economic burden. Overall Medicare costs for people with CKD were over $81.8 billion in 2018, or $23,700 per person. Total Medicare spending (excluding prescription drugs) for patients with ESKD reached $36.6 billion in 2018, or $80,000 per person, accounting for about 7% of the Medicare paid claims costs.

**Methods:** Reflecting the importance of CKD, 24 CKD objectives were included in the Healthy People 2020 (HP2020) as national health goals. These objectives focused on improving cardiovascular care in patients with CKD; increasing the proportion of patients with CKD and diabetes who received recommended evaluation and treatment; improving follow-up care in people with acute kidney injury, reducing the death rate and percentage of the US population with CKD, and increasing CKD awareness in persons with impaired kidney function. All CKD objectives in HP2020 were measurable, having at least one data point from national data systems including the NHANES, National Death Index, and the US Renal Data System.

**Results:** As of the HP2020 Final Review, 15 objectives had met their target (n=11) or showed improvement (n=4). Four objectives, including CKD prevalence and awareness, showed little or no detectable change, and three objectives on receiving kidney transplant and on the number of deaths for persons with a functioning kidney transplant moved away from the target. The remaining two objectives were informational (i.e., no targets set) and were not evaluated. Disparities persisted by sex, age/ethnicity, and socioeconomic status.

**Conclusions:** Several of these measures will continue to be tracked over the next decade as CKD objectives in HP2030. The HP website includes HP2020 and HP2030 data.

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**PO2350**

**International Variation in the Incidence of Kidney Failure in the CKDopps**

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**Background:** Data from kidney replacement therapy (KRT) registries suggest large international variation in the incidence of kidney failure (KF). However, these data strongly depend on treatment availability and practices of KRT initiation. Measuring the incidence of sustained low eGFR, i.e. <15 mL/min/1.73 m², would enable to explore differences in progression to KF across countries and after adjusting for individual characteristics.

**Methods:** We analyzed data from patients with CKD stages G3-G4, under nephrology care in representative samples of clinics in Brazil (n = 747), France (n = 2786), Germany (n = 2539), and the United States (n = 1309), participating in the CKDopps. We used Weibull PH models to compare the risk of KF initiation across countries, and illness-death models for interval censored data, to compare the risk of sustained low eGFR and to estimate probabilities of KF (composite of KRT initiation and sustained low eGFR).

**Results:** Median age (years) ranged from 67 in Brazil to 75 in Germany, mean baseline eGFR (mL/min/1.73m²) from 27 in Germany to 33 in France; male sex from 52% in the United States to 66% in France. After a median follow-up of 4.0 (2.6-5.0) years, 1648 patients met a sustained low eGFR, and 1343 initiated KRT. Compared with the United States, the adjusted hazard ratios indicated 44% lower risk of KF initiation in Brazil (HR 0.59, 95% CI 0.39 to 0.89) and similar risk in France (1.05, 95% CI 0.83 to 1.33), and 41% higher risk in Germany (95% CI 1.12 to 1.77). The same pattern was observed for sustained low eGFR, but differences were narrowed. Two-year cumulative probability of KF ranged from 13% in Brazil to 16% in Germany (Figure).

**Conclusions:** The incidence of KF varies across CKDopps countries, but to a much lesser extent than the incidence of KRT initiation. This finding highlights the relevance of such approach to disentangle the effects on KF progression from those on care.

**Funding:** Commercial Support - Akriba Therapeutics, Inc.; Agena Inc (since 1996, founding sponsor); AstraZeneca Pharmaceuticals LP; Bard Peripheral Vascular, Inc.; Baxter Healthcare Corp; Bayer Yakuhin, Ltd; Chugai Pharmaceutical Co., LTD; Dyalize Direct, LLC; Fresenius Medical Care Asia-Pacific Ltd; GlaxoSmithKline LLC; Japanese Society for Percutaneous Dialysis; JMS Co., Ltd.; Kidney Research UK Kidney Foundation Japan; Kissei Pharmaceutical Co., Ltd; Kyowa Kirin Co., Ltd. (since 1999 for Japan DOPPS); Merck Sharp & Dohme Corp; Nikkiso Co., Ltd.; ONO Pharmaceutical Co., Ltd; Sanofi-Aventis Deutschland GmbH; Terumo Corporation; Torii Pharmaceutical Co., Ltd; Vifor Fresenius Medical Care Renal Pharma Ltd, Government Support - Non-U.S.
PO2351
Development and Validation of an Algorithm to Predict Risk of 90-Day Hospitalization for Patients with CKD

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Background: Patients with chronic kidney disease (CKD) are at higher risk of being admitted to the hospital than the general population. Hospitalizations in CKD patients are often associated with higher medical costs, increased morbidity, and increased risk of transition to end-stage kidney disease (ESKD). Nationally, there seems to be an increasing focus on the management of CKD upstream of ESKD. Identification of CKD patients at greatest risk of hospitalization may hold promise to improve clinical outcomes and judicious allocation of health care resources.

Methods: This model was developed using Medicare Part A and Part B claims from calendar years 2017-2019. Data from 50,000 unique patients diagnosed with CKD stages 3-5, no evidence of ESKD, or claims for dialysis were split into derivation (n ~ 40,000) and validation (n ~ 10,000) sets. The predicted outcome was all-cause hospital admissions, which occurred in 10.4% of patients 90 days after scoring. Overall performance of candidate models was assessed using area under the curve (AUC) of the receiver operating curve in addition to positive predictive value (PPV) and sensitivity across a variety of thresholds.

Results: The best model that we tested was a gradient boosting machine algorithm based on 399 input terms, which represented 147 unique clinical constructs. The model demonstrated good ability to discriminate (AUC = 0.73), which was stable when tested in a validation set (AUC = 0.73). The PPV in the validation set was 30.6%, 24.0%, and 21.6% at the 10%, 20%, and 30% thresholds, respectively. The sensitivity in the validation set was 28.8%, 45.3%, and 60.9% at the 10%, 20%, and 30% thresholds, respectively.

Conclusions: We developed an algorithm that uses only information derived from medical claims to identify CKD 3-5 patients at highest risk of being hospitalized in the near-term. This algorithm could be used as a decision support tool for clinical programs focusing on the management of CKD patient populations.

PO2352
CKD and Risk of Incident Hospitalization with Clostridioides difficile Infection: Findings from the Atherosclerosis Risk in Communities Study

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Background: Clostridioides difficile (C. difficile) infection is a major public health priority in the US. Individuals with CKD are at high risk of hospitalization and infection in general; however, the association of CKD with the risk of C. difficile disease has not been systematically evaluated.

Methods: We evaluated data from 11,017 participants of the ARIC Study (mean age, 63 years; 56% female; 22% Black) to explore the association of CKD with the risk of incident hospitalization with C. difficile infection. We categorized the study population into four risk categories defined by eGFR and ACR: CKD was defined as eGFR <60 ml/min/1.73m2 or ACR ≥30 mg/g, and no CKD was defined as low risk. CKD was subdivided into moderate, high, and very high risk. Adjusted HRs were estimated using Cox regression models.

Results: During a median follow-up of 20.1 years, 309 participants had incident hospitalization with C. difficile infection. In multivariable Cox regression analysis, there was a graded association of CKD risk category with the risk of hospitalization with C. difficile infection, with adjusted HRs of 4.74 [2.29 to 10.23] for CKD with very high risk, 2.33 [1.39 to 3.90] for CKD with high risk, and 1.34 [0.93 to 1.93] for CKD with moderate risk compared to no CKD (P-for-linear-trend, <0.001) (Figure 1). These findings were consistent in subgroup analyses and sensitivity analyses, including analyses that accounted for frequency of prior hospitalization and for the risk of hospitalization itself.

Conclusions: In this community-based cohort, CKD was associated with the risk of hospitalization with C. difficile infection. Individuals with CKD should be a key target population for public health initiatives and clinical approaches to prevent C. difficile infection.
PO2354
Albuminuria Testing in Hypertension and Diabetes
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Background: Albuminuria is an under-recognized component of chronic kidney disease (CKD) definition, staging, and prognosis. Despite significant advances in therapies for patients with albuminuria, guidelines, particularly for hypertension, conflict on recommendations for urine albumin-to-creatinine ratio (ACR) measurement.

Methods: We separately analyzed 1,305,841 adults with diabetes in 25 cohorts and 2,111,587 non-diabetic adults with hypertension in 21 cohorts from the CKD Prognosis Consortium. We estimated ACR testing rates during a 2-year window, and developed and utilized risk prediction models for prevalent albuminuria (ACR ≥30 mg/g) to determine if high-risk patients for albuminuria are more likely to be tested and to estimate the burden of undetected albuminuria.

Results: Overall, the ACR testing rate was 35.3% in diabetes and 4.1% in hypertension. Among patients with diabetes, testing rates varied greatly across the different health systems and were largely unrelated to the predicted risk of prevalent albuminuria (Figure A). Among patients with hypertension, testing rates were low and also unrelated to the predicted risk of prevalent albuminuria (Figure B). The estimated ratio (cohort range) of undetected (due to lack of testing) to detected prevalent albuminuria was 1.8 (0.2-7.6) in diabetes and 19.5 (0.8-78.3) in hypertension.

Conclusions: Real-world ACR testing is low, particularly among non-diabetic patients with hypertension, and testing is unrelated to predicted risk. There are large swaths of the population with diabetes or hypertension with undiagnosed CKD, suggesting that regular albuminuria screening should be emphasized for early detection of CKD and appropriate initiation of treatment with cardiovascular and kidney benefits.

Funding: NIDDK Support, Private Foundation Support

PO2355
Increasing Proteinuria Screening to Reduce CKD Progression in High-Risk Patients

Background: Chronic Kidney Disease (CKD) affects 15% of the US population and is underrecognized by patients and clinicians. Screening for proteinuria is essential in prompting primary care doctors (PCPs) to initiate treatments proven to decrease progression to end stage renal disease, cardiovascular events and mortality in these patients. However, screening rates remain low -- one study showed only 13% of adults with CKD had proteinuria/albuminuria testing. Our objective was to identify the high-risk patients with CKD who did not receive annual proteinuria testing, with the long-term goal of addressing barriers to quality care.

Methods: We identified 4214 patients between October and December 2020 within our healthcare system who had a diagnosis of CKD 3 or 4 and categorized them as having diabetes/not having diabetes and having hypertension/not having hypertension. We then assessed how many patients had proteinuria testing in the last year, which included a urinalysis, urine protein to creatinine ratio or urine microalbumin.

Results: Results showed that 100% of patients with diabetes had screening in the last year regardless of CKD stage or hypertension (HTN). For those with CKD3A/HTN only 14% (171/1226) had screening in the last year and those with CKD3B/HTN only 28% (98/347) had screening in the last year. For patients with CKD3A and CKD3B (without HTN/diabetes), 14% (125/892) and 34% (48/142) respectively had appropriate screening.

Conclusions: Within our large, integrated healthcare system, rates of proteinuria screening in diabetic patients were strikingly high. In contrast, most patients with CKD3 and HTN did not receive testing in the last year. One explanation for this is the workflow in place to help PCPs manage their patients with diabetes, which includes automated reminders and a dedicated multidisciplinary team. Applying a similar systematic, protocol-based workflow to all patients with CKD may help to increase screening rates and improve overall quality of care.

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PO2356
The Association of CKD Severity with Stroke Subtype Using the TOAST Classification
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Background: Ischemic stroke affects approximately 67.5 million people worldwide. The risk of acute ischemic stroke largely increases with advanced chronic kidney disease (CKD). However, whether the risk of specific ischemic stroke subtype varies with declining kidney function remains unclear. The purpose of this study was to assess the association between ischemic stroke subtypes (cardioembolic [CE], arterial, lacunar, other) classified using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) and CKD stage.

Methods: This is a cross-sectional, retrospective cohort study of adults (≥18 years) with an ischemic stroke who presented to the emergency department in Ontario, Canada between April 1, 2002- March 31, 2013 and who had an inpatient serum creatinine measurement or were on chronic dialysis. All patients captured in the stroke registry with an estimated glomerular filtration rate (eGFR) were included and CKD severity was categorised as ≥60, 30-59, <30 mL/min/1.73m² or chronic dialysis.

Results: A total of 17,434 individuals with an ischemic stroke were included (58.9% eGFR ≥60, 34.7% ≥30-59, 6.0% ≤30, 0.5% on chronic dialysis). Normal/mildly decreased eGFR were associated with the risk of CE stroke on chronic dialysis patients (37.3%). The odds of CE stroke vs. non-CE stroke were eGFR 30-59 odds ratio (OR) 1.20 95% CI 1.10-1.31, eGFR 30-59, 6.0% ≤30, 0.5% on chronic dialysis; mean age of 73 years; 48% female). Among patients with an eGFR 30-59 (30.4%) and ≤30 (50.6%), CE stroke was more common compared to those with an eGFR >60 (36.8%) or on chronic dialysis patients (37.3%). The odds of CE stroke vs. non-CE stroke were eGFR 30-59 odds ratio (OR) 1.25 95% CI 0.68-2.28, eGFR 30-59 OR 1.21 95% CI 1.02-1.44, dialysis OR 0.86 95% CI 0.84-1.57, eGFR=60 (referred). We found lower adjusted odds of lacunar stroke in those with advanced CKD (lacrinar vs. non-lacunar: eGFR 30-59 OR 0.85 95% CI 0.77-0.93, eGFR=30 OR 0.73 95% CI 0.61-0.88, dialysis OR 1.25 95% CI 0.68-2.28, eGFR=60 (referred). In subgroup analyses (eGFR>30 and ≤30), CE strokes were also more common in those >65 years, with atrial fibrillation, no anticoagulation or an INR <2.

Conclusions: Chronic kidney disease (eGFR=60, pre-dialysis CKD) is associated with a higher odds of CE stroke compared to patients with normal to high kidney function or those on chronic dialysis. Normal/mildly decreased eGFR were associated with the development of lacunar strokes. Detailed stroke subtyping in CKD may therefore provide mechanistic insights and refocus treatment strategies in this vulnerable group.
PO2357
Major Cardiovascular Events and Subsequent Risk of Kidney Failure: A CKD Prognosis Consortium Study

Background: Chronic kidney disease (CKD) increases risk of cardiovascular disease (CVD). However, less is known about how CVD is associated with future risk of kidney failure. We quantified the association of incident major CVD events with subsequent risk of kidney failure requiring replacement therapy (KFRT).

Methods: We analyzed data on 18,671,338 individuals from 80 cohorts in the CKD Prognosis Consortium with baseline eGFR and CVD data. We assessed impact of incident coronary heart disease (CHD), heart failure (HF), atrial fibrillation (Afb) and stroke events as a time-varying exposure on the outcome of KFRT in Cox proportional hazard models.

Results: Mean age was 55 years and mean eGFR was 88 ml/min/1.73m². 57% were women, 9% were black, 12% had diabetes and 30% had ACR available (median 13 mg/g); 9% had prevalent CHD, 3% HF, 2% Afb, and 4% prior stroke. During follow up there were 175,886 CHD, 480,963 HF, 428,413 Afb and 211,423 stroke incident events and 85,513 (0.5%) patients required KFRT. Each CVD event increased the adjusted hazard ratio (HR) for subsequent KFRT (Table). The increased hazard was highest in the first year after CVD incidence and attenuated thereafter. HRs were modestly weaker at lower eGFR. HF showed the strongest association before and after adjustment for other CVD subtype incidence. Absolute risk of KFRT associated with incident CVD after accounting for competing risk of mortality was higher for lower baseline eGFR and higher ACR, with 2-year KFRT risk of 25%, 28% and 20% for CHD, HF, Afb and stroke in subjects with eGFR 15-29 ml/min/1.73m² and ACR >300 mg/g.

Conclusions: Incident CVD events are strongly and independently associated with risk for KFRT, with greatest risk in the first year following HF, then CHD and stroke. These data highlight need for greater awareness of KFRT risk following CVD events. Specific strategies to elucidate mechanisms and test interventions to reduce the KFRT risk post CVD events warrant investigation.

Funding: NIDDK Support, Private Foundation Support

PO2358
Bidirectional Association Between Kidney Function and Atrial Fibrillation in the General Population
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Background: A potential bidirectional relationship between kidney dysfunction and atrial fibrillation (AF) has been suggested, but has not been studied in the general population. Therefore, we aimed to study the association of different assessments of kidney function with prevalent and incident AF in the general population.

Methods: Participants aged 45 years from the Rotterdam Study, a population-based cohort study, with information on kidney function and AF were included. Assessments of kidney function included single assessments of estimated glomerular filtration rate (eGFR) based on serum creatinine (eGFRcreat), serum cystatin C (eGFRcys), or both (eGFRcreact-cys),; uric acid (ACR) and repeated assessments of eGFRcreact. Incident chronic kidney disease (CKD) was defined as the first time eGFRcreact dropped <60 ml/min per 1.73 m². Cox-proportional hazards, logistic regression, linear mixed, and joint models were used to investigate the associations of eGFR with incident and prevalent AF. Absolute 10-year risk of AF was computed using a competing risk analysis. All models were adjusted for potential confounders including cardiovascular risk factors.

Results: Among 5,138 participants (mean age 64.9 years, 57.2% female). Lower eGFRcreact and eGFRcreact-cys were significantly associated with an increased risk of incident AF (hazard ratio (HR) 1.08, 95% confidence interval (CI) 1.03-1.14 and HR 1.07, 95% CI 1.01-1.14, respectively, per 10 ml/min per 1.73 m² decrease in eGFR), while eGFRcreact was not. No association between uric acid ACR and incident AF was found. Absolute 10-year risk of developing AF increased from 4.9% to 7.1%, when comparing eGFRcreacts of 90 to 60 ml/min per 1.73 m². Prevalent AF (409 cases) was associated with an average 2.85 ml/min per 1.73 m² lower eGFRcreact levels over time and furthermore, a faster decline of eGFRcreact with aging was revealed when compared to participants without prevalent AF. Prevalent AF was also associated with a 1.3 fold increased risk of incident CKD.

Conclusions: Kidney function and AF are bidirectionally associated. This insight may be used to improve prediction and prevention of both conditions, for example through targeted screening programs in the general population.

Funding: NIDDK Support, Other NIH Support - National Institute of General Medical Sciences

PO2359
Longitudinal Ankle Brachial Index and Risk of CKD Progression
Kirsten S. Dorans,1 Jing Chen,2 Xingyan Li,1 Hua He,3 Jordana B. Cohen,4 Alan S. Go,5 L. Lee Hamm,2 Edward J. Horwitz,2 Bernard G. Jaar,2 James P. Lash,2 Rupal Mehta,2 Sylvia E. Rosas,5 Anand Srivastava,3 Jonathan J. Taliecher,6 Jiang He,5 CRIC Study Investigators 1 Tulane University School of Public Health and Tropical Medicine, New Orleans, LA; 2 Tulane University School of Medicine, New Orleans, LA; 3 University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; 4 Kaiser Permanente Northern California, Oakland, CA; 5 Johns Hopkins Medicine, Baltimore, MD; 6 University of Illinois at Chicago, Chicago, IL; 7 Northwestern University Department of Medicine, Chicago, IL; 8 Joslin Diabetes Center, Boston, MA; 9 MetroHealth Medical Center, Cleveland, OH; 10 Cleveland Clinic, Cleveland, OH.

Background: Individuals with chronic kidney disease (CKD) are more likely than the general population to have low or high ankle brachial index (ABI). Low ABI is a predictor of adverse outcomes in CKD, but the relationship of ABI with renal outcomes in CKD is not well studied. As ABI is a simple noninvasive measure, it is important to better understand how ABI relates to CKD progression.

Methods: We carried out a prospective study of 3216 participants with CKD in the Chronic Renal Insufficiency Cohort (CRIC) Study without clinical peripheral arterial disease. We used Cox proportional hazards regression to test the associations of baseline ABI and of cumulative average ABI with risk of CKD progression (50% reduction in estimated glomerular filtration rate (eGFR) or end-stage renal disease (ESRD)) and with risk of ESRD, adjusting for important confounding factors. ABI was measured at annual visits. The shapes of the relationships of exposures with outcomes were assessed with restricted cubic splines.

Results: At baseline, average age was 57.8 years and average eGFR was 44.8 ml/min/1.73m². During follow-up, 1297 individuals had CKD progression (median follow-up 6.9 years, 7 ABI measurements) and 1049 developed ESRD (median follow-up 10.8 years, 6 ABI measurements). In multivariable-adjusted models, there were U-shaped associations of baseline ABI with CKD progression and with ESRD (p for curvatures <0.001). In models adjusted for baseline ABI, similar U-shape relationships were observed for the associations of cumulative average ABI with CKD progression and with ESRD (p for curvatures <0.001; Figure).

Conclusions: This study indicates that both high and low ABI are associated with increased risk of CKD progression and ESRD and that even after adjustment for baseline ABI, repeated measures of ABI averaged over time are associated with CKD progression and ESRD. These findings suggest that ABI can be used to facilitate risk stratification for CKD progression.

Funding: NIDDK Support, Other NIH Support - National Institute of General Medical Sciences

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PO2360

Urinary Peptidome Analysis to Predict the Risk of CKD Progression to Kidney Failure
Zhao Mas,1,2 Oriane Lambert,2 Mohammed Sedki,3 Griet L. Glorieux,1 Francis Verbeke,1 Harald Mischak,7 Justyna Siwy,4 Benedicte Stengel,1 Joost Chanstra,1 Julie Klein,1 CKD-REIN Investigators 1-3, but did not significantly ameliorate the prediction obtained by a combination of RF alone (Figure). We performed on samples collected at baseline using capillary electrophoresis compared to mass spectrometry. Three logistic regression models with elastic-net penalty were developed with different sets of predictors: (1) peptides alone, (2) RF including age, sex, eGFR, and urinary albumin to creatinine ratio, and (3) peptides and RF. RF showed excellent precision, and the addition of peptides did not significantly improve this prediction (Figure).

Conclusions: We have identified a UP signature that predicts RF risk with high precision, but did not significantly ameliorate the prediction obtained by a combination of age, sex, eGFR and albuminuria.

Funding: Government Support - Non-U.S.

PO2361

Plasma Biomarkers in Incidental CKD in Individuals Without Diabetes
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Background: Earlier prediction of CKD may facilitate risk factor mitigation prior to advanced disease. Albuminuria and reduced GFR are relatively insensitive markers of early CKD. We examined the association of several novel plasma biomarkers with incident CKD.

Results: In a cohort of 2089 SPRINT trial participants with baseline eGFR < 60ml/min/1.73m2, we measured a panel of 10 solutes in serum and urine, that were previously identified as markers of tubular secretion. We created a standardized composite secretory score using the urine to plasma ratios of all 10 biomarkers. We evaluated associations of this composite score with annual % eGFR decline and progression of CKD (>30% loss of eGFR) using multivariable linear regression and Cox regression models, respectively.

Conclusions: Mean participant age at baseline was 73 years, 41% were female, and 24% were identified as Black. The mean eGFR varied by secretion score quartile: from 60ml/min/1.73m2 in the lowest quintile to 51ml/min/1.73m2 in the highest quintile. In multivariable adjusted analyses, eGFR declined faster for participants in the lower two quintiles of secretory score compared with participants in the higher two quintiles (Figure). There was no significant interaction between secretion score and randomization treatment assignment for the outcome of eGFR decline. In unadjusted models, each 1-SD

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PO2363

The Use of Plasma Biomarker-Derived Clusters for Clinicopathologic Phenotyping: Results from the Boston Kidney Biopsy Cohort

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Background: Protein biomarkers may provide non-invasive insight into kidney disease pathology. Prior studies have not evaluated whether unsupervised clustering analyses of multiple plasma protein biomarkers may identify phenotypically distinct kidney diseases.

Methods: We performed unsupervised hierarchical clustering on 225 plasma biomarkers measured in 541 individuals enrolled into the Boston Kidney Biopsy Cohort, a prospective cohort study of individuals undergoing clinically indicated native kidney biopsy with adjudicated clinicopathologic diagnoses and semiquantitative scores of histopathology. Chi-square tests compared differences in proportions of clinicopathologic diagnoses by cluster membership. We examined contributions of biomarkers to each cluster and explored cluster-specific pathways using principal component analysis and pathway enrichment analysis, respectively.

Results: The biomarker-derived clusters partitioned subjects into 3 groups. The mean eGFR was 71.4 ± 29.2, 72.5 ± 34.3, and 39.3 ± 31.3 mL/min/1.73m² in Cluster 1, 2, and 3, respectively. Compared to Cluster 1, individuals in Cluster 3 were more likely to have tubulointerstitial disease (p < 0.001) and diabetic nephropathy (p < 0.001), (Figure 1). The top-contributing biomarker in Cluster 2 and 3 was Placental growth factor (p < 0.001).

Conclusions: Clusters of plasma biomarkers may identify individuals with distinct forms of CKD, which may uncover relevant pathways and biomarker candidates for clinicopathologic phenotyping of kidney diseases.

Funding: NIDDK Support

Figure 1

Figure 1. Distribution of clinicopathologic diagnoses by cluster membership.

PO2364

DAPA-CKD: A Regional Analysis of Kidney and Cardiovascular Outcomes

Ricardo Correa-Rotter,1 Priya Vart,2 Niels Jong,2 Fan Fan Hou,3 Glenn M. Chertow,4 Anna Maria Langkilde,5 John McMurray,6 Peter Rossing,7,8 David Sjostrom,9 Bergur V. Stefansson,10 Robert D. Toto,11 Walter Dohmatt,12 Elizabeth T. Escudero,13 Rey A. Isidro,14 Dinesh Khullar,15 Harpreet S. Bajaj,16 David C. Wheeler,17 Hildo J. Leerspink,2,3,18 The National Medical Science and Nutrition Institute Salvador Zubiran, Mexico City, Mexico; 2University Medical Center Groningen, Groningen, Netherlands; 3Southern Medical University, National Clinical Research Center for Kidney Disease, Guangzhou, China; 4Stanford University School of Medicine, Stanford, CA; 5AstraZeneca, Gothenburg, Sweden; 6University of Glasgow, Glasgow, United Kingdom; 7Steno Diabetes Center Copenhagen, Gentofte, Denmark; 8University of Copenhagen, Copenhagen, Denmark; 9UT Southwestern Medical Center, Dallas, TX; 10Hospital Privado Universitario de Cordoba, Cordoba, Argentina; 11Hospital Arzobispo Loayza, Cayetano Heredia University, Lima, Peru; 12Healthlink Medical, Dental, Surgical Clinics and Diagnostics Center, Hoilo City, Philippines; 13Max Super Speciality Hospital Saket, New Delhi, India; 14LMC Diabetes and Endocrinology, Brampton, ON, Canada; 15University College London, London, United Kingdom; 16The George Institute for Global Health, Newtown, NSW, Australia.

Background: The DAPA-CKD trial (NCT03036150) demonstrated that dapagliflozin reduced the risk of kidney and cardiovascular (CV) events in patients with chronic kidney disease (CKD) and albuminuria, with and without type 2 diabetes. We aimed to determine whether the effects of dapagliflozin varied by pre-specified geographic region.

Methods: We randomized 4304 adults with baseline estimated glomerular filtration rate (eGFR) 25–75 mL/min/1.73m² and urinary albumin-to-creatinine ratio 200–5000 mg/g to dapagliflozin 10mg or placebo once daily; median follow-up was 2.4 years. We compared baseline data, primary and secondary outcomes, and safety of the 4 regions (Asia, Northern America, Latin America, Europe).

Results: Compared to other regions, participants from Asia had lower body mass index, less frequent use of diuretics and better blood pressure control. The figure displays the primary and secondary outcomes by region and treatment assignment. Dapagliflozin consistently reduced the risk of the primary composite endpoint (eGFR decline ≥ 50%, end-stage kidney disease, or kidney or CV death) across the 4 regions by 30 to 49%, with no significant heterogeneity (p = 0.77). Similarly, there was no evidence of differences in secondary outcomes between regions. Serious adverse events in the dapagliflozin and placebo groups were similar across the 4 regions.

Conclusions: Despite differences in patient characteristics, the beneficial effects of dapagliflozin on kidney and CV endpoints in patients with CKD and albuminuria were similar across pre-specified geographic regions.

Funding: Commercial Support - AstraZeneca

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
**PO2365**

**Effects of Dapagliflozin in Patients with CKD and Albuminuria, with and Without Diabetes, by Use and Non-Use of Cardiovascular Medications: DAPA-CKD Trial**

**Ricardo Correa-Rotter,1 Glenn M. Chertow,2 Patrick B. Mark,3 Michal P. Nowicki,4 Priya Vart,5 Niels Jongs,6 Anna Maria Langkilde,7 John McMurray,8 Peter Rossing,9 Per G. Sjostrom,10 Bergur V. Stefansson,11 Robert D. Toto,3 David C. Wheeler,10 Hiddo J. L Heerspink,2,11 The National Medical Science and Nutrition Institute Salvador Zubiran, Mexico City, Mexico; 2Stanford University School of Medicine, Stanford, CA; 3University of Glasgow, Glasgow, United Kingdom; 4Medical University of Lodz, Lodz, Poland; 5University Medical Center Groningen, Groningen, Netherlands; 6AstraZeneca, Gothenburg, Sweden; 7Steno Diabetes Center Copenhagen, Gentofte, Denmark; 8University of Copenhagen, Copenhagen, Denmark; 9UT Southwestern Medical Center, Dallas, TX; 10University College London, London, United Kingdom; 11The George Institute for Global Health, Newtown, NSW, Australia.

**Background:** The DAPA-CKD trial (NCT03036150) demonstrated that dapagliflozin reduced the risk of kidney and cardiovascular (CV) events in patients with chronic kidney disease (CKD) and albuminuria with and without type 2 diabetes. We aimed to determine whether baseline CV medications modified dapagliflozin treatment effect.

**Methods:** We randomized 4304 adults with baseline eGFR 25–75 mL/min/1.73m² and urinary albumin-to-creatinine ratio 200–5000 mg/g to either dapagliflozin 10 mg or placebo once daily. The primary endpoint was a composite of a ≥50% estimated glomerular filtration rate (eGFR) decline, end-stage kidney disease, and kidney or CV death. Here we categorized patients according to baseline CV medication use.

**Results:** Patients were required by protocol to receive a stable dose of a renin-angiotensin system inhibitor. The figure shows the effect of dapagliflozin compared with placebo, according to use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (97.0%), calcium channel blockers (30.7%), beta-blockers (39.0%), diuretics (43.7%), antithrombotic (47.4%) and lipid-lowering (69.4%) agents. The benefit of dapagliflozin was consistent across all background treatment subgroups, and findings were similar for pre-specified secondary outcomes (composite kidney endpoint, composite CV endpoint, and all-cause mortality).

**Conclusions:** The beneficial effects of dapagliflozin on kidney and CV endpoints in patients with CKD and albuminuria were evident among patients treated and not treated with a variety of CV medications.

**Funding:** Commercial Support - AstraZeneca

**PO2367**

**Efficacy and Safety of Roxadustat for the Treatment of CKD Anemia in Patients Enrolled in the United States as Compared with the Global Cohort**

**Shweta Bansal,1 George M. Nassar,2 Robert I. Lynn,3 Pablo E. Pergola,4 Tyson T. Lee,5 Khali G. Saikali,6 Lynda Szczeklewski,7 The University of Texas Health Science Center at San Antonio, TX; 8Brigham and Women’s Hospital, Boston, MA; 9Duke University Medical Center, New York, NY; 10Houston Methodist Hospital, Houston, TX; 11Albert Einstein College of Medicine, Bronx, NY; 12Renal Associates PA, San Antonio, TX; 13Fibrogen Inc, San Francisco, CA.

**Background:** Roxadustat, a hypoxia-inducible factor prolyl hydroxylase inhibitor increases hemoglobin (Hb) in non-dialysis (NDD) and dialysis dependent (DD) chronic kidney disease (CKD). Because of different clinical practices and demographic factors, it is important to evaluate efficacy and safety by region. In a secondary analysis of data from 3 phase 3 studies of Roxadustat vs. placebo in NDD, and 3 phase 3 studies of Roxadustat vs. epoetin alfa in DD-CKD, US patients were compared to the global cohort. Mean change from baseline in Hb averaged over weeks 28–52 regardless of rescue therapy and treatment emergent adverse events with occurrence in ≥5% of patients were assessed.

**Results:** Of the patients enrolled in the NDD and DD trials, 23.2% and 45.4% were enrolled in the US, respectively. Compared with global patients, US patients were older, had a higher BMI, and more frequently had type 1 or 2 diabetes mellitus and cardiovascular/thromboembolic diseases (Table). US DD patients had a higher mean baseline Hb (SD) (10.16 g/dL [0.92]) compared with the global cohort (9.65[1.30]). Efficacy was similar between US and global patients; least square mean (LSM) differences in NDD patients were 1.61 g/dL (95% CI: 1.48, 1.74) vs. 1.72 (95% CI:1.65, 1.79) (both p<0.0001) comparing roxadustat to placebo; LSM differences in DD patients were 0.33 (95% CI: 0.24, 0.42) vs. 0.26 (95% CI: 0.20, 0.33) (both p<0.0001) comparing roxadustat to epoetin alfa. Safety was comparable between treatment arms in US and global patients.

**Conclusions:** Patients enrolled in the US were older and more likely to have comorbidities in both the NDD and DD trials, Roxadustat efficacy and safety in the US were similar to global patients.

**Funding:** Commercial Support - Fibrogen Inc., Astellas, AstraZeneca

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**PO2366**

**Quëtelet (Body Mass) Index and Effects of Dapagliflozin in CKD**

**Glenn M. Chertow,1 Priya Vart,2 Anna Maria Langkilde,3 John McMurray,4 Ricardo Correa-Rotter,5 Peter Rossing,6 Per G. Sjostrom,10 Bergur V. Stefansson,11 Robert D. Toto,3 Tom Greene,4 David C. Wheeler,10 Hiddo J. L Heerspink,2,11 Stanford University School of Medicine, Stanford, CA; 4University Medical Center Groningen, Groningen, Netherlands; 5AstraZeneca, Gothenburg, Sweden; 6University of Glasgow, Glasgow, United Kingdom; 7The National Medical Science and Nutrition Institute Salvador Zubiran, Mexico City, Mexico; 8Steno Diabetes Center Copenhagen, Gentofte, Denmark; 9University of Copenhagen, Copenhagen, Denmark; 10Southwestern Medical Center, Dallas, TX; 11University of Utah Health, Salt Lake City, UT; 12University College London, London, United Kingdom; 13The George Institute for Global Health, Newtown, NSW, Australia.

**Background:** The DAPA-CKD trial (NCT03036150) demonstrated a reduction of the risk of kidney and cardiovascular (CV) events with dapagliflozin in patients with chronic kidney disease (CKD) and albuminuria with and without type 2 diabetes. We aimed to assess the effects of the SGLT2 inhibitor dapagliflozin in patients stratified by Quëtelet (body mass) index (BMI).

**Methods:** We randomized 4304 adult patients with estimated glomerular filtration rate (eGFR) 25–75 mL/min/1.73m² and urinary albumin-to-creatinine ratio 200–5000 mg/g to dapagliflozin 10 mg or placebo once daily. The primary outcome was a composite of sustained decline in eGFR of ≥50%, kidney failure, or death from kidney or CV causes. Secondary outcomes were a kidney composite endpoint, a CV composite endpoint, and all-cause mortality. We categorized patients according to World Health Organization criteria: lean or ideal (BMI <25 kg/m²), overweight, grade 1 obesity, and grade 2/3 obesity (BMI ≥35 kg/m²).

**Results:** Among 4296 (99.8%) randomized patients with available height and weight data, 1491 (34.9%) were categorized as lean or ideal, overweight, grade 1 obesity, and grade 2/3 obesity groups, respectively. Hazard ratios (HRs) (dapagliflozin versus placebo) and 95% confidence intervals (CIs) for the primary composite endpoint were 0.60 (0.43–0.85), 0.55 (0.40–0.75), 0.71 (0.49–1.04), and 0.57 (0.37–0.87), among patients in the lean or ideal, overweight, grade 1 obesity, and grade 2/3 obesity groups (interaction p=0.72), respectively, indicating no significant heterogeneity in the dapagliflozin treatment effect. Corresponding HRs (95%CI) for the primary composite endpoint: 0.53 (0.38–0.80), 0.54 (0.37–0.78), 0.51 (0.32–0.83), and 0.60 (0.36–0.98) (interaction p=0.08), CV composite endpoint: 0.88 (0.44–1.74), 0.72 (0.44–1.19), 0.94 (0.60–1.48), and 0.46 (0.27–0.77) (interaction p=0.21) and all-cause mortality: 0.78 (0.44–1.40), 0.51 (0.33–0.79), 0.98 (0.60–1.62), and 0.65 (0.36–1.18) (interaction p=0.27).

**Conclusions:** Among patients with CKD and albuminuria, with or without type 2 diabetes, kidney and CV benefits of dapagliflozin were evident across the spectrum of body size.

**Funding:** Commercial Support - AstraZeneca
Table 1. Differences between US and global cohorts in demographic and disease characteristics

<table>
<thead>
<tr>
<th>Parameters</th>
<th>ESKD subgroup</th>
<th>Global (N=4270)</th>
<th>US subgroup (N=1762)</th>
<th>Global (N=2080)</th>
</tr>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;65</td>
<td>296 (10.9)</td>
<td>2224 (52.6)</td>
<td>1196 (67.9)</td>
<td>2846 (72.4)</td>
</tr>
<tr>
<td>&gt;50</td>
<td>233 (7.3)</td>
<td>1102 (25.7)</td>
<td>181 (21.6)</td>
<td>705 (17.1)</td>
</tr>
<tr>
<td>&gt;35</td>
<td>122 (4.0)</td>
<td>895 (20.8)</td>
<td>185 (21.6)</td>
<td>531 (13.0)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>40 (1.2)</td>
<td>60 (1.4)</td>
<td>21 (1.6)</td>
<td>134 (3.2)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>83 (2.6)</td>
<td>154 (3.6)</td>
<td>78 (4.8)</td>
<td>533 (13.7)</td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0.0)</td>
<td>343 (8.0)</td>
<td>70 (9.8)</td>
<td>784 (18.4)</td>
</tr>
<tr>
<td>Native Hawaiian or Other Pacific Islander</td>
<td>3 (0.1)</td>
<td>8 (0.2)</td>
<td>11 (0.8)</td>
<td>12 (0.3)</td>
</tr>
<tr>
<td>Other</td>
<td>626 (19.5)</td>
<td>2086 (47.4)</td>
<td>879 (20.3)</td>
<td>2315 (60.0)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>36 (1.1)</td>
<td>20.9 (0.5)</td>
<td>20.9 (0.5)</td>
<td>27.9 (0.2)</td>
</tr>
<tr>
<td>18.5–24.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥25</td>
<td>42 (1.4)</td>
<td>15.8 (0.1)</td>
<td>15.8 (0.1)</td>
<td>14.2 (0.3)</td>
</tr>
</tbody>
</table>

Baseline Disease characteristics

1. Diabetes Mellitus (Type I or II, %) | 70.5 (27.5) | 63 (13.9) | 100 (26.9) | 128 (31.7) |
2. Cardiac, Cerebrovascular, or Thoracic Obstructive Disease, n (%) | 472 (16.7) | 37 (0.9) | 115 (2.7) | 187 (4.5) |

PKs were randomized to dapagliflozin 10 mg or placebo once daily, added to standard care, and followed for 12 months. The median change in proteinuria and eGFR between baseline and 12-month follow-up were compared between groups.

Results: Out of 3564 pts recruited into the SKS from Oct 2002 to Dec 2019, 526 diabetic pts were eligible for matching with the 304 AMETHYST-DN pts. Propensity score matching yielded a well-matched cohort of 142:142 pts for the trend analysis. Median age was 68 yrs, 68% were male, median BP was 152/80 mmHg, and 27% had HF. Median eGFR was 32.5 mL/min/1.73m² and uACR was 283 mg/g. RAASi use was 100%, and 99% of pts were on a stable dose in AMETHYST-DN vs SKS pts. AMETHYST-DN pts were more likely to be on RAASi, and within each cohort, SKS was more likely to be on RAASi compared to AMETHYST-DN pts (p=0.023). No significant differences were observed in PKs change (Table).

Conclusions: PAT enabled sustained RAASi use in 99% of pts in AMETHYST-DN, compared to 43% of pts in a matched SKS cohort over 12 months. AMETHYST-DN pts had significantly reduced proteinuria at follow-up compared to SKS CKD pts, possibly due to continuation of RAASi enabled by PAT. No significant changes in eGFR were observed in either group.

Funding: Commercial Support - Vifor Pharma

PO2370

Patiromer Enables Sustained RAAS Inhibitor Therapy over 52 Weeks: A Post Hoc Analysis of 246 Patients Who Completed the AMETHYST-DN Study

Murray Epstein,1 Susan Arthur,2 Jeffrey J. Budden,2 1University of Miami School of Medicine, Miami, FL; 2Vifor Pharma Group, Redwood City, CA.

Background: Hyperkalemia (HK) is a common electrolyte abnormality in CKD patients (pts) with type 2 diabetes mellitus (T2DM) and leads to underutilization of RAAS inhibitors (RAASI). KDIGO guidelines recommend RAASI dose should be reduced or discontinued only as a last resort in HK pts after measures to control serum potassium (sK) have failed. Patiromer (PAT) is a non-absorbed, sodium-free, K binder that reduces sK and is used to treat hyperkalemia in patients (pts) with diabetes and CKD treated with RAASI. This analysis compared the progression of proteinuria and eGFR in AMETHYST-DN pts with a matched, real-world group of CKD pts with diabetes not receiving PAT.

Methods: Pts from AMETHYST-DN were closely matched with Salford Kidney Study (SKS) pts (a large CKD cohort in the United Kingdom). Matching was performed for age, gender, baseline systolic and diastolic blood pressure (BP), heart failure (HF) status, serum K+ and eGFR by propensity scores generated from a logistic regression analysis (1:1, nearest neighbour method). All pts were followed up for a median duration of 12 months. The median change in proteinuria and eGFR between baseline and 12-month follow-up were compared between groups.

Results: Out of 3564 pts recruited into the SKS from Oct 2002 to Dec 2019, 526 diabetic pts were eligible for matching with the 304 AMETHYST-DN pts. Propensity score matching yielded a well-matched cohort of 142:142 pts for the trend analysis. Median age was 68 yrs, 68% were male, median BP was 152/80 mmHg, and 27% had HF. Median eGFR was 32.5 mL/min/1.73m² and uACR was 283 mg/g. RAASi use was 100%, and 99% of pts were on a stable dose in AMETHYST-DN vs SKS pts. AMETHYST-DN pts were more likely to be on RAASi, and within each cohort, SKS was more likely to be on RAASi compared to AMETHYST-DN pts (p=0.023). No significant differences were observed in PKs change (Table).

Conclusions: PAT enabled sustained RAASi use in 99% of pts in AMETHYST-DN, compared to 43% of pts in a matched SKS cohort over 12 months. AMETHYST-DN pts had significantly reduced proteinuria at follow-up compared to SKS CKD pts, possibly due to continuation of RAASi enabled by PAT. No significant changes in eGFR were observed in either group.

Funding: Commercial Support - Vifor Pharma

PO2369

A Comparison of the Efficacy of Patiromer Plus RAAS Inhibitor Therapy in Patients with CKD and Diabetes to a Cohort of Patients Not Using Patiromer: A Real-World Analysis Using Propensity Score Matching

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Background: The AMETHYST-DN trial evaluated the use of patiromer (PAT) to treat hyperkalemia in patients (pts) with diabetes and CKD treated with RAASI. This analysis compared the progression of proteinuria and eGFR in AMETHYST-DN pts with a matched, real-world group of CKD pts with diabetes not receiving PAT.

Methods: Pts from AMETHYST-DN were closely matched with Salford Kidney Study (SKS) pts (a large CKD cohort in the United Kingdom). Matching was performed for age, gender, baseline systolic and diastolic blood pressure (BP), heart failure (HF) status, serum K+ and eGFR by propensity scores generated from a logistic regression analysis (1:1, nearest neighbour method). All pts were followed up for a median duration of 12 months. The median change in proteinuria and eGFR between baseline and 12-month follow-up were compared between groups.

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Conclusions: PAT enabled sustained RAASi use in 99% of pts in AMETHYST-DN, compared to 43% of pts in a matched SKS cohort over 12 months. AMETHYST-DN pts had significantly reduced proteinuria at follow-up compared to SKS CKD pts, possibly due to continuation of RAASi enabled by PAT. No significant changes in eGFR were observed in either group.

Funding: Commercial Support - Vifor Pharma
Predict Hyperkalemia in Advanced CKD Patients Using Machine Learning Algorithms
Hsin-Hsiung Chang,1 Chia-Lin Wu2.1 Poaiichien Hospital, Pingtung, Taiwan; 2Changhua Christian Hospital, Changhua, Taiwan.

Background: Hyperkalemia is a common and fatal problem in advanced chronic kidney disease patients. The incidence rate was about 40-50%. It may cause muscle weakness, paralysis, and even cardiac arrhythmia. Our goal is to develop machine learning models to predict hyperkalemia in advanced chronic kidney disease patients, which could help physicians make clinical decisions.

Methods: We collected clinical data for advanced CKD (CKD stage 4 and 5, eGFR < 30 ml/min/1.73m2) patients receiving Output Patient Care in one medical center in Taiwan from January 2010 to December 2019. 1,965 patients were included. Four machine learning models (multilayer perceptron [MLP], logistic regression with regularization, XGBoost, and random forest [RF]) were used to estimate serum potassium concentration 3 months later. 2 Nephrologists participated in human-machine competition. Area under the receiver operating characteristic curves (AUCs), sensitivity, specificity, positive (PPV) and negative (NPV) predicted values, and accuracy were used to evaluate the performance of machine learning models with that of these physicians.

Results: In a test set including 2,074 records, the AUC of machine learning models was 0.881 compared to XGBoost (0.843; 95% confidence interval [CI], 0.822-0.864). Moreover, the NPV and specificity were 0.875 and 0.943, respectively. The AUC for detecting hyperkalemia by humans was 0.602, 95% CI, 0.580-0.623. XGBoost model performed significantly better than humans (p < 0.001, using the DeLong test).

Conclusions: Machine learning models may help physicians make clinical decisions in advanced CKD patients who suffer from hyperkalemia in outpatient department care and possibly reduce cardiac arrhythmia.

Association Between Dietary Potassium Intake and Abdominal Aortic Calcification in US Adults
Yaping Xie,1 Matthew K. Abramowitz,2 Wei Chen.3 Children's Hospital at Montefiore, Bronx, NY; 2Albert Einstein College of Medicine, Bronx, NY.

Background: In ApoE-deficient mice, low dietary potassium intake promoted vascular calcification and high dietary potassium intake attenuated vascular calcification. We hypothesized high dietary potassium intake was associated with lower abdominal aortic calcification (AAC) among adults in the US.

Methods: Cross-sectional analyses were performed on 2,351 participants from the National Health and Nutrition Examination Survey 2013-2014. Dietary potassium intake was obtained from 24-h recall interviews and were categorized into quartiles (Q1:0.3-1.9, Q2:2.0-2.4, Q3:2.5-3.1 and Q4:3.2-6.8 g/day). AAC was measured using dual-energy X-ray absorptiometry in adults over 40 years old and quantified using the Kaupilia score system. AAC scores were categorized into: no AAC (AAC=0, reference group), mild/moderate (AAC=0-6) and severe AAC (AAC=6). Multinomial logistic regression was used to study the association between AAC and dietary potassium intake. Model was adjusted for demographics, hypertension, diabetes, smoking, eGFR, albuminuria, BMI, energy intake and physical activity.

Results: In the entire cohort, mean dietary potassium intake was 2.4±0.9 g/day; 21% had mild/moderate AAC and 9.8% had severe AAC. Dietary potassium intake was not associated with mild/moderate AAC (table). For severe AAC, dietary potassium intake was only associated with AAC when comparing dietary potassium in Q2 with Q1: Q2 was associated with lower odds of having severe AAC (OR 0.65 [95% CI: 0.46-0.92], p=0.02). This association remained significant in the fully adjusted model (OR 0.50 [95% CI: 0.29-0.86], p=0.02).

Conclusions: We found that higher dietary potassium intake was associated with lower odds of having severe AAC, but the association is only significant when comparing dietary potassium intake in Q2 with Q1. This nonlinear relationship between dietary potassium intake and AAC requires further investigations.

Funding: NIDDK Support

Multinomial logistic regression models of AAC with dietary potassium intake(g/day) in quartiles, N=2,353

Table 1: Multinomial logistic regression models of AAC with dietary potassium intake (g/day) in quartiles

<table>
<thead>
<tr>
<th>Dietary potassium intake (g/day)</th>
<th>Mild/moderate AAC vs no AAC</th>
<th>Severe AAC vs no AAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 (0.3-1.9)</td>
<td>OR=0.9 (0.5-1.6)</td>
<td>OR=1.2 (0.4-3.9)</td>
</tr>
<tr>
<td>Q2 (2.0-2.4)</td>
<td>OR=0.8 (0.5-1.6)</td>
<td>OR=0.5 (0.2-1.3)</td>
</tr>
<tr>
<td>Q3 (2.5-3.1)</td>
<td>OR=0.5 (0.3-0.9)</td>
<td>OR=0.2 (0.0-1.8)</td>
</tr>
<tr>
<td>Q4 (3.2-6.8)</td>
<td>OR=0.2 (0.0-1.8)</td>
<td>OR=0.1 (0.0-1.0)</td>
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</tbody>
</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underlines represent presenting author.
The Effect of Fibrates on Kidney Function and CKD Progression: A Systematic Review and Meta-Analysis of Randomised Studies
Alexandros Hadjiyiannakis,1 Andreas Kousios,2 Panayiotis Kouis,3 Andric G. Panayiotou,4 Technologiko Panepistimio Kyprou, Limassol, Cyprus; 5Hammersmith Hospital, London, United Kingdom; 6Imperial College, London, United Kingdom.

Background: Fibrates have proven efficacy in cardiovascular risk reduction and are commonly used, in addition to statins, to control hyperglycemia. Their use is often limited due to reduction in glomerular filtration rate at treatment initiation. However, recent studies suggest benign change in kidney function and improvement of proteinuria; an established early marker of microvascular disease and kidney disease progression. We summarize the evidence from existing trials and provide summary effects of fibrates, alone or in combination, on kidney disease progression and proteinuria.

Methods: Systematic review and Meta-analysis of randomised controlled trials (PROSPERO CRD202018784).

Results: Out of 12243 potentially eligible studies, 29 were included in qualitative and quantitative analysis, with a total of 20176 patients. Mean creatinine increased by 1.05 (95% CI 0.63 to 1.46) units in patients receiving fibrates vs comparator, and this was similar in all other subgroups. eGFR showed a bigger decrease in the fibrates arm (SMD -1.19; 95% CI -3.49 to 0.48) when all studies were pooled together. Notably, short- term serum creatinine and eGFR changes remained constant in the long-term. Pool estimates show that fibrates improve albuminuria progression, RR 0.86; 95% CI (0.76 to 0.98); albuminuria regression, RR 1.19; 95% CI (1.08 to 1.31). Two studies showed reduction in progression to ESKD, although without statistical significance.

Conclusions: Fibrates improve albuminuria in patients with and without diabetes when used to treat hyperlipidemia. The modest creatinine increase should not be a limiting factor for fibrate initiation in patients with preserved renal function or mild CKD. The long-term effects on kidney disease progression warrant further study.

The Effect of Atrasentan on Kidney and Heart Failure Outcomes by Baseline Albuminuria and Kidney Function: A Post Hoc Analysis of the SONAR Trial
Simke W. Wanger,1 Ron T. Gansevoort,2 Ricardo Correa-Rotter,3 Fan Fan Hou,4 Donald E. Kohan,5 Hirofumi Makino,8 John McMurray,6 Vlado Perkovic,5 Sheldon W. Tobe,6 Hans-Henrik Parving,10,11 Dick de Zeeuw,2,3 Hiddo J. Heerspink,1,2 Universiteit Medisch Centrum Groningen, Groningen, Netherlands; 3The University of Chicago Medicine, Chicago, IL; 4Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico; 5Medical University of Graz, Graz, Austria; 6University of Utah Health, Salt Lake City, UT; 7University of Glasgow, Glasgow, United Kingdom; 8The George Institute for Global Health, Newtown, NSW, Australia; 9Okayama Daigaku, Okayama, Japan; 10Sunnybrook Health Sciences Centre, Toronto, ON, Canada; 11Rigshospitalet, Copenhagen, Denmark; 12Aarhus Universitet, Aarhus, Denmark.

Background: Atrasentan reduces kidney failure risk, but increases risk of edema and possibly heart failure in patients with diabetic kidney disease. Patients with advanced chronic kidney disease (CKD) may obtain greater absolute renal benefit from atrasentan but may be at higher risk of kidney retention due to impaired renal excretory capacity. We assessed effects of atrasentan on kidney and heart failure events according to baseline eGFR and albumin/creatinine ratio (UACR) in a post-hoc analysis of the SONAR trial.

Methods: The effect of atrasentan versus placebo in 3668 patients with type 2 diabetes and CKD with elevated UACR was examined in SONAR. We used Cox regression to study effects on the primary kidney outcome (doubling of serum creatinine, end-stage kidney disease or renal death) and heart failure hospitalization across subgroups of eGFR (<30, 30-44, 45-59, 60-75, ≥75 ml/min/1.73m2) and UACR (<1000, ≥1000, ≥3000, ≥8000 mg/g).

Results: Atrasentan reduced the relative risk of the primary kidney outcome consistently across baseline UACR and eGFR subgroups. The absolute risk reduction was highest in the lowest eGFR UACR subgroup (HR 0.71, 95%CI 0.58-0.88) consistently across subgroups of baseline eGFR and UACR (table). Patients in the highest UACR and lowest eGFR subgroups showed the largest absolute benefit (all P-interaction <0.01). The relative (HR 1.39, 95%CI 0.97-1.99) and absolute risk of heart failure hospitalization was consistent across eGFR or UACR subgroups (all P-interaction >0.09).

Conclusions: Atrasentan reduced the relative risk of the primary kidney outcome consistently across baseline UACR and eGFR subgroups. The absolute risk reduction was highest in the lowest eGFR UACR subgroup who were at highest baseline risk. However, the relative and absolute risk of heart failure hospitalization were similar across baseline UACR and eGFR subgroups. These results support the initiation of atrasentan in high risk patients with CKD and significant albuminuria.
PO2379
Association of Long-Term Aspirin Use with Progression of Kidney Disease
Jun Zang Lu,1 Fridjof Thomas,1 Keiichi Sumida,1 Waleed Hassan,1 Csaba P. Kovsey,1,2 The University of Tennessee Health Science Center, Memphis, TN; 1VA Memphis Medical Center, Memphis, TN.

Background: Aspirin (ASA) has been used to control inflammation for over a century. Recently, chronic microinflammation was detected to be a major contributor to the progression of chronic diseases such as cancer and chronic kidney disease (CKD). However, it is unclear if long-term use of ASA could lower mortality and slow renal deterioration in patients with CKD.

Methods: We identified 860 US Veterans with non-dialysis dependent CKD followed at a single medical center between October 2014 to September 2015. Associations between long-term ASA use (at least 90 days) with mortality, and with a combined renal outcome (dialysis or eGFR dropping 40% from baseline) were examined in multivariable adjusted Cox proportional hazards models. Besides the crude model (model 1), we adjusted for demographics, BMI, smoking status, blood pressure (model 2), for comorbidities (Model3), and for antihypertensive medications, NSAIDs, steroids, baseline eGFR, medication adherence rate, and proteinuria (Model 4).

Results: The mean age (SD) of ASA users vs. non-users was 68.1 (9.9) vs. 64.2 (13.1) years, and the mean eGFR (SD) was 36.9 (0.7) ml/min/1.73m2 vs. 43.7 (2.0). Over a 4.6-year median follow-up period, 37% of patients reached the combined renal endpoint (event rate: 102.8/1000 patient-years) and 372 (43%) patients died. ASA users had a lower mortality rate (HR 0.40 [95% CI: 0.26, 0.64], p=0.001) in the fully adjusted model [Figure].

Conclusions: CKD patients receiving ASA for 90 days or longer had slower deterioration of kidney function and lower mortality. Further clinical trials are required to investigate the benefits of ASA in this population.

PO2380
Treatment of Hyperuricemia and Incident CKD in Patients with Normal Kidney Function
Waleed Hassan,1 Praveen Kumar Potukuchi,1 Ankur A. Dashpurne,1 Keiichi Sumida,1 Fridjof Thomas,1 Elani Streja,1 Kamyar Kalantar-Zadeh,3 Csaba P. Kovsey.1,4 The University of Tennessee Health Science Center College of Medicine, Memphis, TN; The University of Tennessee Health Science Center, Memphis, TN; 1University of California Irvine, Irvine, CA; 1,4VA Memphis Medical Center, Memphis, TN.

Background: Hyperuricemia is associated with incident chronic kidney disease (CKD) independent of established metabolic risk factors. Treatment of hyperuricemia with uric-acid lowering therapy (ULT) was not beneficial in clinical trials of patients with CKD, but the effects of ULT on incident CKD in patients with no pre-existing CKD is unclear.

Methods: We identified a national cohort of US Veterans with normal kidney function (eGFR >60 ml/min/1.73m2 and no proteinuria) and serum uric acid measurement. We examined the association of incident new ULT use (vs. no ULT), with the incidence of CKD (defined as 2 measurements of eGFR <60 ml/min/1.73m2 or UACR >30 mg/gm at least 90 days apart), using time dependent Cox models adjusted for baseline demographic characteristics, comorbid conditions, and time dependent eGFR and serum uric acid concentration.

Results: We identified 1,152,040 patients with a serum uric acid measurement, of whom 111,508 (10%) patients received de novo ULT during 2006-2019. The overall mean (SD) age was 59 ±13 years, 94% were male, 76% were white, and the mean (SD) eGFR was 84 (17) ml/min/1.73m2 at the cohort entry. There were 308,311 cases of incident CKD (event rate, 40.4/1000 PY; 95% CI, 40.3-41.6) over a median follow-up of 6.1 years. ULT was associated with higher risk of incident CKD in both crude models (hazard ratio, 2.09, 95% CI, 2.05-2.13), and after multivariable adjustments (HR, 1.45; 95% CI, 1.44-1.47) [table].

Conclusions: Although hyperuricemia is independently associated with risk of CKD, treatment of hyperuricemia with ULT was not associated with lower risk of incident CKD in patients with baseline normal kidney function and no proteinuria in a large national cohort.

Funding: Veterans Affairs Support
PO2382
Effect of Oral Sodium Bicarbonate on Biomarkers of Bone Turnover in CKD: A Secondary Analysis of the BASE Pilot Trial
Kalani L. Raphael,1 Ronit Katz,1 Tamara Isakov,1 Stuart M. Sprague,2 Myles Wolf,3 Dominic S. Raj,1 Andrew N. Hoofnagle,4 Brett Larive,5 Cynthia A. Kendrick,5 Jennifer J. Gassman,6 Linda F. Fried,6 Alfred K. Cheung,7 Joachim H. Ix,8 Oregon Health & Science University School of Medicine, Portland, OR; 9Portland VA Medical Center, Portland, OR; 10University of Washington, Seattle, WA; 11Northwestern University, Evanston, IL; 12NorthShore University HealthSystem, Evanston, IL; 13Duke University, Durham, NC; 14George Washington University Medical Faculty Associates, Washington, DC; 15University of Utah Health, Salt Lake City, UT; 16University of California San Diego, La Jolla, CA; 17Cleveland Clinic, Cleveland, OH; 18VA Pittsburgh Healthcare System, Pittsburgh, PA

Background: CKD clinical practice guidelines recommend treatment with alkali to mitigate adverse effects of metabolic acidosis on several organ systems, including bone. The effect of alkali supplementation on bone turnover in CKD is unclear. We performed a secondary analysis of the Bicarbonate Administration to Stabilize eGFR (BASE) Pilot Trial to investigate the effect of NaHCO₃ on biomarkers of bone turnover.

Methods: BASE randomized 194 individuals with eGFR 20-59 ml/min/1.73m² to receive placebo (n=52) or one of two doses of NaHCO₃ (0.5 mEq/kg/d, n=52; 0.8 mEq/kg/d, n=90) for 28 weeks. We measured serum parathyroid hormone (PTH), bone-specific alkaline phosphatase (B-SAP), c-telopeptide (CTX, marker of bone resorption), and procollagen type I intact N-terminal propeptide (PINP, marker of bone formation) levels from stored samples collected at baseline, week 12, and week 28, and compared the mean change from baseline between placebo and those treated with NaHCO₃ using linear mixed models.

Results: 68 of 194 participants (66%) submitted samples for post-hoc measurements (placebo, n=46; lower-dose, n=47; higher-dose, n=75). Baseline characteristics were age 67±12 years, female 28%, Black, 32%, Hispanic 15%, eGFR 37±67 ml/min/1.73m², serum total CO₂ 24±5 mEq/L, B-SAP 8.7±5.1 μg/L, CTX 0.36±0.38 μg/mL, PINP 57±31 μg/mL. NaHCO₃ treatment raised PTH and lowered B-SAP; however there was no significant difference when compared to placebo. NaHCO₃ treatment had no effect on CTX or PINP (Table).

Conclusions: NaHCO₃ treatment did not have consistent effects on biomarkers of bone turnover as assessed by PTH, B-SAP, CTX, or PINP, and no significant effects relative to placebo in patients with CKD.

Funding: NIDDK Support

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PO2383
Can Structured, Moderate Exercise Slow Kidney Function Decline in Sedentary Elders?
Michael S. Sedentary Elders?

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Michael S. Sedentary Elders?
Results: Patients were 69±11 years old; 93% were male; 74% were African American; 30% were diabetic; and baseline eGFR was 77±16 ml/min/1.73m². Among 66,602 patients, 1,047 (1.6%) started biologic therapy, and 504 (0.8%) experienced an incident ESKD. In a sociodemographic-adjusted model, incident biologic use (vs. non-use) was associated with lower risk of incident ESKD (adjusted HRs [95%CI], 0.55 [0.29-1.49], in model 1) albeit not reaching statistical significance. This association was attenuated after further multivariable adjustment (0.98 [0.41-2.35], in model 4; Figure). Conclusions: Biologic agent administration is not associated with higher risk of incident ESKD. Clinical trials are warranted to test whether active interventions with biologic agents are safe and effective in preventing adverse renal outcomes associated with IBD.

Funding: Veterans Affairs Support

PO2387

Association of Kidney Measures with Cardiovascular Events, Kidney Outcomes, and Mortality Among Older Adults

Valentina Turbay Caballero,1 Ana C. Ricardo,1 Jinsong Chen,2 Kirolos Iskander,2 Gustavo Aroca Martinez,3 James P. Lash,4 Carlos G. Musso,5 Universidad del Norte, Barranquilla, Colombia; 2University of Illinois at Chicago, Chicago, IL; 3Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; 4Universidad Simon Bolivar, Barranquilla, Colombia.

Background: Based on current criteria (glomerular filtration rate [GFR] <60 ml/min/1.73m² or urine albumin-to-creatinine ratio [UACR] ≥30 mg/g), the prevalence of CKD in U.S. older adults is up to 42% among those aged 65-79 years. However, the risk implications of this CKD definition in this population are controversial. We evaluated the risk of adverse outcomes among older adults across CKD stages based on the Kidney Disease: Improving Global Outcomes (KDIGO) definition.

Methods: This study included 2640 older adults (age ≥75 years) without diabetes enrolled in the Systolic Blood Pressure Intervention Trial (SPRINT). We compared the risk of the primary composite SPRINT outcome, and all-cause death, across GFR and albuminuria categories based on KDIGO guidelines. To estimate GFR, we used the CKD Epidemiology Collaboration (CKD-EPI) equation and the Berlin Initiative Study (BIS1), a novel estimator of GFR in elderly persons.

Results: Mean age was 79.8 years, 37.9% were female, 17.0% of participants self-identified as non-Hispanic Black, 6.6% as Hispanic, and 74.6% as non-Hispanic White. Mean estimated GFR was 63.3 ml/min/1.73 m², and median UACR 55 mg/g. In multivariable regression analysis, there was no statistically significant difference in the risk of the primary outcome among participants with UACR <30 mg/g, regardless of GFR level (Table). However, compared with participants with GFR ≥60 ml/min/1.73 m² and UACR <30 mg/g, those with UACR ≥30 mg/g had higher risk of the primary outcome at all levels of GFR, with the highest risk observed among those with GFR <45 ml/min/1.73 m². Similar results were observed with the BIS1 equation was used to estimate GFR.

Conclusions: Among older adults without diabetes, increased albuminuria was associated with adverse cardiovascular outcomes at all levels of GFR. However, low GFR was not associated with adverse outcomes in participants with normal albuminuria. These results support the proposal of an age-adapted definition of CKD.

Funding: NIDDK Support

PO2386

Decreased Progression of CKD in Patients Undergoing Fecal Microbiota Transplantation (FMT)

Giovanna Y. Arteaga Muller,1 Adrián Camacho-Ortiz, Elvira Garza-Gonzalez, Samanith M. Flores-Treviño, Paola Bocanegra-Barreras, Graciela C. Fabelo-Valdez, Norma Y. Rodriguez-Arroyo, Hospital Universitario Jose Eleuterio González Universitaria Autonoma de Nuevo Leon, Monterrey, Mexico.

Background: Prevalence of CKD is 8 to 16% in different stages, considered the main cause of emergency and hospital care in Mexico and catastrophic disease, its main causes: diabetes, arterial hypertension and glomerulonephritis. Treatment to prevent progression consists of inhibitors of the renin angiotensin aldosterone system, control of the underlying disease and blood pressure. The estimate of the loss of glomerular filtration rate is 2.3 to 4.5 ml/min per year in CKD patients. The intestinal microbiota has protective, structural and metabolic functions, there is a bidirectional interference of the microbiota and the host maintaining a symbiotic relationship, in CKD patients uremia affects the composition and metabolism of the microbiota, generating dysbiosis that is the absence of balance in the microbiological community generating an increase in the progression of CKD and an increase in the production of N-trimethylamine oxide, indoxyl sulfate and p-cresol sulfate associated with greater cardiovascular events in CKD patients, FMT has been used to correct dysbiosis in some pathologies.

Methods: A prospective, randomized, double-blind, comparative, placebo-controlled clinical trial, carried out at the University Hospital in Monterrey Mexico, in patients diagnosed with CKD due to diabetes and or hypertension, in stages 2, 3, 4 and 5 without renal replacement therapy, divided into 2 groups, MFT group: Microbiota fecal capsules, placebo group: placebo capsules, in both groups 15 capsules were administered every 12 hours for 2 days, on days 0, 10, 30, with a 6-month follow-up to demonstrate the difference in the progression of renal failure.

Results: 28 patients were randomized, the CKD of the placebo group progressed by 73% and the CKD of the MFT group progressed by 16% (p = 0.041) compared to the baseline. FMT was associated with a protective factor.

Conclusions: The difference in the proportion of patients who did not decrease their GFR at 6 months was statistically significant, in the present study the patients who received FMT had less progression of CKD at 6 months. FMT was associated with a protective factor.

Funding: Private Foundation Support

Table

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PO2388

Validation of Novel Cystatin C (CysC) Rapid Measurement Assay with Human Saliva

Manal Beshay1, Trong Nguyen1, Maria Ortega1, Danh V. Nguyen2, Connic Rhec3, Kamyar Kalantar-Zadeh3,1 Intelligent Optical Systems, Inc., Torrance, CA; 2University of California Irvine, Irvine, CA.

Background: Rapid, frequent point-of-care (POC) monitoring of kidney filtration markers such as cystatin C (CysC) that does not require laborious blood specimen draws/processing can improve chronic kidney disease (CKD) patient outcomes and care. Saliva as a non-invasive biofluid for monitoring kidney function addresses a clinical need for rapid diagnostics in POC and home-based testing. Emerging data suggests CysC as a more reliable kidney filtration marker than creatinine because it is not affected by age, race, ethnicity, or body mass.

Methods: Our Enhanced Lateral Flow (ELF) immunoassays were validated against a commercial ELISA kit for quantitative measurement of CysC in 76 human healthy and CKD patient saliva samples. We applied Pearson correlation and Bland-Altman analysis to compare the two data sets, and assessed inter-assay reproducibility by validating the coefficient of variation (CV) at predetermined concentrations for the samples. Each sample was measured in triplicate (n=3) to obtain the CV value. The ELF assay was tested with 116 samples, and ELISA with 51 samples, due to limited resources.

Results: The ELF assay CysC assessment showed high correlation to the ELISA measurements, with Pearson r = 0.78 (Fig. A). Bland-Altman analysis showed a minor bias of -0.017 mg/L between the two assays (Fig. B). Both assays demonstrated a <10% CV for most of the tests, with the ELF assay presenting a lower overall mean CV (6.5%) than the ELISA kit (7.2%) (Fig. C). Data from stability studies verified that the ELF assay maintained functionality at Day 510 when stored at room temperature.

Conclusions: We have demonstrated rapid measurement of CysC in human saliva with our novel ELF assay, with acceptable POC characteristics, and repeatability and reproducibility equivalent to ELISA. The ELF assay provided more accurate and faster
results (<30 min. vs. 3 hr. for ELISA), and also demonstrated a longer shelf life (stable at 510 days at -20°C without ELISA requirements for storage at -20°C with a 1 yr. expiration date). Future validation studies could lead to a saliva testing framework for kidney function markers, and a potential paradigm shift in the monitoring and care of CKD patients.

**Funding:** NIDDK Support

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**PO2389**

Kidney Filtration Markers: Accuracy and Reproducibility of Novel Serum Cystatin C Measurements in a Point-of-Care Rapid Test Platform

**Kamyar Kalantar-Zadeh,1,2 Manal Beslau,3 Connie Rhee,1 Trong Nguyen,4 Maria Ortega,5 Amy S. You,1 Rene Amel Peralta,1 Danh V. Nguyen,6 1University of California Irvine, Irvine, CA; 2Intelligent Optical Systems, Inc., Torrance, CA.

**Background:** Emerging data suggests cystatin C (CysC) as a more reliable kidney filtration marker than creatinine because it is unaffected by age, race, ethnicity, or body mass. In the US, the standard approach to assess blood-based CysC measurements is invasive phlebotomy followed by laborious blood specimen processing. There is a major unmet need for non-invasive point-of-care (POC) measurement of this kidney filtration marker. To fill this gap, we have recently developed and validated novel Enhanced Lateral Flow (ELF) immunoassays to measure CysC in human blood.

**Methods:** Validation of our ELF assays was performed in two steps. First, Pearson correlation and Bland-Altman analysis were used to assess the correlation, agreement and bias of ELF measurements to UCI Medical Center lab standard measurements from a set of 70 serum samples obtained from chronic kidney disease (CKD) patients. Then, Receiver Operating Characteristic (ROC) curve analysis was used to assess the medical diagnostic value of the ELF assay, with ELF assay measurements of 70 CKD samples and 20 healthy reference samples to determine ROC curve and Area Under Curve (AUC) of the assay.

**Results:** The ELF assay measurements showed high correlation to standard lab measurements, with Pearson r=0.94 (Figure A). Bland-Altman analysis showed bias of -0.5 mL/L for the ELF assay, which could be adjusted if it is consistent when we continue monitoring the assay on a broader concentration set of samples (Figure B). The ROC analysis showed excellent diagnostic value, with AUC=0.83, which shows potential for discriminating healthy and CKD subjects (Figure C and D).

**Conclusions:** We have demonstrated feasibility and validation of a novel POC assay to measure CysC in human blood-based samples. The ELF assay possesses acceptable POC characteristics, correlates well to standard laboratory measurements, and shows good diagnostic value. Future development could lead to a fully available POC measurement framework for CysC as a kidney function marker, and a potential paradigm shift in patient monitoring and care.

**Funding:** NIDDK Support

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**PO2390**

Serum Creatinine Concentration and Estimates of Muscle Mass Among Race/Ethnicity Groups with End-Stage Kidney Failure

**Cynthia Delgado,1,2 Neil R. Powe,3,4 Glenn M. Chertow,2 Barbara A. Grimes,3 Kirsten L. Johannsen,5 1San Francisco VA Health Care System, San Francisco, CA; 2University of California San Francisco, San Francisco, CA; 3Zuckerberg San Francisco General Hospital and Trauma Center, San Francisco, CA; 4Stanford University School of Medicine, Stanford, CA; 5Hennepin Healthcare, Minneapolis, MN.

**Background:** Racial differences in serum creatinine concentration have been attributed to differences in muscle mass. We examined this hypothesis among End Stage Kidney Disease patients receiving hemodialysis, whose serum creatinine concentration (SCr) should not be highly influenced by glomerular filtration.

**Methods:** 501 participants were enrolled from 2 centers who were at least 1 year post start of hemodialysis and for whom we measured SCr and body composition (including height-adjusted intracellular water [ICW] as a surrogate of muscle mass) using bioelectrical impedance spectroscopy. In multivariable linear regression we examined the independent association of race/ethnicity (Black, Asian, Non-Hispanic White [NHW], and Hispanic) with estimated muscle mass. We then examined whether race/ethnicity was associated with SCr with adjustment for demographics, clinical factors and body composition including ICW.

**Results:** Black (0.24 (-0.01,0.49)) and Hispanic (0.05 (-0.26, 0.37)) participants had similar SCr to that of NHW, but ICW was higher among Asians (0.42 (0.11, 0.72)). In contrast, Scr concentrations were significantly higher among Blacks, Hispanics and Asians compared with NHW. Adjustment for ICW did not change these associations or attenuate the difference in Scr between any racial/ethnic group and NHWs.

**Conclusions:** Among prevalent dialysis participants, ICW, a muscle mass surrogate, was higher among Asian, but not among Black, participants when compared to NHW. After adjusting for ICW, higher Scr was observed across all race ethnicity categories and muscle mass did not appear to explain differences in Scr by race/ethnicity.

**Funding:** NIDDK Support

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**PO2391**

Patient-Reported Symptoms and Subsequent Risk of Myocardial Infarction in CKD

**Benjamin Ligard,1 Leila R. Zelnick,2 Kevin D. O’Brien,3 Nisha Bansal.4 University of Washington, Seattle, WA.

**Background:** Patient-reported symptoms often precede clinical acute presentations of atherosclerotic cardiovascular disease (ASCVD), and include chest pain, shortness of breath, and inability to climb stairs. Patients on dialysis frequently have atypical or absent symptoms related to ASCVD; however, it is unknown whether these same findings are observed in patients with non-dialysis requiring chronic kidney disease. We examined time-updated symptoms of ASCVD and their associations with incident acute myocardial infarction (MI) in a large prospective CKD cohort.

**Methods:** We studied participants from the Chronic Renal Insufficiency Cohort (CRIC) study who had available symptom data. Chest pain, shortness of breath, and inability to climb stairs were evaluated using the Kidney Disease Quality of Life Instrument (KDQOL-36) at each annual study visit, and were categorized as "no symptoms", "mild symptoms", "moderate or worse symptoms". Associations between categorical time-updated symptoms and interim MI were assessed using Cox regression models with adjustment for potential confounders. We tested for interaction by prior MI, eGFR, and diabetes.

**Results:** Among 3909 study participants, the mean age was 58 years, and the mean eGFR was 44.3 mL/min/1.73 m2; 22% had prior MI. There were 367 MIs over a median of 7.98 years; median time between symptom assessment and MI was 213 days (IQR 111 to 314 days). Moderate or worse shortness of breath was associated with an 1.83-fold increased risk of MI (95% CI 1.25, 2.67) after adjustment. These associations were also seen for chest pain and inability to climb stairs (HR for moderate or worse chest pain 1.65, HR for severe limitation climbing stairs 1.85) (Table). P-values for interaction by prior MI, diabetes, and eGFR were all not statistically significant (p>0.05).

**Conclusions:** Chest pain, shortness of breath, and inability to climb stairs were significantly associated with increased risk of MI in a large cohort of participants with CKD. This highlights the importance of symptom assessment as early warning signs of ASCVD in patients with CKD.

**Funding:** NIDDK Support, Private Foundation Support

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**PO2392**

SGLT2 Inhibitors: Will They Change the Face of Kidney Care?

**Tucker B. Hurtado,1 Meghan Staudt,2 Jennifer Robinson.3 Spherox Advanced Analytics Group Spherox Global Insights, Exton, PA.

**Background:** This research examines the evolving care and treatment of patients with chronic kidney disease (CKD) and type 2 diabetes (T2D), including the introduction and adoption of SGLT2 inhibitors. It includes trending on perceptions across segments.

**Methods:** A total of 1,030 CKD non-dialysis patient records were collected from 183 nephrologists via an online, HIPAA-compliant form in October and November 2020

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Results: CKD patients often experience a range of comorbidities and treatments throughout their disease. The optimal eGFR level nephrologists report they would initiate a CKD patient on an SGLT2 inhibitor is 57.1 ml/min/1.73m², or early in Stage 3, which is much earlier than the initiation of other treatments such as nutritional vitamin D and ESAs. Upon referral to a nephrologist, one-in-ten patients with CKD and T2D are already prescribed an SGLT2 inhibitor; this increases as the patient is under nephrology care, up to nearly one-in-five patients; however, there remains room for substantial growth - most notably in CKD patients without T2D, with just 3% having ever been treated with an SGLT2 inhibitor. While nephrologists have been slow to adopt SGLT2 inhibitors firmly into their treatment paradigms, other physicians report a higher percentage of their DKD patients treated with an SGLT2 inhibitor, especially endocrinologists (34%). One-third of nephrologists report trepidation over prescribing SGLT2 inhibitors in their DKD patients, a percentage that has stayed remarkably consistent over the past year and is nearly mirrored by those who claim they have no trepidation in prescribing. This hinderance only increases (to 44%) when they consider prescribing the agents in non-diabetic CKD patients. However, anticipated use of SGLT2 inhibitors in DKD patients is high across specialists, highlighting the opportunity this class of drugs has to make an impact on the treatment of CKD non-dialysis patients.

Conclusions: As SGLT2 inhibitors offer benefits to diabetic and non-diabetic CKD patients, physicians are poised to begin treatment earlier in disease progression, especially with dapagliflozin now approved for CKD patients with and without diabetes.

PO239

Prescribing Patterns of Sodium-Glucose Cotransporter 2 Inhibitors in Patients with CKD

Min Zhu, 1,2 Jiuhua Li, 2 David B. Mount, 2 David J. Steele, 2 David J. Lucier, 3 Mallika L. Mendu, 2 ‘Beth Israel Deaconess Medical Center, Boston, MA; 2Brigham and Women’s Hospital Department of Medicine, Boston, MA; 3Massachusetts General Hospital, Boston, MA.

Background: Since the publication of the EMPA-REG trial in 2015, sodium-glucose cotransporter-2 inhibitors (SGLT-2i) have been demonstrated to slow chronic kidney disease (CKD) progression in patients with diabetic kidney disease (DKD). More recently in October 2010, the DAPA-CKD trial demonstrated SGLT-2i slows CKD progression regardless of diabetes (DM) status. We evaluated the adoption of these novel therapeutics in CKD patients, without and with DM.

Methods: A cross-sectional study of the Mass General Brigham Health System CKD registry was conducted in March 2021. All adult patients with non-dialysis CKD stages 3-5 were included. Multivariable logistic regression models were used to assess factors associated with SGLT-2i use in patients without and with DM.

Results: Among 49,587 non-DM, CKD patients, 1,145 (3.3%) were taking SGLT-2i. Of 22,653 DM, CKD patients, 1,442 (6.4%) were taking SGLT-2i. As shown in the Figure, younger age, Male sex, Black race, history of heart failure, and cardiologist visit in the past year were associated with higher rates of SGLT-2i use in both cohorts. In patients with DM, nephrologist visit in the past year was associated with a higher rate of SGLT-2i use, whereas advanced CKD stages were associated with lower rates of SGLT-2i use.

Conclusions: Despite a well-demonstrated benefit of SGLT-2i, the adaption of these novel agents remained extremely low in the CKD population, particularly among patients without DM. Given the approval of SGLT-2i in CKD in May 2021, interventions to increase SGLT-2i usage and improve outcomes in patients with CKD are urgently needed.

PO2394

Identification of Common Medication Therapy Problems in a High-Risk CKD Population

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Background: Medication therapy problems (MTPs) are commonly experienced by patients with chronic kidney disease (CKD) and have the potential to increase morbidity, mortality, and healthcare costs. As part of the Kidney Coordinated Health Management Partnership (Kidney CHAMP), an NIH funded, pragmatic randomized controlled trial testing an electronic health record (EHR) based population health management approach to improve CKD care, we characterize the types and prevalence of MTPs in a population of high-risk CKD patients.

Methods: Eligible patients are 18 to 85 years old with CKD who have a high risk of progression to ESKD and are not being followed by a nephrologist. MTPs are identified through pharmacist-led telephonic medication therapy management (MTM) and electronic consult by nephrology specialists. Recommendations for resolution of MTPs are provided in the EHR to the primary care provider for review at the upcoming office visit.

Results: To date, in 493 intervention patients, 724 MTPs have been identified. Most patients (76%) experienced at least one MTP. The most common MTP identified was ‘needs additional medication therapy,’ followed by ‘suboptimal medication,’ and ‘dosage too high.’ New indications for SGLT2 inhibitors contributed largely to the ‘needs additional medication therapy’ category. The most common suboptimal medications identified were NSAIDs, with 15% of patients reporting over the counter or prescription use.

Conclusions: Patients with high-risk CKD experience a sizeable burden of MTPs. Identification of existing MTPs in the community setting is an important first step in the optimization of a medication paradigm, with the succeeding goal to resolve and prevent MTPs and improve CKD care and outcomes.

Funding: NIDDK Support

PO2395

Treatment with IL-17 Inhibitors Is Associated with Reduced eGFR in Patients with Psoriasis or Psoriatic Arthritis: A Retrospective Cohort Study

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Background: The complex interplay of the cytokines within the IL family can both mediate and modulate inflammation. Specifically, the cytokine IL-17 has been implicated in several disease processes including hypertension, cardiovascular, autoimmune, and chronic inflammatory diseases. However, there is emerging evidence that IL-17 can also favorably modulate inflammation. It has been demonstrated that low-dose IL-17 therapy may prevent and reverse diabetic nephropathy in mouse models. We aimed to study the effect of IL-17 inhibitors on eGFR in human subjects.

Methods: We conducted a single-center retrospective cohort study of patients who had been treated with an IL-17 inhibitor ( ixekizumab or secukinumab), for the treatment of psoriasis (P) or psoriatic arthritis (PA). Demographics and serum creatinine values were extracted from the electronic medical record. Aggregated data in a 6 month window at 6-months prior to initiation of the IL-17 inhibitor and 12 months after initiation of the IL-17 inhibitor were analyzed using paired t-test. Estimated GFR was calculated using the CKD-EPI equation.

Results: We identified 307 patients who had been treated with IL-17 inhibitors. We included 65 patients who had serum creatinine values at pre-specified time periods before and after initiation of treatment. At baseline, the mean age was 50.3±12 years, 43% were men, 51(78%) had a diagnosis of hypertension, 11(17%) had a diagnosis of diabetes, and mean eGFR was 83.6 mL/minute/1.73 m². One year after initiation of IL-17 inhibitor therapy, mean eGFR was significantly lower at 78.7 mL/minute/1.73 m² (p < 0.001). After excluding patients taking medications known to affect eGFR (n=26), there was still a significant decrease in eGFR after 1 year (58 versus 33 mL/minute/1.73 m², p < 0.01).

Conclusions: In patients with P or PA, IL-17 inhibitor therapy is associated with a reduction in eGFR at 1 year after initiation of treatment. Prospective study with longer follow-up is needed to determine the long-term effect of IL-17 inhibitor therapy on kidney function.
PO2396
Network Meta-Analysis for Prevention of Kidney Function Decline Using Uric-Acid-Lowering Therapy in CKD Patients

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Background: Several previous studies have suggested that uric-acid-lowering therapy (ULT) can slow the progression of chronic kidney disease (CKD). However, few studies have evaluated the effects of each ULT treatment on kidney function, although this topic is crucial for CKD patients. This systematic review aimed to summarize evidence from randomized controlled trials (RCTs) concerning the effects of ULT on kidney function.

Methods: We performed a systematic search and selected RCTs in CKD patients comparing the effects of ULT on kidney function. We performed a network meta-analysis to compare each ULT indirectly. The primary outcome was change in estimated glomerular filtration rate (eGFR) from baseline. Treatment effects were summarized using random-effects model.

Results: Ten studies were selected with a total of 1480 patients. Topiroxostat significantly improved eGFR compared to placebo (MD [95% CI]; 1.49 [0.08; 2.90], P = 0.038) (Fig. 1). Although Febuxostat did not show a positive effect overall, it significantly improved renal function (eGFR) in a subgroup analysis of CKD patients with hyperuricemia (MD [95% CI]; 0.85 [0.02; 1.67], P = 0.045) (Fig. 2). Allopurinol and pegloticase did not show good effects.

Conclusions: Topiroxostat and febuxostat have better renoprotective effects in CKD patients. We believe that the results of this study allow us to recommend ULT with topiroxostat or febuxostat for patients with CKD.

PO2397
Prevalence of Polypharmacy and Associated Adverse Health Outcomes in Patients with CKD: A Systematic Review and Meta-Analysis

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Background: Patients with chronic kidney disease (CKD) are at increased risk of adverse health outcomes associated with excessive medication use (polypharmacy) due to impaired kidney function and multimorbidity. However, data on the associations of polypharmacy and adverse health outcomes in this population are limited. We conducted a systematic review and meta-analysis to determine the prevalence of polypharmacy and its associated health consequences in CKD.

Methods: The study was conducted using a pre-specified study protocol and adheres to PRISMA reporting guidelines. Six electronic databases were searched from inception to September 2020 for studies that included patients with CKD, use of polypharmacy, and associated adverse health outcomes. Random effects models were used to pool the prevalence of polypharmacy and associations with health outcomes.

Results: 53 eligible articles (n = 477,909 patients) met criteria for inclusion. The pooled prevalence of polypharmacy and excessive polypharmacy was 76.2% (95% CI 73.2%-79.1%) and 91.5% (95% CI 90.0%-92.6%), respectively (Fig. 1). The prevalence of polypharmacy was 72.7% and 87.1% in non-dialysis CKD and dialysis populations, respectively. 17 studies reported significant associations between polypharmacy and adverse health outcomes. These studies found an increased risk for potentially inappropriate medication use, drug-drug interactions, drug-related problems, medication-related problems, adverse drug reactions, decreased quality of life, decreased kidney function, hospitalization, and mortality.

Conclusions: Polypharmacy is common in CKD and linked to adverse health outcomes. Our findings highlight the need for improved prescribing practices in CKD and the development of strategies to reduce polypharmacy.

PO2398
Risk of Bias in Observational Studies Assessing the Relationship Between Proton Pump Inhibitors and Adverse Kidney Outcomes

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Background: Proton pump inhibitors (PPIs) are widely prescribed as acid-suppression therapy. However, some observational studies suggest that long-term use of PPIs is potentially associated with adverse kidney outcomes. We assessed potential bias in observational studies reporting on putative associations between PPIs and adverse kidney outcomes.

Methods: Searches in EMBASE and PubMed identified relevant English language articles published in the last 10 years. Risk of bias on an outcome-specific basis was evaluated using Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) by 2 independent reviewers (PROSPERO Registration: CRD42021227555).

Results: Of 620 identified records, 26 studies met a priori eligibility criteria and underwent risk of bias assessment. 19 studies were rated as having a moderate risk of bias.

Conclusions: Observational studies suggesting kidney harm by PPIs were found to have a moderate to serious risk of bias using the ROBINS-I tool, making it challenging to establish causality. Additional high-quality, real-world evidence among generalizable populations is needed to better understand the relation between PPI treatment and acute/chronic kidney outcomes, taking into account the effects of varying time periods of PPI treatment, potential self-treatment with over-the-counter PPIs, and adequate control for potential confounders.

Funding: Commercial Support - Takeda
Treatment Adherence Support and Relationships with CKD Providers: A Qualitative Analysis

**Background:** Adherence is critical in chronic kidney disease (CKD) to delay progression to kidney failure. Treatment plans for CKD can include medications, diet, and exercise. Overall adherence to treatment is low in CKD, and also as few as 40% of new kidney failure patients have any documented CKD-related care. The purpose of this study was to explore CKD patients’ experiences of adherence to treatment plans and what role their healthcare providers had in supporting adherence.

**Methods:** As part of a larger mixed-methods study of Chronic Renal Insufficiency Cohort (CRIC) study participants, a subset was randomly selected for 1:1 interviews. All CRIC participants are >45 years with CKD stages 1-4, and this sample consisted of University of Pennsylvania participants interviewed in 2019-2020. Participants described their experiences with adherence and what they have done when experiencing difficulty. Interviews were recorded, transcribed, and coded using conventional content analysis.

**Results:** The sample (n=32) had a mean age of 67 years, 53% women, 59% non-white. After analysis of factors relevant to treatment planning and adherence, four themes emerged: patient factors (multiple chronic conditions, motivation, outlook), provider factors (attentiveness, availability, communication), treatment planning factors (lack of plan, proactive patient research, provider-focused goals, and shared decision making), and patient responses to the treatment plan (disagreeing with treatment, frustration with their lack of adherence (“I know what to do”), lack of information, and positive feedback). Patients also described the impact of COVID on access to care and the positive impact of family, ancillary providers, and routines/habits.

**Conclusions:** These themes align with behavioral learning theory, which includes: interoceptive (patient factors), external antecedents (provider factors), behavior (treatment planning and attempts at adherence), and consequences (adherence and responses to the treatment plan). Our results provide many potential points of intervention to support treatment adherence in CKD, and a tailored approach is needed to address patients’ specific adherence factors.

**Funding:** Other NIH Support - NINR, NIA
measures include intensive care unit (ICU) admissions, number of hospitalisations per year, number of dialysis sessions, and patient’s choice of treatment methods, including home dialysis. It uses an EHR-based mail-in cohort to mail-invite advanced CKD Veterans; those who do not call-back within 15 days to opt-out, are telephoned for up to 3 times for their interest. Staff survey(n=6) are used to determine effort (time) associated with each activity and aggregated for opt-in/opt-out processes. We examined approach success rates, and study enrollments and efficiency(time per enrollments) as outcomes.

Results: Of the total of 226 randomly selected Veterans mail-invited for study participation over the initial 15 months, approach success rate was 3.9%(n=9) for opt-in method, and 183(69%) for the opt-out approach, with 4(4.8%) requested additional time for decision. Of the remaining 217, study staff were able to approach 157 invites(success rate of 72.4%), resulting in 86(54.8%) enrollments, while 18(10.8%) requested additional time. Significant differences in personnel efforts were seen with an estimated 147±69.2 and 183±70 min, minutes per enrollments(p<0.05) in the opt-in vs. opt-out respectively though, efficiency for enrollment was significantly better for opt-out vs. opt-in 60.2 vs. 30.7(min) approach.

Conclusions: Patient driven opt-in approaches are less effective and efficient for enrollments in clinical and research activities involving the universally recommended servelike kidney disease education.

Funding: Veterans Affairs Support

PO2402
Well-Managed CKD and Its Association with Healthcare Resource Utilization and Costs
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Background: Diabetes and hypertension are prevalent in CKD. The association of coordinated care with outcomes in the setting of these coexisting comorbidities is not well understood. This study evaluated the association between well-managed care and healthcare resource utilization (HCRU) and costs.

Methods: Using the Humana Research Database, this retrospective cohort study identified 241,628 patients with CKD Stage ≥ 3a (3% diabetes, 40% hypertension, 50% diabetes and hypertension, 7% neither diabetes nor hypertension) in 2017. Eligible patients were indexed on first evidence of CKD and required to be enrolled in a Medicare Advantage Prescription Drug plan for ≥12 months pre- and post-index date. Patients who had kidney transplant or hospice episode pre-index were excluded. Well-managed care measures included hemoglobin A1c (HbA1c) monitoring, adherence to glucose medications, cardiovascular (CV) therapy, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARBs), and routine primary care provider (PCP) nephrology visits. HCRU and costs were evaluated within 12-months post-index.

Results: The cohort was 55% female, 77% White, average age of 75 years, and comprised of 67%, 23%, 10%, and 1% patients with Stages 3a, 3b, 4 and 5 CKD, respectively. Patients with diabetes and hypertension who were adherent to well-managed care were significantly less likely to experience an inpatient (IP) admission or emergency department (ED) visit (Table 1) and incurred lower mean monthly costs compared with patients who were not adherent to well-managed care. Similar results were observed for patients with diabetes only, hypertension only, or neither condition.

Conclusions: Well-managed diabetes and/or hypertension in patients with CKD was associated with lower HCRU and costs. Findings may inform innovative models of CKD care coordination.

PO2404
CKD Healthcare Utilization Preceding Unplanned Dialysis in a Large Accountable Care Organization
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Background: Unplanned dialysis initiation or “crash starts” is associated with worse outcomes and higher costs in chronic kidney disease (CKD). Avoiding these events should be a quality improvement priority for accountable care organizations (ACOs). We examined care utilization associated with unplanned dialysis initiation in a large ACO.

Methods: Unplanned dialysis (UDD) initiations in dialysis patients within a large Medicare Advantage Accountable Care Organization and value-based care (VBC) program. A claims analysis of CKD patients who transitioned to dialysis attributed to the ACO or a VBC contract in 2020 with a lookback 2017-2020 was done. Crash start patients initiated hemodialysis (HD) with a central venous catheter in the hospital. Optimal start patients initiated dialysis with outpatient HD or peritoneal dialysis (PD). Those with acute kidney injury, hospital death, urgent start PD, or preemptive transplant were excluded.

Results: A total of 261 patients met criteria for crash starts and 133 for optimal starts. Outpatient utilization and average visits per specialty by patient category are shown in Table 1. Forty percent of crash start patients had no preceding nephrology care in the 12 months prior to dialysis. Optimal start HD patients had more visits with nephrologists and vascular surgery than crash start patients. PD patients had the highest percentage and number of nephrologist visits. Crash start patients with outpatient pre-dialysis care saw a mix of employed nephrologists (45%), independent nephrologists (35%), and non-ACO nephrologists (20%). Average total cost of care was $95,036 for crash starts versus $25,671 for optimal starts in the 12 months prior to dialysis start date including the index admission.

Conclusions: In a large ACO, unplanned dialysis initiation was associated with lower pre-dialysis nephrology and vascular surgery utilization and substantially higher costs. ACOs managing CKD population risk should address the systemic factors leading to crash dialysis starts.

PO2403
Opt-In vs. Opt-Out Approach for Kidney Disease Education and Associated Research
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Background: Clinical research mail-invites require patients to call back for their ability to participate (opt-in). This patient-initiative need reduces efficiency, requires more effort, and limits external validity. Opt-out approach, where research team actively contacts those not choosing to call back, can improve efficiency, especially when those less likely to be admitted to ICU (52.7% vs. 80.2%, p<0.001). In patients who chose RPC, those with ACP were less likely to have a change in decision for conservative management of CKD (8.6% vs. 20.2%, p=0.018), had fewer hospital admissions a year (1.21 vs. 1.92, p=0.001) and were less likely to require palliative referral (44.2% vs 61.5%, p<0.001).

Conclusions: ACP should be considered in CKD patients to help align goals of care and treatment preferences. When considering patients who chose RPC, patients who undergo ACP are more likely to be consistent with their plan for conservative management of CKD, including a reduced utilization of resources like ICU care, palliative care involvement and hospital admissions. This ensures appropriate diversion of resources and allows alignment to patient’s treatment preferences.

PO2405
Comparing Tele nephrology (TN) vs. Face-to-Face (F2F) Visits: A Comprehensive Outpatient Nephropthologist Patient Perspective-Based Randomized Controlled Trial

Background: Little is known about patient perspectives on the quality of care provided via TN compared to F2F visits. We aimed to use objective survey data to study patients’ perspectives on outpatient nephropthology care received via TN (phone and video) versus F2F visits.

Methods: We retrospectively studied adults who received outpatient nephropthology care at Mayo Clinic, Rochester, MN, from March 1st - July 31st 2020. We used a standardized structured survey methodology to evaluate patient satisfaction across TN versus F2F visits. The primary outcome was the percent of patients who responded with a score of very good (4) or very good (5) on a 5-point Likert scale on survey questions that asked their perspectives with regard to access to their nephropthologist, their relationship with care provider, and when relevant – their opinions on the tele nephrology technology, and

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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their overall assessment of the care they received during the nephrology visit. Wilcoxon rank sum tests and chi-square tests were used as appropriate to compare tele nephrology versus face-to-face visits

Results: 3,486 of the patient encounters were face-to-face, 808 via phone and 317 via video. 443 patients responded to satisfaction surveys, and 21% of these had TN encounters. Established patients made up 79.6% of TN and 60.9% of F2F visits. There was no statistically significant difference in patient perceived access to health care, satisfaction with their care provider, or overall quality of care between patients who received care via TN versus F2F.

Conclusions: Patient satisfaction was equally high amongst those patients seen face-to-face or via telenephrology.

Table 1: Patient Survey Results

<table>
<thead>
<tr>
<th>Description</th>
<th>Access</th>
<th>Phone</th>
<th>Video</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ease of booking your appointment</td>
<td>0.90% (66/7329)</td>
<td>1.0% (17/1690)</td>
<td>2.1% (26/1232)</td>
</tr>
<tr>
<td>Ease of contacting your provider</td>
<td>0.90% (66/7329)</td>
<td>1.0% (17/1690)</td>
<td>2.1% (26/1232)</td>
</tr>
<tr>
<td>Overall satisfaction</td>
<td>0.90% (66/7329)</td>
<td>1.0% (17/1690)</td>
<td>2.1% (26/1232)</td>
</tr>
</tbody>
</table>

Wilcoxon Rank Sum test was used. F2F = Face-to-face; TN = Telemphrology; Video = Video Call

PO2406

Depressive Symptom Trajectory and CKD Progression: Findings from the Chronic Renal Insufficiency Cohort (CRIC) Study

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Background: While depressive symptoms (DS) are highly prevalent in adults with early-stage chronic kidney disease (CKD), little is known about its course over time. We identified trajectories of DS and evaluated their association with CKD progression in adults with CKD enrolled in the CRIC study.

Methods: DS were assessed using the Beck Depression Inventory (BDI), at baseline and biennially. Higher BDI scores are consistent with more severe DS. Glomerular filtration rate (GFR) was estimated at baseline and annually. Group-based trajectory models were used to determine trajectories of BDI and eGFR over time. The association between these trajectories was assessed using multinomial logistic regression, adjusting for socio-demographics, lifestyle factors, and comorbidities.

Results: Among 3113 participants at baseline: μ = 58 years, 45.5% female, μGFR = 74 mL/min/1.73 m² and μBMI = 7.6. We identified three BDI trajectory patterns (persistently low, persistently moderate, and persistently high [Figure 1a]), and three trajectory patterns for eGFR (non-linear decline, linear decline, and stable [Figure 1b]). Odds of non-linear eGFR decline were higher for adults with persistently moderate BDI (OR, 1.51; 95% CI, 1.11-2.06) and those with persistently high BDI (OR, 1.75; 95% CI, 0.99-3.07), compared to counterparts with persistently low BDI scores. No association was evident between BDI scores and linear eGFR decline.

Conclusions: In this CKD cohort, moderate and high DS that persisted over time were associated with non-linear eGFR decline. Intervention studies are warranted to test the effect of depression prevention and treatment on CKD progression.

PO2407

Health-Related Quality of Life and Depression Score Differences in Brazilian and US CKD Patients

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Background: CKD patients suffer from many issues, increasing in prevalence and severity as disease progresses, that may affect their perceptions of health-related quality of life (HRQOL) and increase depression symptoms (DS). A patient-centered care approach including systematic assessment of self-reported HRQOL and DS as CKD progresses facilitates tailoring the treatment to individual patient concerns. This study examines the relationship at baseline between CKD stage and patient responses to the KDQOL-36 and CEDS-10.

Methods: We studied 1,801 CKDOPPS participants (629 Stage 3, 1,009 Stage 4, and 263 Stage 5) from Brazil (n=598) and the US (n=1203). Patients at different CKD stages at study selection were compared for differences at baseline in scores of DS (CESD-10 [Kohout, higher score worse, max 40]) and HRQOL (KDQOL-36, higher score better, each scale max 100). The KDQOL-36 yields the Physical Component Summary (PCS) and Mental Component Summary (MCS) from the SF-12v1; Burden of Kidney Disease (BKD); Symptoms of Kidney Disease (SKD); and Effects of Kidney Disease (EKD).

The Kruskal-Wallis Test assessed differences among groups.

Results: Patients’ mean age, albumin, and BP did not differ in the 3 CKD groups. Mean Hb was lower for CKD 5 (10.8) and 4 (11.3) than for CKD 3 (12.7); patients, but only slight mean difference occurred in DS and MCS by CKD stage. Mean PCS scores was 39.8 and 37.9 in CKD 3 and 5 respectively. The largest mean difference in HRQOL scores by CKD stage was for BKD: 77.3 in CKD 3, 69.4 in CKD 4, and 58.0 in CKD 5 (p <.0001). Lower HRQOL scores were found for more advanced CKD stage: FKD (85.13, 79.7, and 76.0 in CKD 3, 4, and 5, p<.0001) and SKD (79.95, 77.8, 77.1, p=0.007). Compared to U.S. patients, those in Brazil had higher PCS scores (40.1 vs 37.5) but lower BKD scores (62.3 vs 74.4); other scores did not differ by country.

Conclusions: HRQOL baseline scores for CKD patients show a greater difference in the BKD scores; differences by CKD stage were not seen in MCS and CEDS-10 scores; and minimal difference occurred for PCS scores. These results potentially can help address patients’ problems and concerns at different CKD stages.

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PO2408

The Spectrum of Kidney Disease and Outcomes in US Veterans with Inflammatory Bowel Disease

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Background: Glomerular and tubulointerstitial diseases have been associated with inflammatory bowel disease (ulcerative colitis, UC and Crohn’s disease, CD). However, the clinical outcomes of UC and CD patients who underwent kidney biopsy are not well described. We present a case series of the kidney biopsy findings and clinical outcomes of veterans with UC and CD from the US Department of Veteran’s Affairs (VA) health system.

Methods: We performed a retrospective review of the VA electronic health record. Patients were included if they had UC or CD diagnosed by gastroenterology evaluation and biopsy. Kidney biopsy data including primary and secondary diagnoses, degree of interstitial fibrosis and tubular atrophy (IFTA), and degree of arteriosclerosis were extracted from biopsy reports. Incident end-stage kidney disease (ESKD) was defined as requirement of renal replacement therapy. All analyses were performed using SAS.

Results: Of 59,007 patients with an ICD code of inflammatory bowel disease, 66 patients had kidney tumor biopsies and 140 patients (91 with UC and 49 with CD) underwent biopsy to evaluate intrinsic kidney disease. At the time of kidney biopsy, the mean serum creatinine was 2.9 mg/dL for UC and 3.4 mg/dL for CD and the mean
urine protein to creatinine ratio was 3.8 g/g for UC and 3.0 g/g for CD. The 5 most common primary diagnoses were IgA nephropathy (16%), diabetic nephropathy (14%), acute interstitial nephritis (12%), FSGS (8%), and membranous glomerulopathy (6%). Additionally, 13% of patients had interstitial nephritis (acute or chronic) as a secondary diagnosis. Moderate or severe IFTA was seen in 45% of biopsies. 24 UC patients (26%) and 10 CD patients (20%) progressed to ESKD, with a mean time from kidney biopsy of 3.1 and 1.9 years, respectively. 41 UC patients (45%) and 17 CD patients (34%) died, with a mean time from kidney biopsy of 4.3 and 4.6 years, respectively.

**Conclusions:** Among US Veterans with UC or CD who underwent kidney biopsy, the most common findings were: IgA nephropathy, interstitial nephritis, and diabetic nephropathy. Patients who had advanced kidney disease at biopsy, and subsequent ESKD or death were common within a relatively short time period. These findings suggest a delay in diagnosis and possibly a low rate of diagnosis. Greater provider awareness may lead to earlier detection and improve outcomes.

**Methods:** In a cohort of 418,830 MA enrollees, we identified trajectories of stage 2 CKD progression (measured by the Kidney Failure Risk Equation [KFRE]) from 2014-2018 via group-based trajectory modeling. Multinomial logistic regression was used to identify patient factors associated with each trajectory. Mean total costs one year before and two years after baseline are described.

**Results:** The cohort had a mean age of 72.6 years, was predominantly female (57.2%) and White (67.8%), with mean baseline eGFR of 75.3 ml/min/1.73m². Median follow-up was 2.6 years. We identified 5 trajectories of kidney function: stable function (22.1%); slow decline with mean baseline eGFR 78.3 (30.1%), slow decline with mean baseline eGFR 71.0 (28.5%); steep decline (16.4%); accelerated decline (2.9%). In adjusted analyses, higher odds of accelerated decline (vs. stable kidney function) were found in those aged 75 and older, (odds ratio (OR)=2.84, 95% confidence interval (CI): 2.38-3.38), living in a non-metropolitan area (OR=1.26, 95% CI: 1.18-1.35), with lower eGFR at baseline (OR=0.64, 95% CI: 0.63-0.64), greater comorbidity (OR=1.28, 95% CI: 1.27-1.29), having a nephrologist visit (OR=2.06, 95% CI: 1.81-2.34) or clinical diagnosis of CKD (OR=4.41, 95% CI: 4.11-4.74) during the year prior to baseline. Mean total MA costs of enrollees with accelerated kidney function decline were nearly twice as high as costs of MA enrollees in the other 4 trajectories in every year ($27,856 versus $13,507) for stable kidney function during the first year.

**Conclusions:** The small fraction of MA enrollees with accelerated loss of kidney function have disproportionately higher costs than other enrollees with stage 2 CKD and may benefit from closer clinical management to minimize progression and contain costs.

**Funding:** Other U.S. Government Support

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**PO2409**

**Healthcare Costs Associated with Systemic Lupus Erythematosus (SLE) in the Year Prior to Diagnosis of ESKD: Real-World Evidence from Two Databases in the United States**

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**Background:** Approximately 40% of patients with SLE develop lupus nephritis (LN), many of whom may progress to ESKD; however, data on the economic burden of ESKD in patients with SLE are scarce. This study described healthcare resource utilization (HCRU) and costs for patients with SLE in the 12 months before ESKD diagnosis in the US.

**Methods:** This was a retrospective study (GSK Study 215925) of 2 US administrative claims databases (IBM MarketScan [DB#1], Optum Research [DB#2]), conducted from March 1, 2011, to December 31, 2019. Patients were adults with SLE and newly diagnosed ESKD. Study results focus on patients with 12-month continuous enrollment prior to ESKD diagnosis reported by HCRU and costs (2019 US$) during this period.

**Results:** In total, 1,356 (DB#1) and 425 (DB#2) patients with SLE and ESKD were identified (DB#1/DB#2): female 81.8%/79.3%; mean (standard deviation [SD]) age: 46.7 (12.3)-46.3 (14.0) years. Mean (SD) Quan-Charlson Comorbidity Index score in the 12 months prior to ESKD was 2.95 (1.9) and 3.05 (2.0) in DB#1 and DB#2, respectively. The mean (SD) healthcare cost in the 12 months pre ESKD was $64,887 (106,822) (DB#1) and $68,219 (137,704) (DB#2) (Table). In the 12-month pre-ESKD period, HCRU was similar across databases and oral corticosteroids were the most commonly prescribed SLE-related medications (Table).

**Conclusions:** Patients with SLE incur substantial HCRU and costs 1 year before ESKD diagnosis, reflecting the clinical and economic burden of SLE and ESKD.


**Funding:** Commercial Support - GSK

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**PO2410**

**Patterns of Progression of Stage 2 CKD and Associated Costs in Medicare Advantage Enrollees**

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**Background:** The prevalence of chronic kidney disease (CKD) in Medicare beneficiaries has quadrupled in the past two decades. Little is known about progression of CKD in older adults with early CDK. We identify CKD progression trajectories, risk factors and baseline costs for these trajectories in a large cohort of Medicare Advantage (MA) enrollees with stage 2 CKD.

**Methods:** Applying Predictive and Causal Analytics to Design Inteligently Targeted Outreach to Address Underrecognition of CKD

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**Background:** 43% of adults with advanced Chronic Kidney Disease (CKD) are unaware of their disease. 2 priorities for The National Institute of Diabetes and Digestive and Kidney Research are to create diagnostic models of kidney function, and to promote studies with responsive outcomes. We propose a novel approach to identify undiagnosed members and increase CKD testing.

**Methods:** To target Commercial and Medicare members for CKD testing, we combined 3 techniques: i) machine learning, ii) causal inference, and iii) clinical practice.

**Results:** Using a machine learning model predicted members’ risk of stage 3b+ CKD. With causal inference, we calculated the average per member per year cost-difference over 6 years between an early or late CKD test. Using the members’ risk score, their associated costs, and their expected behavior change we created a targeting threshold. When the cost-difference of testing a member was larger than the threshold, we enrolled those members into our intervention.

**Funding:** Commercial Support - Tricida, Inc.
direct mailers (Dir. M). Members were randomized into a i) control group for Dir. M, ii) a computer-generated randomization for any additional comorbidities, iii) Dir. M with interactive voice response (IVR), iv) Dir. M only, v) Dir. M and email, and vi) Dir. M and email with IVR. Logistic regression was used for the primary outcome of testing for CKD.

Results: We enrolled 76,388 members of which 35,933 were allocated to the control group and 40,455 to the intervention group. A composite of 31 comorbidities and control (age: 80.4 ± 8.3 vs 80.4 ± 8.3, male: 36% [36.3-36.4%] vs 35.9% [35.6%-36.0%], diabetes: 40.8% [40.3-41.2%] vs 41.1% [40.5-41.6%], hypertension: 88.8% [88.5-89.1%] vs 88.6% [88.3-88.9%]). Members that received only Dir. M were not ever statistically different from control. In the intervention group, 85% were reached by 1.62±1.6 contact attempts. Post-hoc analysis found an increase in laboratory services, PCP and Nephrologist usage, nephroprotective drug claims, and new or updated CKD diagnosis at 90 and 180 days (all p<0.05). Direct medical costs were unchanged.

Conclusions: Low-cost outreach with individualized targeting led to significant increases in CKD stage diagnosis and care-gap closure. The study was under powered to observe direct medical cost savings.

Funding: Commercial Support - CVS and Aetna a CVS Health Company

PO2413

Association of Kidney Function with Major Postoperative Events After Noncardiac Ambulatory Surgeries: A Population-Based Cohort Study

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Background: Though people with chronic kidney disease (CKD) frequently receive outpatient surgical care, the associated risks of major postoperative outcomes is unknown. In this study, we estimated the association between estimated glomerular filtration rate (eGFR) and a composite of acute myocardial infarction (AMI) or death after ambulatory non-cardiac surgery.

Methods: This retrospective population-based cohort study used administrative health and laboratory data from Alberta, Canada, and included adults with measured preoperative kidney function undergoing ambulatory non-cardiac surgery between April 2005 and February 2017. We categorized participants into six eGFR categories (in mL/min/1.73m²) of ≥60 (G1-2), 45-59 (G3a), 30-44 (G3b), 15-29 (G4), <15 not receiving dialysis (G5ND), and those receiving chronic dialysis (G5D). The odds of AMI or death within 30 days of surgery were estimated using multivariable generalized estimating equations. Secondary outcomes included the odds of hospitalization, emergency department (ED) and urgent care center (UCC) visits.

Results: We identified 543,160 procedures in 323,521 people with a median age of 66 years (IQR 56-76); 52% were female. Overall, 2,338 people (0.7%) died or had an AMI within 30 days of surgery. Compared with the G1-2 category, the adjusted odds ratio (OR) of death or AMI increased from 1.1 (95% Confidence interval [CI]: 1.0, 1.3) for G3a to 3.1 (CI: 2.6, 3.6) for G5D. The associations between eGFR and the independent components of this outcome were consistent for both death and AMI, and similar for 30-day hospitalization. ED and UCC visits within 30 days were frequent (17%), though similar across eGFR categories.

Conclusions: We found that ambulatory surgery was associated with a low overall risk of major postoperative events, though was significantly higher for people with CKD. This study may inform their perioperative shared decision-making and management, and suggest future refinement of risk stratification approaches based on eGFR may be warranted.

Funding: Government Support - Non-U.S.

PO2414

Association of Multimorbidity and Mortality Risk in US Veterans with New-Onset CKD

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Background: Many patients with CKD live with multiple chronic conditions. We examined the association among multimorbidity and 10-year risk of death in US veterans with incident CKD.

Methods: The cohort included 382,055 veterans with new-onset CKD (estimated GFR<60 mL/min/1.73 m² for ≥3 months) between 2004 and 2018 in the US Veterans Health Administration, followed for up to 10 years or December 31, 2018. Multimorbidity was measured by the total number of comorbidities among 16 conditions based on ICD-9/ICD-10 codes during the 2 years before and up to 6 months after CKD onset, and categorized as 0–1, 2, 3, 4, 5, 6, 7, and 8+ categories. We estimated mortality risk by age groups at CKD onset.

Results: The median number of comorbidities at CKD onset was 4 (interquartile range: 3–6). After multivariable adjustment, the association between increasing multimorbidity and mortality risk was seen in all age groups, but was stronger in younger than older groups (Table). Death risk when having ≥2 comorbidities was >8-fold higher in ages 18-44, but only >2-fold higher in ages 85–100, compared to their age counterparts with 0-1 comorbidity. Multimorbidity patterns also differed by age. For example, among those with ≥2 concurrent comorbidities, the association of multimorbidity and mortality was greater for younger patients. Effective plans for early CKD diagnosis and timely treatment of comorbidities may improve survival in CKD, especially for younger patients.

Funding: NIDDK Support, Other U.S. Government Support

Hazard ratios (95% CI) of death across multimorbidity categories at CKD onset

PO2415

Self-Reported Walk Pace and Cardiovascular Events in Adults with CKD

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Background: Physical function, as measured by self-reported walk pace, is lower in patients with CKD compared to the general population. While slower walk pace has been found to be associated with cardiovascular outcomes in non-CKD populations, its relationship to cardiovascular outcomes in CKD patients has not been fully explored.

Methods: We used data from 3925 adults with mild-to-moderate CKD enrolled in the Chronic Renal Insufficiency Cohort (CRIC) Study. Walk pace (scored 0-4) was self-reported using the Multi-Ethnic Study of Atherosclerosis Typical Week Physical Activity Survey. Outcomes included atherosclerotic events (a composite of myocardial infarction, stroke or peripheral arterial disease), incident heart failure, all-cause death, and cardiovascular death. Multivariable Cox proportional hazard models with time-updated covariates were used to evaluate the association of walk pace with outcomes.

Results: At baseline, mean age was 58 years, 45% were women, 33% had self-reported cardiovascular disease, mean eGFR was 45 mL/min/m², 12% reported brisk or striding walk pace (>3 mph), 39% reported average walk pace (2-3 mph), and 48% reported walk pace of none or casual (<2 mph). During a median follow-up of 11.5 years, there were 725 atherosclerotic events, 790 incident heart failure events, 1333 deaths from any cause, and 434 cardiovascular deaths. In fully adjusted models, there was a graded association between walk pace and risk for each outcome (Figure).

Conclusions: In this cohort of adults with CKD, faster self-reported walk pace was associated with lower risk of cardiovascular events and mortality. These findings may have implications for risk stratification, as well as for future interventions targeting physical function in patients with CKD.

Funding: NIDDK Support
Low Magnesium Predicts Cardiovascular Outcomes in Pre-Dialysis CKD Patients: Results from the KNOW-CKD Study

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Background: There are few large-scale studies of the association between magnesium (Mg) and cardiovascular (CV) outcomes in pre-dialysis chronic kidney disease (CKD) patients. Therefore, we analyzed the effects of Mg on CV outcomes in a large-scale cohort of pre-dialysis CKD patients.

Methods: We investigated the association between serum Mg and CV outcomes in a prospective, multi-center cohort of pre-dialysis CKD patients (n=1,646). Patients were divided into four groups according to serum Mg concentration. The primary endpoint was composite outcome, defined as either a CV event and/or all-cause death. Secondary outcomes were coronary artery calcification (CAC) progression and arterial stiffness progression as assessed by mean brachial-ankle pulse wave velocity (baPWV).

Results: During a median follow-up of 6.0 years, 196 (11.9%) patients had the composite outcome of a CV event and/or all-cause death. In a multivariable causal-specific model, patients in the lowest Mg group (serum Mg ≤2.0 mg/dL) had an elevated risk of a composite outcome (hazard ratio (HR) 1.71 [95% CI 1.02-2.84]; P=0.038; serum Mg ≤2.2 mg/dL as the reference group). Subgroup analyses showed that low Mg was particularly associated with risk of a composite outcome in patients with early CKD and those who were male. Patients in the lowest Mg group also had increased risks of progression to CAC and arterial stiffness relative to the reference group (Mg =2.2 mg/dL).

Conclusions: Low Mg level is a predictor of cardiovascular outcomes in pre-dialysis CKD patients.

Baseline Renal Function and Left Ventricular Assist Device Outcomes Among Patients with CKD

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Background: Chronic kidney disease (CKD) is associated with increased risk of cardiovascular disease. Coronary artery disease is one of the most important causes of heart failure with reduced ejection fraction, a condition for which advanced therapies such as left ventricular assist device (LVAD) and orthotopic heart transplant (OHT) are increasingly utilized. Information about outcomes of CKD patients with LVADs is limited.

We studied the outcomes of patients with CKD who had received LVAD in a large cohort.

Methods: We performed a retrospective multi-center cohort study using TriNetX Research Network database, a federated electronic medical records network, to identify 4939 patients between 18 years from 31 healthcare organizations, from the United States, who had undergone LVAD implantation between 1/1/2010 and 12/31/2019. We excluded 1552 patients with estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m². We grouped the eligible patients into stages of CKD, based on eGFR: stages: 2 (n=1140), 3a (n=821), 3b (n=563), 4 (n=182), and 5 (n=631)). The primary and secondary outcomes were survival and receiving an OHT within one year of LVAD implantation, respectively.

We used CKD stage 2 as the reference and calculated the odds ratio (OR) with [95% confidence interval (CI)] of each of the two outcomes.

Results: A total of 172 patients died within one year of LVAD implantation. When compared with Stage 2 CKD, and after propensity score matching, there was a decrease in the OR of survival at one year with higher stages of CKD: —Stage 3b: OR: 0.64 (95% CI 0.41-0.99), —Stage 4: OR: 0.42 (0.24-0.73), —Stage 5: OR: 0.57 (0.38-0.86).

The table shows significant difference in the odds of survival between stage 3a and the reference group. A total of 274 heart transplants were performed within the first year after LVAD implantation. Patients in the reference group were more likely to receive an OHT within the first year in comparison with CKD stage 5 patients (OR: 1.61; CI: 1.06-2.45).

Conclusions: An advanced stage of CKD is associated with decreased survival in LVAD patients. Patients with CKD stage 2 are more likely to undergo OHT compared to those with CKD stage 5.

Association Between Estimated Glomerular Filtration Rate Decline and Clinical Outcomes in Non-diabetic CKD

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Background: There is limited evidence on association between surrogate laboratory endpoints and hard clinical outcomes in chronic kidney disease (CKD). This real-world data analysis investigated dependence between relative estimated glomerular filtration rate (eGFR) decline of ≥30%, ≥40%, and ≥57% and cardiovascular and renal-renal outcomes in non-diabetic CKD patients treated in routine clinical practice.

Methods: Individual-level data from the US claims database, Optum Clinformatics Data Mart (CDM), for years 2008 – 2018 were analysed. Adult individuals were required to have had at least one eGFR value in the follow-up period of a median 744 days. Proportion of the patients with eGFR decline of ≥30%, ≥40%, ≥57% was 5%, 3% and 1%. More rapid eGFR decline was associated with increased risk of the outcome. The hazard ratio for HFI and a composite of ESKD/kidney failure/need for dialysis. To investigate the association between eGFR decrease and clinical outcomes, an intercurrent event analysis was performed using eGFR decline of ≥30%, ≥40% or ≥57% as an intercurrent event.

Results: Of 64 million individuals in Optum CDM, 504,924 satisfied the selection criteria, median age 75 years, 60% female, 10% Black. At baseline, eGFR values were available for 62% of individuals; median eGFR was 53; 94% of those patients had at least one eGFR value in the follow-up period of a median 744 days. Proportion of the patients with eGFR decline of ≥30%, ≥40%, ≥57% was 5%, 3% and 1%. More rapid eGFR decline was associated with increased risk of the outcome. The hazard ratio for HIFH was 3.03, 3.41, 3.66 and for ESKD/kidney failure/need for dialysis was 5.61, 8.29 and 18.63 in patients with eGFR decline of ≥30%, ≥40%, ≥57% as compared to those with no such decline, respectively.

Conclusions: In this analysis of the US non-diabetic CKD patients treated in routine clinical practice, a relative eGFR decline of ≥30%, ≥40%, ≥57% was associated with a subclinical HR for HIFH and ESKD/kidney failure/need for dialysis, supported by the carefully selected lab-based surrogate measures may be used as early indicators of hard clinical outcomes.

Funding: Commercial Support - Bayer AG

Effect of Obesity and Metabolic Dysfunction on Cardiovascular Events and Progression to ESRD in CKD

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Background: Obesity and metabolic dysfunction increased the risk of cardiovascular event and chronic kidney disease (CKD) progression. However, there are conflicting results on clinical outcomes in obese patients without metabolic dysfunction and it is unclear whether metabolically healthy obesity increases the risk of cardiovascular events and progression to end-stage renal disease in CKD patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
Methods: We enrolled 166,397 CKD patients from Korea National Health Insurance Service (KNHIS) Database Cohort between January 2009 and December 2011. Obesity is defined as body mass index greater than 23kg/m². Metabolic dysfunction was assessed using following components: waist circumference, blood pressure, fasting blood sugar, triglyceride level, high-density lipoprotein cholesterol level. The primary endpoint was the ischemic heart disease, ischemic stroke and progression to end-stage renal disease (ESRD).

Results: Of total CKD patients, the proportion of patients with metabolic dysfunction was significantly higher in obese patients than in non-obese patients (25.1% vs. 5.4%; p < 0.001). The increased progression analysis compared to metabolic health in non-obese patients, metabolic dysfunction significantly increased the risk of ischemic heart disease and progression to ESRD in patients with and without obesity. Patients with metabolically healthy obesity were significantly associated with increased risk of ischemic heart disease (HR 1.22; 95% CI 1.00-1.50) and ischemic stroke (HR 1.46; 95% CI 1.10-1.91). However, the risk of progression to ESRD was not significantly increased (HR 0.98; 95% CI 0.87-1.10).

Conclusions: The metabolic dysfunction was significantly associated with worse clinical outcomes in CKD patients, irrespective of obesity. The metabolically healthy obesity increased risk for ischemic heart disease and ischemic stroke, but not for progression to ESRD.

PO2421

Diet Quality and Kidney Outcomes in Adolescent and Adult Americans: The Strong Heart Family Study

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Background: The burden of chronic and end stage kidney disease (CKD and ESKD), is exceedingly high amongst American Indians (AIs). We sought to examine the relationship of diet quality, a modifiable risk factor, and kidney outcomes in AI adolescents and adults, hypothesizing that poorer quality diets would be associated with incident albuminuria and accelerated eGFR decline in this population.

Methods: This is a secondary analysis of data from the Strong Heart Family Study, a longitudinal study of cardiovascular disease and its risk factors among AIs from Arizona, North and South Dakota, and Oklahoma (n=1721, mean age 39 +/- 16 years, 16% adolescents aged 14-21 years, 61% female, 28% with hypertension, 13% with diabetes, 52% with obesity, 4% with CKD at baseline). Participants completed two exams (baseline: 2001-2003; follow-up: 2007-2009). The primary exposure (at baseline) was the Alimentary Health Effectiveness Index (AHEI), a measure of diet quality on a 119-item food frequency questionnaire. The primary outcomes (at follow-up) were: 1) incident albuminuria (albumin to creatinine ratio 30mg/g); 2) eGFR decline of 30%. Generalized estimating equations were used to examine the association of AHEI (in quartiles) with incident albuminuria and eGFR decline.

Results: In total, 9.9% (5.6% of adolescents) had incident albuminuria and 5.6% of participants (9.2% of adolescents) had eGFR decline of 30%. Median AHEI for the poorest diet quartile was 34 compared to 55 for the healthiest diet quartile, each 10-20 points lower than AHEI scores from studies of the general population. The unadjusted odds ratio (OR) for incident albuminuria comparing extreme quartiles of diet quality (poorest versus healthiest [reference] quartiles) was 1.32 (95% CI 0.92, 1.89). After adjustment for baseline diabetes, eGFR and age, the OR for incident albuminuria was 1.79 (95% CI 1.24, 2.58). There were no significant unadjusted or adjusted associations of diet quality with eGFR decline.

Conclusions: These preliminary results suggest an association of diet quality and incident albuminuria in AI. Given the high burden of CKD in this population, further research is required to determine whether interventions to improve diet quality may improve kidney outcomes.

Funding: NIDDK Support, Other NIH Support - National Heart, Lung and Blood Institute, National Institute of Health, Department of Health and Human Services

PO2422

Renal Function and Effect of Body Mass Index on Mortality Risk After Acute Myocardial Infarction

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Background: Obesity is paradoxically linked to greater survival benefit after acute myocardial infarction (AMI). In patients with renal impairment, higher body mass index (BMI) is also associated with protective effects against cardiovascular and all-cause mortality. However, there are no studies investigating the interactive effects of BMI and renal function on mortality risk after AMI.

Methods: We enrolled 12,647 AMI patients from Korea Acute myocardial Infarction Registry between November 2011 and December 2015. Patients were categorized based on renal function; normal (a90 ml/min/1.73m²), mild (90-45 ml/min/1.73m²), and moderate impairment (<45 ml/min/1.73m²). BMI was divided into four groups; underweight (<18.5 kg/m²), ideal (18.5-25 kg/m²), overweight (25-29.5 kg/m²) and obesity (≥25 kg/m²). The primary endpoint was 2-year mortality after AMI treatment.

Results: In multivariable Cox-regression analysis, compared to ideal weight patients, overweight and obese patients were associated lower risk of mortality and underweight patients had the increased risk of mortality in all renal function categories. However, the survival effect of each BMI stratum was decreased as renal function worsened.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PO2425

Association of Proximal Tubular Secretory Clearance with Decline in Cognitive Function

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Background: Persons with chronic kidney disease (CKD) are at risk for cognitive decline. The retention of protein bound organic solutes, normally cleared by renal tubular secretion, is hypothesized to contribute to cognitive dysfunction in CKD. We tested whether lower kidney clearance of secretory solutes is associated with cognitive decline in a multi-center CKD cohort.

Methods: We studied participants from the Chronic Renal Insufficiency Cohort (CRIC) study, excluding persons with prior stroke or baseline cognitive impairment. We estimated tubular secretory clearance by 24-hour kidney clearance of eight solutes primarily eliminated by tubular secretion. Cognitive function was measured by annual Modified Mini Mental Status (3MS) exams. We defined cognitive decline as a sustained >5 point decrease in the 3MS score from baseline. Associations were assessed with Cox survival models; we controlled for multiple comparisons by calculating q-values as well as the false discovery rate.

Results: Among 2366 study participants, the mean age was 58 years, mean eGFR was 46 ml/min/1.73 m2, and median baseline 3MS score was 96; 23% developed cognitive decline over a median of 7.22 years of follow-up (1.48 events per 100 person-years). Lower kidney clearance of five of the eight solutes was associated with cognitive decline after adjustment for baseline eGFR, urinary albumin excretion, and other potential confounders (q-value<0.05).

Conclusions: Lower kidney clearance of secreted solutes was associated with cognitive decline over long-term follow-up in a prospective CKD cohort. The retention of secretory solutes may be a novel cause of impaired cognition in persons with CKD.

Funding: NIDDK Support

PO2426

Clinical Features and Outcomes of Immunoglobulin G4-Related Disease Including Kidney Involvement

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Background: Immunoglobulin G4-related disease (IgG4-RD) is a newly recognized disease, and a few epidemiologic studies about this disorder have been published. This research aimed to describe the clinical, laboratory, and histopathological features and outcomes of IgG4-RD.

Methods: Ninety-four patients who satisfied the comprehensive diagnostic criteria on IgG4-RD were included in this study. Fifty-eight (61.7%) were women. The mean age was 54.8 years, and the median follow-up duration was 32.9 months. The clinical feature between single and multiple organ involvement and with or without kidney involvement groups were evaluated based on symptoms and laboratory findings. The clinical outcome was assessed according to treatment strategies and response.

Results: Of 94 patients, 56 (59.6%) had multiple organs involvement. It showed a variety of symptoms and organs involved. Patients with multiple organ involvement had higher serum IgG and IgG4 levels than those with single organ involvement. Those with IgG4-related kidney disease (IgG4-RKD) had worse renal function. The incidence of peripheral blood eosinophilia and hypocomplementemia was higher in patients with renal involvement than in those without. Glucocorticoids-based therapy was most commonly used. Thirty-nine (41.5%) achieved complete remission. Eighteen (19.1%) relapsed after response to treatment. Eight (61.5%) of 13 patients with IgG4-RKD experienced improvement in renal function after treatment. None of the patients died during the follow-up period.

Conclusions: Kidney or other organ involvement is not significantly associated with clinical outcomes. Since IgG4-RD has different clinical features, it should be accurately diagnosed. Therefore, all physicians must actively diagnose and treat the condition.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
**PO2427**

Evaluation of Changes in Renal Microperfusion in Hyperuremic-Induced Kidney Injury by Contrast-Enhanced Ultrasonography

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**Background:** The diagnostic tools for early detection of renal injury caused by hyperuricemia are particularly lacking. Our study investigated the application of contrast-enhanced ultrasound (CEUS) in both hyperuremic nephropathy (HN) rats and patients with hyperuricemia induced kidney injury.

**Methods:** Animal study was performed in hyperuricemic rat induced by feeding with a mixture of adenine and potassium oxonate for 4 weeks. In addition, 10 healthy volunteers and 40 patients with hyperuricemia induced kidney injury from CKD 1 to 4 stage were enrolled. CEUS was performed and low acoustic power contrast-specific imaging was used for quantitative analysis. Time-intensity curves (TICs) and quantitative indexes were created by Qlab software.

**Results:** In HN rat model evaluated by CEUS technique, a significant decline in renal cortical perfusion as reflected by lower Peak Intensity (PI) value (25.4±3.1 vs. 37.9±1.75db) and longer time to reach peak (TTP) intensity (34.5±5.9 s vs. 8.5±1.6s) was found when compared to control rats one week after administration of adenine and potassium oxonate, with more pronounced decline in HK rats as compared to control. quantitative assessment of PI was well correlated with the serum K-1 level as well as the fibrosis scores in hyperuricemic rats from mild to advanced disease stage. Clinically, an early decline in PI in renal cortical perfusion was found in CKD stage 1 patients with hyperuricemia induced kidney injury as compared to the control group (61.4±5.2 vs. 65.8±10.1 db), which became progressively less visible in patients with more severe kidney injury in these patients of CKD stage 4 (40.9±13.36 db). An early increase of TTP could also be detected in HK patients with CKD 1 stage as compared to normal control (15.4±2.5 vs. 14.2±3.5), which became the most pronounced in these patients of CKD 4 stage (73.2±2.39s). In addition, Peak value measured by CEUS was correlated with renal function in patients with hyperuricemia induced kidney injury.

**Conclusions:** CEUS is able to detect the renal perfusion in a dynamic way. Renal perfusion measured by CEUS correlates with the renal functional impairment and tubulointerstitial fibrosis, suggesting a sensitive, reliable and non-invasive method that could be applied in the diagnosis of hyperuricemia induced kidney injury in clinical practice.

**Funding:** Government Support - Non-U.S.

**PO2428**

The Effect of Kidney Function on Reference Intervals of Serum-Free Light Chains and Free Light Chain Kappa/Lambda Ratio

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**Background:** A kidney reference interval has previously been published for serum free light chain (FLC) ratio (0.37–3.10) but does not take into account the degree of kidney failure. The aim of this study was to establish a kidney reference interval for FLC and validate the current and propose new kidney reference interval for FLC ratio.

**Methods:** A total of 80,759 participants of the Iceland Screens, Treats or Prevents Multiple Myeloma (iStopMM) study were included. Participants were screened with serum FLC (FREELiTE) measurements and serum protein electrophoresis (SPEP) and immunofixation (IFE). Serum creatinine (sCr) value closest to the screening was used to calculate eGFR. Participants with M-protein, eGFR > 59 mL/min/1.73 m², with a mixture of adenine and potassium oxonate for 4 weeks. In addition, 10 healthy volunteers and 40 patients with hyperuricemia induced kidney injury from CKD 1 to 4 stage were enrolled. CEUS was performed and low acoustic power contrast-specific imaging was used for quantitative analysis. Time-intensity curves (TICs) and quantitative indexes were created by Qlab software.

**Results:** Serum FLC were measured in 4885 (12%) participants with eGFR <60 mL/min/1.73 m², without evidence of monoclonality on SPEP or IFE. Median (IQR) kappa level was 20.6 mg/L (16.0–27.7), lambda level 18.6 mg/L (14.7–24.2) and FLC ratio 1.13 (0.95–1.35). Using current reference intervals, 58% and 20% of persons had values outside the normal range for kappa and lambda, respectively. The FLC ratio was outside the standard reference interval (0.62–1.65) in 8% and the kidney reference interval (0.37–3.10) in 0.6% of persons. Based on these findings, new reference intervals for FLC and FLC ratio have been established (Table).

**Conclusions:** New reference intervals for FLC and FLC ratio are inaccurate for patients with decreased kidney function. We propose new reference intervals for FLC and FLC ratio for use in patients with chronic kidney disease.

**Funding:** Government Support - Non-U.S.

**Reference intervals for kappa, lambda, and FLC ratio depending on kidney function**

<table>
<thead>
<tr>
<th>Kidney Function</th>
<th>Reference intervals (2S.D.)</th>
<th>New reference intervals (2S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;25 (K)/&lt;20 (L)</td>
<td>&lt;25 (K)/&lt;20 (L)</td>
</tr>
<tr>
<td>GFR &lt; 60</td>
<td>25 (K)/20 (L)</td>
<td>10 (K)/10 (L)</td>
</tr>
<tr>
<td>GFR &lt; 30</td>
<td>45 (K)/45 (L)</td>
<td>45 (K)/45 (L)</td>
</tr>
<tr>
<td>GFR &lt; 15</td>
<td>60 (K)/60 (L)</td>
<td>60 (K)/60 (L)</td>
</tr>
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**eGFR:** estimated glomerular filtration rate

**PO2429**

Molecular Stratification of CKD

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**Background:** Current classification of chronic kidney disease (CKD) into stages based on the indirect measures of kidney functional state, estimated glomerular filtration rate and albuminuria, is agnostic to the heterogeneity of underlying etiologies, histopathology, and molecular processes. We used genome-wide transcriptionomics from protein-free kidney biopsies, thereby capturing kidney biological processes, to stratify patients from three independent CKD cohorts.

**Methods:** Self-Organizing Maps (SOM), an artificial neural network machine-learning algorithm, assembled CKD patients into four novel subgroups, molecular categories, based on the similarity of their kidney transcriptomics profiles.

**Results:** The unbiased, molecular categories were present across CKD stages and histopathological diagnoses, highlighting heterogeneity of conventional clinical subgroups at the molecular level. CKD molecular categories were distinct in terms of biomarker pathways, transcription regulation and associated kidney cell types, suggesting that the molecular categorization is founded on biologically meaningful mechanisms. Importantly, our results revealed that not all biological pathways are equally activated in all patients; instead, different pathways could be more dominant in different subgroups and thereby differentially influencing disease progression and outcomes.

**Conclusions:** This first kidney-centric unbiased categorization of CKD paves the way to an integrated clinical, morphological and molecular diagnosis. This is a key step towards enabling precision medicine for this heterogeneous condition with the potential to advance biological understanding, clinical management, and drug development, as well as establish a roadmap for molecular reclassification of CKD and other complex diseases.

**Funding:** Commercial Support - This work was done as part of Renal Precompetitive Consortium (RPC2) collaboration (Tomilo et al, Drug Discov Today 2018) and was partly funded by the participating members: AstraZeneca, Eli Lilly, NovoNordisk, Gilead, Janssen.

**PO2430**

Determinants of Serum β2-Microglobulin and β-Trace Protein in South Asians

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**Background:** β2-Microglobulin (B2M) and β-Trace Protein (BTP) are being considered for use with creatinine and cystatin C to improve the GFR estimation (Inker, AJKD 2020). In a Pakistani population, we showed that B2M and BTP did not improve the performance of eGFRs and eGFRCr-(-s) (Wang, Kidney Week 2021). We aimed to evaluate non-GFR determinants of B2M and BTP in a general population in Pakistan.

**Methods:** We used linear regression models to assess associations between possible determinants and log-transformed levels of B2M and BTP adjusting for measured GFR among 557 participants (≥40 years) from Pakistan. The strength of significant associations was defined as strong, intermediate, or weak if the absolute percent difference in B2M or BTP was >10%, 5%-10%, and <5%, respectively. R² was calculated in a model including all participants.

**Results:** Non-GFR determinants with intermediate and strong associations with both BTP included male sex, history of heart disease, and lower waist circumference. Non-GFR determinants of higher B2M included males, higher total body fat, and lower serum albumin. As shown in Table below, the non-GFR determinants assessed in our study along with measured GFR could explain 64.2% and 78.2% variance of BTP and B2M, respectively.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Table. Determinants and log-transformed filtration markers (N=557).

PO2431
Performance of Serum β2 Microglobulin and β-Trace Protein-Based Glomerular Filtration Rate Estimation Equations in South Asians

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Background: Previously we showed that glomerular filtration rate (GFR) estimation based on cystatin C alone (eGFRcys) had a large bias in a general population in Pakistan, and the GFR estimation based on cystatin C and creatinine (eGFR-cys) was not substantially better than eGFRcr-PK (Wang, KI Reports 2021). β2-Microglobulin (B2M) and β-trace protein (BTP) are being considered for use in a panel including creatinine and/or cystatin C to improve GFR estimation (Inker, AJKD 2020). We aimed to evaluate whether adding B2M and BTP would improve the performance of eGFRcys and eGFRcys in a general population in Pakistan.

Methods: We assessed panel eGFR equations using B2M and BTP in addition to cystatin C (3-panel marker) or creatinine and cystatin C (4-panel marker) in a cross-sectional study of 557 participants (≥40 years) from Pakistan. We compared bias (median difference in measured GFR [mGFR] and eGFR), precision (interquartile range of difference), and accuracy (percentage of eGFR within 30% of mGFR [P30] and root mean square error [RMSE]).

Results: As shown in the Table, the 4-panel equation (addition of B2M and BTP to creatinine and cystatin C) had lesser bias, better precision, and better accuracy (all P<0.001) compared to the 3-panel equation (addition of BTP and B2M to cystatin C). The 3-panel equation worsened bias (P>0.05) and did not improve precision or accuracy (P>0.05). Both relative to eGFRcys. Similarly, the 4-panel equation worsened bias (P<0.001) and did not improve precision or accuracy (P>0.05 for both) compared to eGFRcys.

Conclusions: B2M and BTP did not improve the performance of eGFRcys and eGFRcys in South Asians. Evaluation of non-GFR determinants of BTP and B2M would be of interest.

Funding: NIDDK Support, Other NIH Support - Fogarty International Center (1R03TW007588-01A1)

Table. The performances of GFR estimating equations in comparison with measured GFR (N=557).

PO2432
Rare Variant Analyses in 171,172 UK Biobank Participants Reveals Novel Genetic Associations with Renal Function and Kidney Diseases

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Background: GWASs have identified hundreds of common genetic variants associated with chronic kidney disease (CKD), but the burden of rare loss-of-function (LoF) or pathogenic/likely pathogenic (PLP) variants has not been systematically examined.

Methods: We tested gene-based and variant-level association for 5 renal biomarkers (Glomerular Filtration Rate estimated from serum creatinine and/or cystatin C, Blood Urea Nitrogen, Urine Albumin-to-Creatinine Ratio) measured at enrollment and kidney-related diseases (e.g. End-Stage Renal Disease and stage 4/5 CKD, CKD defined by biomarker and/or diagnosis from NHS data, Cystic kidney disease and Renal calculi) in 171,172 UK Biobank participants of genetically assessed European ancestry and with whole exome sequencing (WES). For each trait, we fit a genome-wide regression model and tested for association using REGENIE V2.0, adjusting for age, sex, 10 ancestry PCs, assessment center, and BMI where appropriate. For gene-based analyses, we generated 15 models to collapse ClinVar-classified LoF and deleterious variants predicted by 16 in silico scores (SIFT, PolyPhen, BayesDel, etc.) from dbNSFP 4.1c.

Results: We identified 33 and 18 genes associated with a2 biomarkers and a1 kidney diseases across collapsing models (FDR<0.05), respectively. PKD1/2, COL4A3/4, CUBN, IFT140 were associated with both biomarkers and kidney diseases. Association analyses also highlighted genes including: COL4A1, CST3, LAMC1, LR2, SLC22A2, SLC34A3 and SH2B3. Variant-level analyses further informed impact on protein, e.g. the SLC22A2 association signal was mainly driven by a frameshift (rs177505) with lowering effects on GFR (p=1e-27, beta=-6.2, MAF=0.12%). The exome-wide variant analyses revealed 29 genes (eg. UMOD) with variant associations (p<5e-8) with >3 biomarkers or 1 endpoint, including 2 that were also implicated from gene-based analyses (COL4A4 and CUBN).

Conclusions: This large-scale study elucidates the genetic landscape of kidney diseases. Our findings validate established genes and reveal novel genetic associations with renal function and kidney diseases.

Funding: Commercial Support - Janssen R&D

PO2433
High Dietary Phosphate Intake Causes Inflammation Tubular Injury and Fibrosis in Mice

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Background: Due to the increasing consumption of processed food, the dietary inorganic phosphate intake clearly exceeds the recommended daily allowance. Elevated phosphate levels are associated with a higher cardiovascular and all-cause mortality in the general population and accelerated progression of chronic kidney disease (CKD). It is under investigation whether chronic phosphate load represents a renal health risk in the absence of CKD.

Methods: Male C57BL/6 mice were fed with a 2% high phosphate diet (HPD) or respective 0.8% normal phosphate diet (NPD) for six months. We collected blood, urine and kidneys to investigate phosphate metabolism, kidney function, tissue alterations and inflammation.

Results: Six months HPD significantly increased plasma levels of the phosphaturic hormone fibroblast growth factor (FGF) 23 resulting in enhanced phosphaturia and elevated serum phosphate level. HPD in mice caused albuminuria and increased plasma creatinine level. Histological analyses revealed that mice on HPD develop proximal tubular injury characterized by loss of cell polarity and brush border membranes, flattened
epithelia, increased proliferation, mononuclear interstitial infiltration and fibrosis. The kidney damage was also demonstrated by increased renal expression of the kidney injury marker Kim-1 and Ngf. Kim-1 accumulated in regions of tubular lesions. Flow cytometry analysis demonstrated that the HPD reduced storage of Ly6Chi monocytes in the spleen and concurrently, enhanced accumulation of F4/80+ macrophages and dendritic cells in the kidney. Histological analyses provided accumulation of F4/80+ macrophages and CD3-+ T-cells in areas of tubular injury that associated with increased renal expression of chemotaxis and growth factors for monocytes and macrophages Ccl2, Cxcl1 and Itj4 in HPD mice. Finally, HPD caused renal fibrosis associated with increased collagen I and Tgf-β expression.

Conclusions: Chronic high phosphate load impairs kidney function by causing a strong inflammatory response and proximal tubular injury in healthy mice. Our results indicate that chronic high phosphate intake might be a renal health risk not only for CKD patients but also for the general population.

PO2434

Apataetone Downregulates Fibrotic, Inflammatory and Calcific Processes in Renal Mesangial Cells: Mechanism for Reduced Cardiac Events in CKD Patients

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Background: Major adverse cardiac events (MACE) are prevalent in patients with chronic kidney disease (CKD). Apataetone inhibits BET proteins, which regulate expression of genes involved in fibrosis, inflammation & calcification. In the phase 3 BETonMACE trial, apataetone reduced MACE in patients with CKD (eGFR<60) implying favorable effects on the kidney-heart axis. Here we examine apataetone’s impact on pathways of nephropathy in human renal mesangial cells (HRMCs).

Methods: HRMCs were stimulated with TGF-b1 or LPS ± 2.5µM apataetone. Gene expression was analyzed by qPCR from HRMCs stimulated with TGF-b1 or LPS ± 2.5µM. Smooth muscle actin (a-SMA) was examined by immunofluorescence & alkaline phosphatase (TNAAL) activity in biochemical assays. RNA-seq from TGF-b1 stimulated HRMCs was evaluated by GO and Ingenuity Pathway Analysis (IPA).

Results: In HRMCs, apataetone suppressed TGF-b1 induced pro-fibrotic gene expression including (a) a-SMA, a fibrotic marker, by 90% p<0.001 & de novo a-SMA protein production (b), an extracellular matrix (ECM) component, by 44% p<0.001 (c) NOX4, promoting reactive oxygen species (ROS) production, by 96% p<0.001 (d) TGF-β1 promoting calcification by 96% & TGF-β1 activity by 90% p<0.001. Apataetone opposed LPS induced inflammatory gene expression: IL6 by 94%, IL1β by 95% & PTGS2 (COX2) by 94% p<0.001. In GO, ECM gene sets were in the top 20 affected by apataetone, indicating reduced fibrosis. IPA predicted inhibition of NFκB signaling in HRMCs to suppress inflammation, and activation of a-SMA utilization & tolerance of ROS production pathways, such as Oxidative Phosphorylation (x-score 5.7 p<0.01 at 25µM; z-score 3.5 p<0.05 at 5µM) and NFR2-Mediated Oxidative Stress Response (x score 2.3 p<0.01 at 25µM; z-score 1.6 p<0.01 at 5µM).

Conclusions: Apataetone downregulates responses to TGF-b1 or LPS that promote fibrosis, inflammation & calcification in HRMCs. Changes in energy metabolism pathways predict apataetone enables HRMC to cope with elevated glucose. Our results provide mechanistic insight into reduced MACE in CKD patients receiving apataetone in the BETonMACE trial, & predict efficacy in the upcoming phase 3 BETonMACE2 trial.

Funding: Commercial Support - Resverlogix Corp.
NGAL Is Necessary for Antigen-Presenting Cells Recruitment and Proteinarina in the Mouse Kidney with Ureretal Obstructio

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Background: Elevated levels of proteinuria are present in patients with chronic kidney disease (CKD) undergoing to UUO and to Sham surgery (Control) during 14 days (n=8). Creatinine and proteinuria were measured from pelvis urine of obstructed kidney. DCs (MHC-II+/CD11c+/F4/80+CD11b+ for DCs type-2 phenotype) and MØ (MHC-II+/CD11c+/F4/80+CD11b+CD86 for M1 phenotype) recruitment were measured by flow cytometry. Additionally, WT-MØ were stimulated with albumin (10ng/ml, 24 h) and M1 genes evaluated by real-time PCR.

Results: We observed that the increased protein/creatinine ratio in the obstructed kidney of UO mouse WT mice was reduced in NGAL-KO mice (24.4±9.0 vs. 12±2.6 p<0.01). In vitro, cell culture stimulation with albumin on macrophages from WT mice increased the mRNA levels of pro-inflammatory M1 markers (IL-12, IL-23, TNFα and IFNγ: p<0.001). We did not observe changes in the M2 profile. Finally, we observed an early increase in the recruitment of DCs and M1 macrophages in WT UUO (MØG<sub>alk</sub> < 9.1±2.6 vs MØG<sub>alk</sub> = 60±24.4 cell/mg renal tissue; DC<sub>G<sub>alk</sub></sub> = 34.7±20.0 vs DC<sub>G<sub>alk</sub></sub> = 242±99.9 cell/mg renal tissue; p<0.01), which was prevented in UUO NGAL-KO mice (MØ<sub>G<sub>alk</sub></sub> = 60.0±24.4 vs MØ<sub>G<sub>alk</sub></sub> = 30.2±7.8 cell/mg renal tissue; DC<sub>G<sub>alk</sub></sub> = 242±99.9 vs DC<sub>G<sub>alk</sub></sub> = 83.1±9.6 cell/mg renal tissue; p<0.05).

Conclusions: Our results show that NGAL is necessary for DCs and M0 recruitment, in addition for the proteinuria increment in the obstructed kidney, suggesting a new pro-inflammatory mechanism of NGAL in CKD. Supported by Fondoct #1201251 and #3201016.

Funding: Government Support - Non-U.S.

PO2438

Pro-Inflammatory HLA-DRβ1 Intermediate Monocytes Are Increased in CKD

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Background: People with Chronic Kidney Disease (CKD) suffer high rates of cardiovascular disease and have high numbers of circulating intermediate monocytes (IMs). IM numbers are associated with cardiovascular risk. We previously defined novel IM subpopulations termed HLA-DR<sup>hi</sup> and HLA-DR<sup>lo</sup> IMs, of which HLA-DR<sup>hi</sup> IMs are increased in CKD. To understand how these cells contribute to endothelial damage in CKD we determined the functional properties of HLA-DR<sup>hi</sup> IMs.

Methods: People with CKD, age-matched patient controls (PC) and healthy volunteers (HV) were recruited. Blood samples were used for profiling of IM subpopulation number and phenotype, functional surface markers and serum isolation. Intracellular cytokine production, migration and endothelial adhesion assays were performed using ex vivo cells.

Results: Numbers and proportions of circulating HLA-DR<sup>hi</sup> IMs were higher in CKD compared to PC (3.0±0.1% vs. 1.9±0.01% cells/ml, p<0.007). Following LPS stimulation in vitro, HLA-DR<sup>hi</sup> IMs from both PC and CKD patients produced markedly higher amounts of TNFα (p<0.001) and IL-1β (p<0.001) than other monocyte subpopulations. LPS-stimulated cytokine levels of HLA-DR<sup>hi</sup> IMs did not differ for HV vs. CKD. Surface profiling revealed that HLA-DR<sup>hi</sup> IMs expressed relatively higher levels of specific chemokine receptors (CCR5, CXCR1) and adhesion proteins (CD11a, CD11b, CD14).

Conclusions: HLA-DR<sup>hi</sup> IMs with high capacity for inflammatory cytokine production and high surface levels of specific chemokine and adhesion receptors are increased in CKD. Their脏dependent chemotraction and CXCL1-dependent endothelial adhesion of monocytes are increased in CKD. The results highlight targetable mechanistic links between intermediate monocytes, accelerated atherosclerosis and progressive renal injury in CKD.

Funding: Private Foundation Support

PO2442

Loss of Macrophage Mitofusin 2 but Not Mitofusin 1 Suppresses Mitochondrial Biogenesis and Promotes Kidney Fibrosis

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Background: Iron therapy is common in patients with chronic kidney disease (CKD). Macrophages are a major cell type capable of handling and storing iron. At the same time, macrophages play a critical role in the pathogenesis of kidney fibrosis. Iron has been shown to modulate macrophage polarization in other pathologic conditions. However, the effect of iron therapy on polarization of kidney macrophages during kidney fibrosis is unclear.

Methods: To elucidate this, we took advantage of two mouse models of kidney fibrosis: adenine and the unilateral ureteral obstruction (UO/UO) models. A subset of mice received weekly intraperitoneal injections of iron (0.5 g/kg body weight) in addition to adenine. Same iron administration regimen was used to treat a sub-group of mice for 4 weeks prior to UUO. Mice were euthanized after 8 weeks of adenine diet or 7 days after UUO. Blood for serum creatinine and CBC measurements and kidneys were collected at euthanasia.

Results: Iron therapy improved creatinine and mitigated kidney function decline in CKD mice, as indicated by serum creatinine improvement. Kidney fibrosis was less severe in mice treated with iron compared to untreated mice in both the adenine and UO/UO models. LPS-stimulated cytokine secretion of HLA-DR<sup>hi</sup> macrophages treated with iron, specifically within kidney macrophages, as confirmed by electron microscopy. Flow cytometry demonstrated reduced infiltration of kidney macrophages, as well as a decrease in CCR2<sup>+</sup> and CXCR1<sup>+</sup> myeloid cells in CKD mice treated with iron compared to untreated CKD mice. While macrophage surface markers MHCII, CD86, and CD206 were altered by iron therapy, they did not follow the classical M1/M2 dichotomy. However, expression of pro-inflammatory cytokines TNFα, IL-6 and IL-1β by macrophages was reduced in CKD mice treated with iron compared to untreated CKD mice.

Conclusions: Chronic parenteral administration of iron mitigated kidney fibrosis in two different mouse models, which, at least in part, was likely mediated by iron-induced kidney macrophage skewing towards an anti-inflammatory phenotype and reduced recruitment of pro-inflammatory cells into the kidney.

Funding: NIDDK Support

PO2443

Renal Parenteral Therapy Alters Polarization of Kidney Macrophages and Mitigates Kidney Fibrosis in Mice

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Background: Inflammation, Endothelial Dysfunction, and Signaling PO2440

PO2441

Parenteral Therapy Alters Polarization of Kidney Macrophages and Mitigates Kidney Fibrosis in Mice

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: Myeloid-specific Mfn1 (Mfn1fl/fl, LysMCre-), Mfn2 (Mfn2fl/fl, LysMCre-), & DC knockout (DCO) mice and corresponding controls were fed with control (C) or adenine diet (AD) for 28 days. Kidneys, kidney macrophages, bone marrow-derived macrophages (BMDM) were analyzed by western blot, flow cytometry, immunohistochemistry. Blood urea nitrogen (BUN), creatinine were measured. Reduced mitochondrial bioenergetic regulator: PGC-1α, antioxidant enzyme: superoxide dismutase-2, mitochondrial fusion proteins: Mfn1, Mfn2, and OPA-1 decreased while fission proteins: DRP-1 and phospho-DRP-1-Serine-616 increased in the kidneys after AD and BMDM after TGF-β1 treatment. Kidney macrophage superoxide levels increased in AD compared to C. However, kidney macrophages from ADO and BMDM mice showed significantly decreased collagen deposition and myofibroblast accumulation. In contrast, CCR2 development of cisplatin-induced fibrosis, as measured by statistically significant mitophagy than α1-treatment. However, TGF-β1, & CD206 than corresponding controls. In in the kidney and worsening of kidney function after AD. BMDM from Gunars Lactate Dehydrogenase A Influences Pro-Inflammatory Polarization of Macrophages in cisplatin treated kidneys. Macrophages, but not infiltrating macrophages, decreased accumulation of CD206+ M2 macrophages in the kidney. Therefore, kidney resident macrophages may be key drivers in the development of cisplatin-induced kidney fibrosis.

Results: In this study, we depleted populations of F4/80hi resident macrophages and F4/80+ infiltrating macrophages in C57BL/6 mice using either clodapen or ccr2 genetic knockout. In parallel with this macrophage depletion, mice were given 4 weekly doses of 9 mg/kg clodapen. After euthanization, we evaluated kidney function, injury, and fibrosis development.

Conclusions: Our data suggests that F4/80+ resident macrophage depletion ameliorates development of cisplatin-induced fibrosis, as measured by statistically significant decreased collagen deposition and myofibroblast accumulation. In contrast, ccr2 knockout mice lacking clodapen or ccr2 genetic knockout did not alter pathological outcomes after cisplatin treatment. Additionaly, depletion of resident macrophages, but not infiltrating macrophages, decreased accumulation of CD206+ M2 macrophages in cisplatin treated kidneys.

Poster: PO2443

Lactate Dehydrogenase A Influences Pro-Inflammatory Polarization of Murine Bone Marrow-Derived Macrophages

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Background: Excessive inflammation is a major underlying pathophysiological process in the progression of chronic kidney disease (CKD). Infiltration of pro-inflammatory macrophages can provoke such inflammatory responses. Macrophages undergo transcriptional and metabolic reprogramming and rely heavily on glycolysis. Lactate Dehydrogenase A (LDHA) is a key enzyme involved in the glycolytic switch which catalyzes the conversion of pyruvate to lactate and regenerates NAD+ from NADH. Utilizing LDHA deletion, we investigated the effect of suppression of the glycolytic switch in mice: Expression and its effect on CKD.

Methods: Mature bone marrow-derived macrophages (BMDMs) from wild-type and LDHA knockout mice (KO) were cultured and then polarized for 24 hours using IFN-γ, Bulk RNA seq (transcriptional) and LC-MS/MS (metabolomic) experiments were performed. For in vivo studies, wild-type littermate and myeloid deficient LDHA KO were treated with arthritis (AA) for 6 weeks as a model of CKD.

Results: BMDMs lacking LDHA showed a significant decrease in transcription levels of key genes of the glycolysis (HIF1α and GLUT1). The LDHA deletion resulted in significantly decreased levels of aspartate indicating the arginine-succinate shunt is affected. Carnitine levels and fatty acid metabolism were significantly downregulated in the LDHA deficient macrophages. In contrast, mannose-6-phosphate levels were significantly upregulated. Combined, these changes suggest an anti-inflammatory shift. The Multi-omics approach of combining metabolomics and transcriptomic data revealed significant changes in multiple pathways including pyruvate, nicotinate and nicotinamide metabolism. Lastly, mice lacking LDHA in myeloid cells level showed a significant decrease in renal fibrosis 6 weeks post-exposure to AA in the model of CKD.

Conclusions: LDHA deficient BMDMs exhibited diminished pro-inflammatory profile in vitro and decreased renal fibrosis in vivo. These results highlight LDHA's role as a potential target for manipulation in immunometabolism and may have a significant impact on approach to CKD.

Funding: NIDDK Support, Veterans Affairs Support, Private Foundation Support

Poster: PO2445

Major Vault Protein Promotes Macrophage-to-Myofibroblast Transition and Tubulointerstitial Fibrosis in a Murine Model of CKD

Chuwk Yin Wong, Susan Yang, Caleb C. Chan, Tak Mao D. Chan. Department of Medicine, the University of Hong Kong, Hong Kong, Hong Kong.

Background: Chronic kidney disease (CKD) is characterized by progressive interstitial fibrosis and tubular atrophy, and inflammatory cell infiltration. We found that major vault protein (MVP), a key component of the vault complex, contributed to the M2 matrix protein deposition in an adenine-induced murine CKD model. We continued to investigate whether MVP contributes to interstitial fibrosis.

Methods: CKD was induced in MVP wild-type (WT) and knockout (KO) mice by feeding with casein-based chow containing 0.2% adenine for 8 weeks, and mice were sacrificed and renal cortical tissue harvested for qPCR, immunohistochemistry and flow cytometry analysis. Mice fed casein-based chow served as controls.

Results: MVP WT mice with CKD showed increased MVP mRNA compared to control WT mice. In MVP WT mice with CKD there was increased macrophage infiltration in the tubulo-interstitium that co-localized with collagen I, fibronectin and smooth muscle actins, suggesting macrophage-to-myofibroblast transition. Flow cytometric data showed increased CD45+ cells and F4/80+ / CD11b+ macrophages in MVP WT mice with CKD. MVP KO mice with CKD showed reduced infiltration of macrophages in the tubulo-interstitium, with lower transition to myofibroblasts (P<0.01); and there was decreased MCP-1, MCP-1 receptor and TNF-a mRNA expression, with better preservation of normal renal histology.

Conclusions: The findings suggest that MVP may contribute to the pathogenesis of CKD by promoting macrophage infiltration and their transition to myofibroblasts.

Funding: Government Support - Non-U.S.

Poster: PO2446

Classical Dendritic Cells Mediate Nephrotoxic Serum Nephritis by Activating T Cells

Jiafa Lu,1,2 Jiafa Ren,1,2 Yi Yi,1,2 Jamie Privratsky,1,2 Steven D. Crowley,1,2 Duke University Hospital, Durham, NC; 1 Durham VA Medical Center, Durham, NC.

Background: Glomerulonephritis is a prominent cause of chronic kidney disease (CKD) and features robust chronic inflammation. Following an inflammatory insult, myeloid cells infiltrate the kidney and drive CKD progression. Fhl3-expressing classical dendritic cells (DCs) are the most potent antigen-presenting cells, and heterogeneous deletion of the ubiquitin cullin A20 spontaneously activates DCs. However, the role of Fhl3-expressing classical DCs in the regulation of inflammatory CKD requires elucidation. We hypothesized that classical dendritic cells exacerbate kidney injury by promoting the activation of renal T cells.

Methods: We induced nephrotoxic serum nephritis (NTS) in Fhl3-deficient mice lacking DCs (DC KO), mice with spontaneous DC activation (CD11cCre A20flox/- DC ACT), and wild-type (WT) controls. After 14 days of NTS, kidney injury was assessed by pathology scoring and ACRs. In addition, mRNA levels of renal injury biomarkers were assessed by RT-PCR and western blot. NTS mice were sacrificed and kidneys were harvested for flow cytometry analysis to determine intra-renal immune cell lineage distributions and test their mRNA levels of inflammatory cytokines.

Results: On day 14 of NTS, DC KO mice had attenuated kidney injury scores compared to wildtype controls (1.6±0.3 vs 1.0±0.2 au, p<0.001). Compared to WTs, DC KO had lower ACRs (432±74 vs 648±648 au, p<0.001) and reduced renal mRNA levels for NGAL (1.0±0.1 vs 0.2±0.1 au, p=0.001), collagen-1 (1.0±0.1 vs 4.0±0.1, p=0.003), and fibronectin (1.0±0.1 vs 0.5±0.1, p<0.01). In contrast, DC ACTs had higher ACRs (623±84 vs 117±243, p<0.001) and upregulated mRNA for NGAL (29.2±7.4 vs 1.0±0.3 au, p=0.004), collagen-1 (6.5±0.9 vs 1.0±0.2, p=0.001), and fibronectin (3.9±0.4 vs 1.0±0.1, p=0.001). Renal protein levels for collagen-I and fibronectin recapitulated the mRNA data. In DC ACT kidneys, absolute numbers of CD4 effector memory T cells, marked by a CDEL2*CD44+ surface expression were higher (286±648 vs 836±107 cells, p=0.006) and had higher kidney mRNA levels for TNFα (4.2±0.5 vs 1.0±0.1, p=0.001) and IL1β (2.0±0.3 vs 1.0±0.1, p=0.02) vs in WTs at day 14 of NTS.

Conclusions: The pathogenesis of CKD requires classical DC-mediated T cell activation. Inhibition of classical DCs may ameliorate autoimmune nephritis.

Funding: NIDDK Support
Targeting Innate Immune-Polyamine Axis Prevents CKD-Associated Cardiac Hypertrophy
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Background: It is well recognized in clinic that patients with chronic kidney disease (CKD) have a higher risk for developing cardiovascular diseases including cardiac hypertrophy. However, the pathogenetic mechanisms remain poorly understood.

Methods: The hypertrophic phenotype changes and metabolic characteristics of neonatal rat cardiomyocytes were studied after incubation with serum from 5 stage CKD patients, as well as myocardium from mice with or without CKD, accompanied by bulk RNA-seq analysis. The role and mechanism of CKD in inducing cardiac hypertrophy were evaluated in vivo and ex vivo, and confirmed in targeted gene knockout and cardiomyocyte-specific knockdown mouse models.

Results: Here, we show that adult cardiomyocytes are characterized by restrained polyamine metabolism, while CKD activates polyamine metabolism especially ornithine decarboxylase (ODC1)-putrescine metabolic axis in cardiomyocytes. Then, we reveal that nuclear factor kappa B (NF-kB) driven hypertrophy program, rather than a pathogenetic factor for cardiac hypertrophy. Furthermore, mitochondrial oxidative damage is a prominent feature of cardiomyocytes under CKD milieu. The damaged mitochondria release mitochondrial DNA into the cytosol and stimulates the innate immune cyclic GMP-AMP synthase-stimulator of cytokines in cardiomyocytes, which subsequently activates NF-kB. Therefore, myocardial cGAS-STING-NF-kB pathway plays a critical role in CKD-associated cardiac hypertrophy through immune surveillance of mitochondrial fitness as well as integrating hypertrophic program and polyamine metabolism.

Conclusions: Our study uncovers a previously unrecognized role of innate immune-polyamine axis in CKD-associated cardiac hypertrophy. Targeting innate immune-polyamine axis may represent a promising strategy to prevent and treat CKD-associated cardiac hypertrophy.

Funding: Government Support - Non-U.S.

The Active Ingredient in the Nuphar lutea Plant, 6,6'-Dihydroxythiobinupharidine (DTBN), Ameliorates Kidney Fibrosis, Inflammation, and Anemia in a Mouse Model of CKD
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Background: EPO resistance and iron deficiency in CKD-related anemia are associated with an increase in inflammatory cytokines associated with the innate immune response, such as IL-6, IL-1, and TNF-α. Recently (Bandach et al, Sci Reports 2021) associated with an increase in inflammatory cytokines associated with the innate immune system. The alarmin IL-1α is strongly expressed on the surface of monocytes from patients with acute myocardial infarction (AMI) and patients with CKD and determined its association with atherothrombotic CVD events during follow-up in an explorative clinical study. Furthermore, we assessed the inflammatory effects of IL-1α in several organ injury models in IL1α-/- mice and investigated the underlying mechanisms in vivo in monocytes and endothelial cells.

Results: We assessed the expression of IL-1α on the surface of monocytes from patients with acute myocardial infarction (AMI) and patients with CKD and determined its association with atherothrombotic CVD events during follow-up in an explorative clinical study. Furthermore, we assessed the inflammatory effects of IL-1α in several organ injury models in IL1α-/- mice and investigated the underlying mechanisms in vivo in monocytes and endothelial cells.

Conclusions: Our study uncovers a previously unrecognized role of innate immune-polyamine axis in CKD-associated cardiac hypertrophy. Targeting innate immune-polyamine axis may represent a promising strategy to prevent and treat CKD-associated cardiac hypertrophy.

Funding: Government Support - Non-U.S.
Background: Lupus nephritis (LN) is caused by autoimmune responses and is a significant driver of end-stage renal disease in systemic lupus erythematosus patients. Complement activation, pro-inflammatory cytokine production, and the influx of macrophages have all been implicated in LN pathogenesis. The anaphylatoxin complement 5a (C5a) receptor 1 (C5AR1) is a major driver of the pro-inflammatory functions of complement activation. We examined C5AR1’s expression in kidney in lupus nephritis and investigated its role in controlling pro-fibrotic functions of macrophages.

Methods: C5aR expression, infiltrating immune cells, and fibrosis were examined by immunohistochemistry in LN patient kidney biopsies. M1 and M2 macrophages derived from human peripheral blood monocytes were used in in vitro assays to examine the effect of C5a stimulation and avacopan, a specific C5AR inhibitor, on the secretion of cytokines and other factors.

Results: In LN kidney biopsies, large numbers of macrophages, identified by CD68 staining, were observed in areas with severe fibrosis, and expressed C5aR. In addition, C5aR was detected on distal tubules in biopsies of both normal and lupus nephritis kidneys. C5a increased the production of inflammatory cytokines TNFa and IL-6 from both M1 and M2 macrophages in vitro. Chemokines (MCP-3, MIP-1a, MIP-1b and MIP-3a), matrix metalloproteinases (MMP3 and MMP8), and pro-fibrotic growth factors (fibronectin and aSMA) were strongly increased in M2 macrophages with C5a stimulation, and these increases were blocked by the C5AR inhibitor avacopan.

Conclusions: C5aR activation induced macrophage secretion of factors that are known to contribute to inflammation, fibroblast activation and tissue fibrosis, and thus may contribute to LN disease progression. Inhibiting C5aR activity with avacopan blocks these pathological changes, and may provide therapeutic benefit to LN patients.

Poster

PO2452 Remdesivir Inhibits Tubulointerstitial Fibrosis in Obstructed Kidneys Lin Xu, Ming Wu, Chaoyang Ye, Shuguang Hospital, Shanghai, China.

Background: Kidney impairment is observed in patients with COVID-19. The effect of anti-COVID-19 agent remdesivir on kidneys is currently unknown. We aimed to determine the effect of remdesivir on renal fibrosis and its downstream mechanisms.

Methods: Remdesivir and its active nucleoside metabolite GS-441524 were used to treat TGF-β stimulated renal fibroblasts (NRK-49F) and human renal epithelial (HK2) cells. Vehicle or remdesivir were given by intraperitoneal injection or renal injection through the left ureter in unilateral ureteral obstruction (UUO) mice. Serum and kidneys were harvested. The concentrations of remdesivir and GS-441524 were measured using LC-MS/MS. Renal and liver function were assessed. Renal fibrosis was evaluated by Masson’s trichrome staining and Western blotting.

Results: Remdesivir and GS-441524 inhibited the expression of fibrotic markers (fibronectin and asMA) in NRK-49F and HK2 cells. Intraperitoneal injection or renal injection of remdesivir attenuated renal fibrosis in UUO kidneys. Renal and liver function were improved. Remdesivir reduced TGF-β stimulated UUO mice. Two remdesivir metabolites were detected after injection. Phosphorylation of Smad3 that was enhanced in cell and animal models for renal fibrosis was attenuated by remdesivir. In addition, the expression of Smad7, an anti-fibrotic factor, was increased after remdesivir treatment in vitro and in vivo.

Conclusions: Remdesivir inhibits renal fibrosis in obstructed kidneys. Funding: Government Support - Non-U.S.

Poster

PO2453 Heightened Innate Immune Response to COVID-19 Infection in CKD: Implications to Poorer Outcome During CKD Xiaojia Guo,1 Leyuan Xu,1 Tian-Min Chen,1 Fred Gorelick,1,2 Gary V. Desir,1,2 Robert L. Safflestein,1,2 Yale University School of Medicine, New Haven, CT, ’VA Medical Center West Haven, CT, ’West Haven, CT.

Background: Meta-analyses reveal show a significant association of chronic kidney disease (CKD) with severe COVID-19. The double stranded RNA virus SARS-CoV-2 can contribute to polyinosinic-polycytidylic acid [poly(I:C), a synthetic analog of double-stranded RNA disease (CKD) with severe COVID-19. The double stranded RNA virus SARS-CoV-2 can cause systemic inflammation, endothelial dysfunction, and signaling defect.

Methods: We determined anti-fibrotic effect of SC-19220 - an EP receptor antagonist, in a mouse model of obstructive nephropathy, with or without UUO-induced renal fibrosis.

Results: SC-19220 administration to obstructed kidneys of C57Bl/6j mice reduced renal fibrosis, inflammation, and mortality. SC-19220 treatment significantly decreased expression of the pro-inflammatory and profibrotic growth factors TNFa, IL-6, and MCP-1. SC-19220 also induced expression of the anti-inflammatory cytokine IL-10.

Conclusions: SC-19220 administration abolished tubulointerstitial fibrosis, as demonstrated by reduced fibroblast activation and collagen deposition after UUO. Furthermore, inflammatory response was prevented as demonstrated by decreased macrophage infiltration and expression of inflammatory cytokines (TGF-β, IL-1β and IL-6) in EETs-administered UUO kidneys. The genetic inhibition of sEH also mitigated UUO-induced renal inflammation and interstitial fibrogenesis. The combination of EET administration and genetic sEH inhibition also attenuated inflammation and renal interstitial fibrogenesis after UUO, but no additive or synergic effect of combined sEH inhibition and EETs administration.

Funding: NIDDK Support

Poster

PO2454 Combined Soluble Epoxide Hydrolase Inhibition and Epoxyeicosatrienoic Acid Administration Attenuates the Renal Fibrogenesis Without Additivity or Synergy Mira Noh, Hee-Seong Jang, Babu J. Padanilam. Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Epoxyeicosatrienoic acids (EETs) are arachidonic acid metabolites with biological effects, including anti-apoptotic, anti-inflammatory, and anti-fibrotic functions. Soluble epoxide hydrolase (sEH)-mediated hydrolysis of EETs to dihydroxylisosynoic acids decreases their biological activity. Recent studies have demonstrated inhibition of sEH prevents renal tubulointerstitial fibrosis and inflammation in chronic kidney disease (CKD) model. Here, we demonstrated the role and underlying mechanism of EETs in unilateral ureteral obstruction (UUO)-induced renal fibrogenesis.

Methods: Eight-week-old male wild type (Ephx2−/−) and Ephx2−/− mice underwent sham or UUO surgical procedures and were treated with the combination of 11,12- and 14,15-EETs (15 µg/kg/day, respectively) using osmotic pump for 7 days following UUO surgery.

Results: EETs administration abolished tubulointerstitial fibrosis, as demonstrated by reduced fibroblast activation and collagen deposition after UUO. Furthermore, inflammatory response was prevented as demonstrated by decreased macrophage infiltration and expression of inflammatory cytokines (TGF-β, IL-1β and IL-6) in EETs-administered UUO kidneys. The genetic inhibition of sEH also mitigated UUO-induced renal inflammation and interstitial fibrogenesis. The combination of EET administration and genetic sEH inhibition also attenuated inflammation and renal interstitial fibrogenesis after UUO, but no additive or synergic effect of combined sEH inhibition and EETs administration.

Conclusions: Taken together, our findings provide that the underlying mechanism of EETs in kidney fibrogenesis during obstructive nephropathy, suggesting EETs as a potential therapeutic target of kidney fibrosis progression.

Funding: NIDDK Support

Poster

PO2455 EP1 Receptor Antagonism Mitigates Early and Late-Stage Renal Fibrosis Danielle Kresse,1 Henricus A. Mutsaers,1 Michael S. Jensen,1 Stine Julie H. Tingskov,1 Mia G. Madsen,2 Rikke Nortregaard,1 Aarhus Universitet, Aarhus, Denmark; 2Aarhus Universitetshospital, Aarhus, Denmark.

Background: Renal fibrosis is a hallmark of Chronic Kidney Disease (CKD), which affects 10-16% of the world’s adult population. Yet current treatment strategies are ineffective in attenuating renal fibrogenesis. Therefore, we are in urgent need for new therapeutic strategies against renal fibrosis. The cyclooxygenase/prostaglandin (COX/PG) system plays a key role in renal fibrosis and holds great promise as a suitable therapeutic target. Here, we used a translational approach to evaluate the role of the PGE1, EP1 receptor in the pathogenesis of renal fibrosis in several models of kidney injury, including human (fibrotic) kidney slices.

Methods: The anti-fibrotic effect of SC-19220 - an EP receptor antagonist - was studied in Madin-Darby Canine Kidney (MDCK) cells, mice subjected to seven days of unilateral ureteral obstruction (UUO), and healthy and fibrotic human-preparation kidney slices (PKCS). Progression of fibrosis was evaluated on gene and protein level using qPCR, Western blot and immunohistochemistry.

Results: Pharmacological inhibition of the EP1 receptor using SC-19220 reduced TGF-β-induced fibroblast proliferation (FN expression, ERK1/2 phosphorylation and epithelial-to-mesenchymal transition in MDCK Cells. Moreover, SC-19220 diminished fibrosis in UUO mice, measured by decreased protein expression of FN and smooth muscle actin (αSMA), and a reduction in collagen deposition. In addition, treatment of healthy human PKCS with SC-19220 reduced TGF-β-induced fibroblast as shown by decreased gene levels of collagen 1A1, FN and αSMA as well as reduced collagen deposition. Moreover, similar observations were made using fibrotic human PKCS. Combined Soluble Epoxide Hydrolase and Epoxyeicosatrienoic acid Administration Attenuates the Renal Fibrogenesis Without Additivity or Synergy.

Conclusions: This study highlights that the EP1 receptor is a promising target for preventing both the onset and late stage of renal fibrosis. Moreover, we provide strong evidence that the effect of SC-19220 may translate to clinical care since its effects were observed in UO mice and human kidney slices.
PO2456
Selective Activation of the Prostaglandin E2-EP4 Receptor Can Slow or Reverse the Fibrotic Process in Human Kidney Slices
Michael S. Jensen,1 Henricus A. Mutsuera,1 Mia G. Madsen,2 Rikke Norregaard,1 Norregaard group 1Aarhus Universitet, Aarhus, Denmark; 2Aarhus Universitets hospitals, Aarhus, Denmark.

Background: Chronic kidney disease (CKD) affects approximately 10% of the population, and renal fibrosis, i.e. excessive scar formation in the kidney, is one of the major pathological processes leading to end-stage renal disease (ESRD). Despite overwhelming efforts to find therapies to reduce renal fibrosis, current management strategies are ineffective at preventing disease progression in CKD patients.Activation of the prostaglandin E2-EP4 receptor has been shown to have renoprotective effects in cell and animal studies. However, translational studies using human kidney tissue are lacking.

Methods: In this project, we studied the anti-fibrotic effect of the selective EP4 receptor agonist Rivenprost using a transnational model of renal fibrosis, namely human precision-cut kidney slices (PCKS). This model is ideal to study multicellular pathological processes, e.g. fibrosis, directly in human tissue, since cellular diversity and organ architecture is maintained in the slices. Macroscopically healthy renal tissue (n = 13) was obtained from tumor nephrectomies, whereas fibrotic renal tissue (n = 6) was obtained from ESRD nephrectomies. Subsequently, PCKS were incubated with Rivenprost (75µM) to evaluate its anti-fibrotic effect directly in human tissue. Fibrogenesis was evaluated on a gene level using qPCR. Viability was assessed by ATP measurements using ELISA. Protein and histological analyses are ongoing.

Results: The expression of the EP4 receptor in PCKS was increased twofold after 48h of incubation with the pro-fibrotic cytokine TGF-β, suggesting that the EP4 receptor might play a role in the fibrotic process. Treatment with Rivenprost mitigated TGF-β-induced fibrogenesis in healthy tissue. Moreover, Rivenprost halted disease progression in fibrotic PCKS and appeared to partly reverse fibrosis, as illustrated by a reduction in the gene expression of α-smooth muscle actin, fibronectin and collagen I by at least 50%, without affecting the viability of the human PCKS.

Conclusions: Selective stimulation of the PGE2-EP4 receptor can slow and reverse the process of fibrosis directly in human renal tissue. These findings warrant further research into the clinical application of Rivenprost, or other EP4 receptor agonists, as a treatment for (established) renal fibrosis.

PO2457
Kidney Dysfunction in Response to a High-Fat Diet
Michaela Suwanagul, Ming-Zhi Cao, Jiaqi Pan, Xiaofeng Wang, I. Shinya Taguchi, Bangkong R. Ang, A. Gerrits, Kyra L. Dijkstra, Jan A. Brujin, Hans J. Baele, Marion Scharpfenecker.

Background: Obesity leads to a state of chronic, low-grade inflammation that results in changes in the immune system and affects various organs. Obesity also impacts the kidney, leading to diabetes and dysregulated metabolism. When fed a high fat diet (HFD), cyclooxygenase-2 (COX-2) and its EP4 receptors resulted in increased obesity after the HFD. The current study investigated whether kidney dysfunction was exacerbated in mice with myeloid cell deletion of COX-2 and EP4 receptors in response to a high-fat diet.

Methods: First, we developed myeloid COX-2-/- mice (CD11b-Cre; COX-2flox/flox) and myeloid EP4-/- mice (CD11b-Cre; EP4flox/flox) to study the role of the EP4 receptor in the kidney. Next, we treated myeloid COX-2-/- mice and myeloid EP4-/- mice with high-fat diet (36% fat accounting for 60% of calories) for 12 weeks. The mice were fed a HFD (36% fat accounting for 60% of calories) for 12 weeks.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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PO2460

Guanidinylated Apolipoprotein C3 (ApoC3) Causes Kidney and Vascular Injury

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Background: Cardiovascular diseases (CVD) and chronic kidney diseases (CKD) are highly prevalent in Western populations and account for a substantial proportion of mortality. We found that apolipoprotein C3 (ApoC3), a constituent of triglyceride-rich lipoproteins, induces alternative NLRP3 inflammasome activation in human monocytes and thus causes sterile inflammation. The aim of the present study was to screen ApoC3 for the presence of posttranslational protein modifications and to assess its relevance in vitro, in vivo, as well as in a prospective cohort of CKD patients.

Methods: ApoC3 was subjected to proteomic analysis. The proinflammatory properties of ApoC3 were assessed in human monocytes and in humanized mice. Moreover, posttranslationally modified ApoC3 was quantified in prospective cohort of 543 patients with various etiologies of CKD and linked to kidney and cardiovascular outcomes.

Results: We identified posttranslational guanylimidation of lysine residues of ApoC3 (gApoC3) in patients after acute myocardial infarction and in patients with CKD. gApoC3 accumulates in kidneys and hearts after injury as determined by 2D-proteomic analyses. In human monocytes, guanylation enhanced the binding of ApoC3 to the cell surface and exerted substantially stronger pro-inflammatory effects as compared native ApoC3. In humanized mice, gApoC3 strongly induced kidney fibrosis and abolished the regeneration after vascular injury. In a prospective clinical trial of 543 patients, higher gApoC3 blood levels as determined by mass spectrometry were associated with increased mortality as well as cardiovascular and renal events during a long-term follow-up.

Conclusions: The present study provides evidence preclinical models and a prospective clinical trial that gApoC3 plays an important role in the development of organ injury in patients with CKD, myocardial infarction and other clinical conditions. The clinical study represents one of the largest trials, in which the association of a specific PTM and clinically relevant outcomes was assessed. These findings highlight gApoC3 as a pathophysiologically relevant factor in development of organ dysfunction.

PO2461

Endothelial Function, Oxidative Stress, and Cognitive Performance in CKD

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Background: Cognitive impairment, common in patients with chronic kidney disease (CKD), can be explained at least partially by the high prevalence of cerebrovascular disease in the population. Here, we hypothesized that endothelial dysfunction associates with reduced cognition in patients with CKD.

Methods: We conducted a cross-sectional study of 63 middle-aged/older adults with CKD stage 3b and 4. Cognitive function domains including executive function, memory, language, and processing speed were assessed via the NIH-Toolbox. Endothelial function of the brachial artery was assessed via flow-mediated dilation (FMD) using Doppler ultrasound. The influence of oxidative stress on FMD was determined by infusing a antioxidant, vitamin E. The influence of oxidative stress on FMD was determined by infusing a antioxidant, vitamin E.

Results: The mean±SD age, estimated glomerular filtration rate (eGFR), and FMD of the participants were 64(9), 34(11), and 2.6(1.4). Acrosic acid increased FMD by 4.5±1.7 as compared to saline which increased FMD by 2.5±1.3 (p<0.001). Table 1 illustrates the age-adjusted standard scores for each cognitive domain. We found no association between FMD and any of the cognitive domains. However, a greater response to acrosic acid correlated with better age-adjusted memory performance independently of education (95% CI: 2.08: 0.51,3.65; p<0.05).

Conclusions: Oxidative stress contributes to endothelial dysfunction in CKD and a greater response to acrosic acid is associated with better memory performance. More studies are needed to understand the role of oxidative stress in cognitive impairment in patients with stage 3b/4 CKD.

Funding: Other NIH Support - NHLBI, Veterans Affairs Support

Table 1: NIH Toolbox Cognitive Domain Standard Scores

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Standard Score</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive Function</td>
<td>95.95±2.4</td>
<td></td>
</tr>
<tr>
<td>Memory</td>
<td>100±2.3</td>
<td></td>
</tr>
<tr>
<td>Processing Speed</td>
<td>98±2.3</td>
<td></td>
</tr>
</tbody>
</table>

Normatively age-adjusted standard scores are presented. Standard scores have a mean of 100 and SD of 15.

PO2462

Key Role for EphB2 Receptor in Kidney Fibrosis

Zhimin Huang, Simeng Liu, Anna Tang, Yufeng Huang. University of Utah Health, Salt Lake City, UT.

Background: Eph-ephrin receptor-ligand signaling has been implicated in the development of tissue fibrosis, though it has not been well defined in the kidney.

Methods: We then firstly made use of male EphB2-knockout and littermate control mice (n=5-per group) to receive unilateral renal ischemia-reperfusion (IR) surgery for 35min. In addition, EphB2 signaling was further determined in varied kidney disease models, particularly in diabetes- or hypertension-induced kidney disease models and in the kidney biopsy tissue from IgA nephropathy with glomerulosclerosis and tubular fibroelastosis.

Results: We detected substantial upregulation of expression and phosphorylation of the EphB2 receptor tyrosine kinase in fibrotic kidney tissue obtained both from mice subjected to either the unilateral renal IR model at 14 days or type 2 diabetes or DOCA & Ang II-induced hypertension and in patients suffering from chronic kidney disease (CKD). Knockout mice lacking EphB2 expression exhibited a normal renal structure and function, indicating no major role for this receptor in kidney development or function. Although IR injury is well known to cause tissue damage, fibrosis, and renal dysfunction, we found that kidneys from EphB2 knockout mice showed much less renal tubular injury and retained a more preserved renal function. IR injured kidneys from EphB2 knockout mice exhibited greatly reduced fibrosis and inflammation compared to injured wild-type (WT) littermates, and this correlated with a significant reduction in renal expression of pro-fibrotic molecules, inflammatory cytokines, NADPH oxidases, and markers for cell proliferation, tubular epithelial-to-mesenchymal transition, myofibroblast activation, and apoptosis. A panel of 760 fibrosis-associated genes were further assessed, revealing that 506 genes in WT mouse kidney following IR injury changed their expression. However, 70.9% of those genes were back to or close to normal in expression when EphB2 was deleted.

Conclusions: These data indicate endogenous EphB2 expression and signaling are abnormally activated after kidney injury and subsequently contributes to the development of renal fibrosis via regulation of multiple pro-fibrotic pathways.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Apelin and FGF-23 as Biomarkers for Vascular Calcification in Type 2 Diabetic Patients with CKD

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Background: Cardiovascular disease is the leading cause of death in chronic kidney disease (CKD) patients. CKD-Mineral and Bone Disorder occur from the earliest stages of estimated glomerular filtration rate (eGFR) loss and is associated with an increased risk of cardiovascular calcification (VC), which is one of the strongest predictors of cardiovascular risk and mortality in patients with CKD. Apelin and FGF-23 have emerged as potential markers of VC. The main objective of this study is to evaluate the role of apelin and fibroblast growth factor 23 (FGF-23) in the development of VC in type 2 diabetic CKD patients.

Methods: Observational prospective study enrolling 150 type 2 diabetes mellitus patients with CKD. Sample characteristics were analyzed using descriptive statistics. Independent-samples t-test, Pearson’s correlation test and partial correlations were used to evaluate the association and correlation of several hemodynamic and clinical parameters with vascular calcification score (VCS). Univariate logistic regression and multivariate logistic regression were used to find out predictors of VC.

Results: Lower levels of apelin, 1,25-dihydroxycholecalciferol and eGFR were negatively associated with higher VCS and higher levels of phosphate, calcium × phosphate, parathyroid hormone, interleukin-6 and FGF-23 were positively associated with higher VCS. A negative correlation was found between VCS and apelin (r = -0.429, p<0.0001), and between apelin and FGF-23 (r = -0.483, p<0.0001), while a positive correlation was found between VCS and FGF-23 (r = 0.232, p=0.005). Variables significantly associated with VCS in univariate logistic regression analysis were used in multivariable logistic regression analysis. Multivariable logistic regression analysis demonstrated that lower apelin levels and diminished eGFR were associated with a higher VCS. Contrarily, higher levels of inorganic phosphorus and FGF-23 were linked with a higher VCS.

Conclusions: The results suggest that apelin and FGF-23 are predictors of VC on type 2 diabetic patients with CKD. Therefore, these osteo-mineral markers might be used as diagnostic/therapeutic targets in order to improve management of CKD complications.

Endothelial Dysfunction in Dermal Biopsies of Patients with CKD: Associations with Markers of Inflammation and Volume Overload


Background: Cardiovascular (CV) morbidity is a major health problem in patients with chronic kidney disease (CKD). Besides traditional risk factors, CKD-induced endothelial dysfunction (ED) is involved in CV pathology. Of note, the luminal side of the vascular endothelium is covered by a protective endothelial glycocalyx (eGC) that contributes to vascular homeostasis and microvascular permeability. Moreover, eGC accumulates with integrins at focal adhesions and is involved in intracellular signal transduction pathways. Here, we examined what subunits of the integrin were expressed in HK-2 by using RT-PCR. A specific neutralizing antibody against integrin αvβ3 was also used to suppress the binding of Ulex Eu to the integrin.

Results: A significant increase in total FAK was observed in the chronic phase (day 12) as fibrosis progressed (total FAK/GAPDH; control: 0.81 ± 0.10 vs. day 12 1.96 ± 0.20). Among the phosphorylated FAK (pFAK), Y397 was particularly significant (pFAK/FAK; control: 0.39 ± 0.01 vs. day 12 0.73 ± 0.17). Positive staining for pFAK was observed in tubular epithelial cells. In serum-stimulated HK-2, FAK was phosphorylated, but the addition of the decoy peptide of the CCN2 VI-module decreased the amount of Y397. Results of RT-PCR confirmed the expression of several integrin subunits. The results of studies using neutralizing antibodies revealed that the decrease in pFAK was most pronounced when the anti-integrin αvβ3 antibody was added (pFAK/FAK; control: 0.99 ± 0.13 vs. 0.48 ± 0.06 after addition of the antibody).

Conclusions: By using the IRI model, we found that not only the expression of FAK was increased but also its phosphorylation was promoted in the injured kidney. CCN2 produced in tubular epithelial cells acts via cellular integrin αv in autocrine/paracrine manner, and promotes renal fibrosis through phosphorylation of the tyrosine 397 residue of FAK. CCN2 has been previously shown to activate Wnt/β-catenin and TGF-β/Nodal pathways. However, here we identified another pathway for CCN2 in relation to kidney fibrosis. Several FAK inhibitors have already been investigated as antifibrotic agents. Further clarification of the pathways may prove the therapeutic effects of these inhibitors on CKD.

Multitarget Soluble Epoxide Hydrolase/Farnesoid X Receptor Agonist Combats CKD

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Background: Chronic kidney disease (CKD) is characterized by progressive fibrosis leading to end-stage renal disease. There has been little success in developing agents that can slow the progression of CKD to ESRD. The current study investigated the efficacy of an innovative multi-target ligand drug, DM509, in mitigating renal fibrosis using the unilateral ureteral obstruction (UUO) mouse model. DM509 is a multi-target soluble epoxide hydrolase (sEH) and farnesoid X receptor (FXR) agonist. UUO or sham surgery was conducted in C57BL/6J male mice (n=8/group). Interventional DM509 treatment (10 mg/kg p.o.) was started three days after UUO induction and continued for 7 days. Plasma and kidney tissue were collected at the end of the experimental protocol. Several biochemical, histopathological, immunohistopathological, and gene expression studies were carried out to determine the antifibrotic effects of DM509.

Results: UOx mice demonstrated fibrosis with higher kidney hydroxyproline content (267±40 vs. 53±14 μg/mg protein), collagen area (4.3±0.1% vs. 0.7±0.3%), DM509 reduced hydroxyproline by 41% and collagen area by 78% (both p<0.05). FXR knockdown mouse. In this study, we examined in greater detail the relationship between CCN2 and FAK.

Conclusions: Our data suggest that DM509, a multi-target FXR/sEH agonist, could be useful for treating chronic kidney disease by slowing fibrosis progression and ameliorating the associated renal dysfunction.
Conclusion: These data reveal that DM509 is a promising multi-target antioxidant drug that ameliorates epithelial and vascular kidney fibroblast disease and CKD progression.
Funding: NIDDK Support

PO2468
Single-Nucleus Transcriptional Profiling of CKD After Repeated Low-Dose Cisplatin Treatment
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Background: Cisplatin induces both acute and chronic kidney problems during chemotherapy. Recent studies have established the models of chronic kidney problems after repeated low dose cisplatin treatment (RLDC). RLDC-induced global transcriptional changes in specific renal cells associated with the development of chronic kidney problems is unclear.

Methods: Male C57BL/6 mice were given 4 consecutive weekly injections of 8 mg/kg cisplatin. Renal function was measured at 5 and 9 weeks after the first cisplatin injection. Kidney tissues were collected for histology and single-nucleus RNA sequencing (SN-RNA-seq). Cell-type-specific changes in gene expression were compared between the samples from control and cisplatin treated mice. Transcriptional regulators in proximal tubular cells were identified and qPCR was used to validate the critical genes involved in renal fibrotic and inflammation.

Results: RLDC induced decreases in eGFR and kidney weight in mice at 5 and 9 weeks. The kidneys of these mice showed tubular degeneration and dilation. There was also increases in KIM-1 positive tubules and atubular glomeruli. Sn-RNA-seq identified transcripts corresponding to 23021 genes. The markers for 11 cell types and 12 cell clusters were detected. Cluster-by-cluster comparison demonstrated cell-type-specific changes in gene expression that are important for transport, fibrosis and inflammation in RLDC mouse kidneys. In particular, compared with the untreated control, RLDC resulted in 425 differentially expressed genes (log2FC=1, p<0.05) in proximal tubular cells. More than 3000 genes displaying altered expression were enriched in profibrotic and proinflammatory pathways, respectively. Consistently, RLDC induced NF-kB activation and proinflammatory cytokines (TNFα, IL6 and IL1), and the expression of fibrosis markers (fibronectin, collagen I, vimentin and α-SMA). Furthermore, Runx1 and Sp1 were identified as critical transcriptional factors that drive inflammation and fibrosis progression after repeated cisplatin treatment.

Funding: NIDDK Support, Veterans Affairs Support

PO2469
Activation of EGFR in Myofibroblasts Promotes Renal Fibrosis in Unilateral Ureteral Obstruction
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Background: In response to injury, renal fibroblasts and pericytes differentiate into highly specialized myofibroblasts, which are essential for maintaining kidney structural integrity. It is imperative to identify the molecular mechanism initiating and sustaining myofibroblasts activation in order to identify novel therapeutics to stop or reverse kidney fibrosis. The activation of epidermal growth factor receptor (EGFR) plays an important role in mediation of recovery of epithelial integrity following ischemic acute kidney injury (AKI). However, sustained activation of EGFR triggers renal fibrogenesis after AKI. The role of EGFR in fibroblasts/myofibroblasts in development of renal fibrosis after severe AKI has not been previously investigated.

Methods: Both PDGFRαCreERT2; mCherry mice (WT) and PDGFRαCreERT2; mCherry; EGFR-/- mice (PDGFRαCreERT2; mCherry; EGFR-/-) were treated with tamoxifen 2 weeks before unilateral ureteral obstruction (UUO) was performed for 3 or 7 days. Quantification of proliferation of PDGFRαCreERT2; mCherry; EGFR-/- cells was determined at day 3 after UUO. PDGFRαCreERT2; mCherry; EGFR-/- cells were isolated using PDGFRαCreERT2; mCherry; EGFR-/- mice, selective EGFR deletion was confirmed by >80% EGFR mRNA reduction in isolated renal PDGFRαCreERT2; mCherry; EGFR-/- cells as well as absence of immunofluorescent EGFR expression in α-SMA+ myofibroblasts. Flow cytometry determined that renal CD45+CD31+PDGFRαCreERT2; mCherry; EGFR-/- cells were markedly lower in PDGFRαCreERT2; mCherry; EGFR-/- mice than WT mice 3d after UUO. PDGFRαCreERT2; mCherry; EGFR-/- mice had markedly decreased renal fibrosis, indicated by Sirius red and Masson’s Trichrome staining, and increased mRNA and protein levels of profibrotic and fibrogenic components including α-SMA, collagen I, collagen IV, IL-11, fibronectin, and PDGFRβ. Isolated PDGFRαCreERT2; mCherry; EGFR-/- cells also expressed less col1a1 and col1a1. Unexpectedly, the mRNA levels of proliferative fibronectin, including Tnfα, Il1a, Il1b, Ccl2, Ccl3, Il23a, Infγ, and Il12 in whole kidney tissue as well as in isolated renal myoid cells were comparable between WT mice and PDGFRαCreERT2; mCherry; EGFR-/- mice.

Results: In PDGFRαCreERT2; mCherry; EGFR-/- mice, PDGFRαCreERT2; mCherry; EGFR-/- cells induces myofibroblast proliferation and differentiation to promote subsequent fibrosis.
Funding: NIDDK Support, Veterans Affairs Support

PO2470
Activins Facilitate TGF-β1 Profibrotic Signaling in Kidneys
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Background: Chronic kidney disease (CKD) is a rising health issue in North America and is characterized by increased risk of renal fibrosis leading to end-stage kidney disease requiring dialysis or transplantation. TGF-β1 is a central mediator of kidney fibrosis in CKD of diverse etiology. Directly blocking it is unfeasible due to adverse effects. Alternate approaches to inhibit TGF-β1 signaling are needed to develop tolerable anti-fibrotic therapies. Recent studies suggest that TGF-β1 requires activins for its profibrotic effects. Interestingly, both signal through the same canonical Smad pathway. Here we study the mechanisms by which activins enable TGF-β1-induced fibrosis and assess efficacy of specific activin inhibition in vivo.

Methods: Primary mouse kidney mesangial cells (MC) were used. Activin A and B (AA, AB), the predominant activins, were limited with a neutralizing antibody or follicistatin. ELISA, IB and IF were used to assess cytokine levels, signaling pathways and profibrotic responses. Smad3 transcriptional activity was assessed by CAGA12 luciferase reporter and the alpha smooth muscle actin (αSMA) promoter luciferase. Unilateral ureteral obstruction (UUO) was created in mice overexpressing (OE) TGF-β1 or wild-type controls, and effects of neutralizing anti-AA antibody on kidney fibrosis was assessed.

Results: TGF-β1 stimulated the production of AA more than AB, and AA neutralization inhibited the profibrotic effects of TGF-β1. TGF-β1 provoked strong early Smad3 activation (~90-60min), while AA did so later (~24-48h). Inhibition of AA decreased TGF-β1 (24h)-induced Smad3 activation, assessed by its phosphorylation, nuclear accumulation, and transcriptional activity. Cells retained responsiveness to AA signaling even after becoming refractory to TGF-β1 restimulation, enabling ongoing Smad3 activation. AA additionally regulated noncanonical TGF-β1 signaling. Its inhibition reduced nuclear accumulation of MRTFA, a Smad3 co-activator of αSMA induction by TGF-β1. Fibrosis was augmented in TGF-β1 OE mice. Neutralizing AA attenuated Smad3 activation and fibrosis in both wild-type and TGF-β1 OE mice.

Conclusions: AA facilitates TGF-β1 profibrotic effects through regulation of both canonical (Smad3) and non-canonical (MRTFA) signaling. Importantly, AA inhibition reduced fibrosis in vivo, suggesting a novel potential therapeutic for fibrosis in CKD.

PO2471
CircHIPK3 Aggravates Folic Acid-Induced Renal Interstitial Fibrosis by Sponging miR-30a
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Background: Renal interstitial fibrosis is a major pathological feature of end stage kidney disease and currently lacks effective treatment. CircHIPK3 is reported to participate in various diseases. However, the role of circHIPK3 in renal fibrosis is unreported. We aimed to verify whether circHIPK3 participates in the pathogenesis of renal fibrosis and its corresponding.

Methods: C57BL/6 mice were intraperitoneally injected with folic acid (FA) (250 mg/kg) for 30 days. Renal tissue samples were used for paraffin section PAS and Masson staining to confirm the occurrence of renal fibrosis. The expressions of miR-30a, TGF-β1, FN and COL-1 were detected in immortalized human tubular epithelial cells HK-2 cells overexpressed of circHIPK3 and stimulated with TGF-β1. Finally, fluorescence in situ hybridization (FISH) to measure the localization of circHIPK3 and miR-30a, and immunofluorescence was to detect the expressions of TGF-β1, FN and COL-1.

Results: In mice, renal fibrosis features and expression of profibrotic FN and COL-1 were increased at day 30 after peritoneal injection of FA. Renal circHIPK3 was up-regulated while miR-30a was down-regulated in FA-induced kidney injury, as shown by qPCR and FISH. TGF-β1 expression was increased. In addition, renal circHIPK3 was correlated with miR-30a and kidney miR-30a also negatively correlated with TGF-β1 mRNA expression. In HK-2 cells, circHIPK3, miR-30a, and TGF-β1 co-localized in the cytoplasm on FISH and immunofluorescence staining. Importantly, transient transfection of circHIPK3 down-regulated miR-30a and up-regulated TGF-β1, FN, and COL-1 assessed by qPCR and immunoblotting. Furthermore, exposure of HK-2 cells to human TGF-β1 resulted in increased circHIPK3, decreased miR-30a, and increased expression of profibrotic fibronectin and collagen 1 protein. Kidney biopsies from patients with chronic tubulointerstitial nephritis manifested the same directional relationship of circHIPK3, miR-30a, and profibrotic proteins including TGF-β1, FN and COL-1.

Conclusions: A pro-fibrotic feedback involving in circHIPK3, miR-30a, and TGF-β1 and further indicated that circHIPK3 might contribute to renal fibrosis by sponging miR-30a.
Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
ROCK-Binding ASD2-Domain of Shroom3 Has a Profibrotic Role
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**Background:** We previously showed that a CKD-associated Shroom3 allele was a quantitative trait locus for ShROOM3 expression and promoted CKD and allograft nephropathy.

**Methods:** Here we investigated the mechanism of increased fibrosis downstream of Shroom3. We systematically deleted consensus domains in Shroom3 and evaluated profibrotic signaling in tubular cells (Fig 1).

**Results:** Overexpression of ASD2-domain deleted ShROOM3 mutant (ASD2-SH3 with deficient ROCK binding) consistently reduced TGF-B signaling responses in TGF-B reporter 293-Tcells and in Smad-reporter luciferase assays (vs ASD1, Pdz-, Fyn-binding domain deletion mutants and intact ShROOM3; n=3 sets each). Based on these data we generated doxycycline inducible transgenic mice for ShROOM3 and ASD2-SH3 mutants. Two founder lines of each transgene crossed with CAGS-RTTA mice were selected based on transgene expression in kidney tissues upon DOX-feeding. Adult CAGS-RTTA:SHROOM3-3g, ASD2-3g-3g and control mice were fed dox and UUO surgery performed (n=5 each). At 7 days, UUO kidneys from ASD2-SH3-Tg mice showed reduced Phospho-Smad3, and reduced profibrotic transcripts (Col1a1, Fn1) vs UUO surgery performed (n=5 each). At 7 days, UUO kidneys from ASD2-SH3-Tg mice showed reduced Phospho-Smad3, and reduced profibrotic transcripts (Col1a1, Smad3) vs control kidneys.

**Conclusions:** Our sequential findings show that the profibrotic role of Shroom3 excess is mediated via its ASD2-domain.

**Funding:** NIDDK Support

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**PO2472**

**EPAC1-Mediated cAMP Signaling in Podocytes Protects Kidneys from the Progression of Glomerulonephritis**

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**Background:** We previously showed that a CKD-associated Shroom3 allele was a quantitative trait locus for ShROOM3 expression and promoted CKD and allograft nephropathy.

**Methods:** Here we investigated the mechanism of increased fibrosis downstream of Shroom3. We systematically deleted consensus domains in Shroom3 and evaluated profibrotic signaling in tubular cells (Fig 1).

**Results:** Overexpression of ASD2-domain deleted ShROOM3 mutant (ASD2-SH3 with deficient ROCK binding) consistently reduced TGF-B signaling responses in TGF-B reporter 293-Tcells and in Smad-reporter luciferase assays (vs ASD1, Pdz-, Fyn-binding domain deletion mutants and intact ShROOM3; n=3 sets each). Based on these data we generated doxycycline inducible transgenic mice for ShROOM3 and ASD2-SH3 mutants. Two founder lines of each transgene crossed with CAGS-RTTA mice were selected based on transgene expression in kidney tissues upon DOX-feeding. Adult CAGS-RTTA:SHROOM3-3g, ASD2-3g-3g and control mice were fed dox and UUO surgery performed (n=5 each). At 7 days, UUO kidneys from ASD2-SH3-Tg mice showed reduced Phospho-Smad3, and reduced profibrotic transcripts (Col1a1, Smad3) vs control kidneys.

**Conclusions:** Our sequential findings show that the profibrotic role of Shroom3 excess is mediated via its ASD2-domain.

**Funding:** NIDDK Support

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**PO2473**

**PO2474**

**A Novel Allosteric HIPK2 Inhibitor Attenuates Renal Fibrosis with Superior Pharmacokinetic, Selectivity, and Safety Profiles**

Kyoung Lee,1 Ye Feng,2 Ya Chen,2 Richard T. Beresis,3 Robert Drakas,2 John C. He.1 "Icahn School of Medicine at Mount Sinai, New York, NY; ChemPartner, South San Francisco Innovation Center, South Francisco, CA; ShangPharma Innovations Inc., San Francisco, CA.

**Background:** Renal fibrosis is considered the final convergent pathway for progressive CKD, regardless of the original etiologies of the disease. Although much has been learned of the molecular mechanisms underlying renal fibrogenesis, there is still a paucity of success in translating this knowledge to clinical application. We previously demonstrated HIPK2 as a multifunctional activator of TGF-B/Smad3, NF-kB, and p53 pathways and that the global knockout of HIPK2 in mice attenuated kidney fibrosis in vivo. We recently developed a small molecule inhibitor of HIPK2, BT173, that specifically blocked TGF-B/Smad3 pathway to attenuate renal fibrosis without causing adverse systemic effects. Importantly, BT173 did not alter the activity of p53 to produce unwanted oncogenic side effects. However, the in vivo use of BT173 was limited by its poor solubility and potency.

**Methods:** Based on BT173, we used iterative cycles of chemical synthesis and biological assays to optimize the solubility, bioavailability and potency of TGF-B/Smad3 pathway inhibitor. ADME, selectivity, and safety profiling were performed on the optimized HIPK2 inhibitor compounds. The lead inhibitor was then tested in CKD models to test its efficacy in reducing renal fibrosis.

**Results:** 1) Repeated iteration and in vitro screening assay led to a lead compound, HIPK2-174. 2) HIPK2-174 showed greater potency (IC50=200nM) to disrupt the HIPK2- Smad3 interaction in vitro with enhanced solubility. 3) It showed pharmacokinetics suitable for oral qd dosing. 4) No appreciable kidney inhibition was observed when tested against a panel of 30 diverse kinases. Acceptable selectivity profiles were observed with Eurofins Safety 44 and CEREP selectivity panels. 5) Safety profiling did not show any relevant CYP inhibition, hERG, or other cardiac ion channel liabilities. 6) Daily qd dosing of HIPK2-174 in mouse models of proteinic CKD significantly reduced proteinuria and renal fibrosis development.

**Conclusions:** The optimized HIPK2-174 effectively improved renal function, reduced renal fibrosis development and CKD progression in vivo. Moreover, its enhanced selectivity, bioavailability, and biological activity demonstrate a favorable safety profile in preclinical species for IND-enabling studies.

**Funding:** Commercial Support - Shang Pharma Innovation Inc.

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**PO2475**

**Inhibition of RNA-Binding Protein HuR Protects Kidney from Ischemia-Reperfusion-Induced Injury and Fibrosis**

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**Background:** Upregulation of an RNA-binding protein HuR has been implicated in glomerular diseases both in patients and in animal models. Herein, we further evaluated whether upregulation of HuR is involved in and promotes renal injury and subsequent fibrosis by using a renal ischemia/reperfusion (IR) mouse model and a selective HuR inhibitor, KH3.

**Methods:** All mice were received unilateral renal IR surgery for 35 min. The contralateral kidney served as a control. Mice were randomly assigned into either vehicle or KH3-treated groups (n=5/group). KH3 was given via daily intraperitoneal injection from day 3 after IR at the dose of 50 mg/kg/day to day 14. In addition the effect of HuR inhibition on TGFß-induced tubular cell injury was further investigated in vitro.

**Results:** IR-injured kidneys showed a significant upregulation of HuR in tubular and tubulointerstitial cells determined by positive cytoplasmic staining of HuR and western blot assay, which was accompanied by extensive tubular damage and fibrosis. However, KH3-treated and IR-injured kidneys exhibited greatly reduced damage and fibrosis, and this correlated with a reduction in renal expression of profibrotic molecules, inflammatory cytokines, NADPH oxidases, and markers for cell proliferation, tubular epithelial-to-mesenchymal transition (EMT), and apoptosis. A panel of 76 fibrosis-associated genes was further assessed, revealing that 519 genes in mouse kidney following IR injury changed their expression and 71.3% of those genes that are involved in 50 annotated
pathways were ameliorated when treated with KH3. Among those, TGFβ1 was a Hit target which was elevated in the IR-injured kidney. KH3 abrogated TGFβ1-induced tubular HuR cytoplasmic translocation and subsequent tubular EMT in cultured HK-2 cells.

**Conclusions:** These results suggest that upregulation of HuR contributes to renal tubular injury and fibrosis by dysregulating multiple pro-fibrotic pathways. HuR-targeted inhibitory approaches offer promising novel treatment in the future for preventing or reversing the progression of CKD.

**Funding:** NIDDK Support

PO2476

Spiny Mice (*Acomys cahirinus*) Activate Unique Transcriptional Programs After Severe Kidney Injuries and Regenerate Organ Function Without Fibrosis

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**Background:** Fibrosis-driven solid organ failure is a pervasive burden on global health. Although rodents of the genus *Acomys* (spiny mice) are terrestrial mammals that evolved remarkable abilities to regenerate severe skin wounds without scar formation to avoid predation. Whether regenerative wound healing extends beyond skin to vital internal organs in spiny mice is not known.

**Methods:** Models of acute and chronic kidney injury (UOL, unilateral IRI, unilateral IRI + nephrectomy) were utilized in *Acomys* and compared to C57Bl/6J and CD-1 mice. Fibrosis, myofibroblasts, macrophages were measured. Total kidney RNA Seq, RNA blotting, and confocal image analysis was performed.

**Results:** Using two aggressive kidney injury models, we show that despite equivalent kidney injury and tubular cell regeneration of nephron structure and function without fibrosis in *Acomys* compared to extensive fibrosis and renal failure in *Mus*. Comparative genome-wide analysis of gene expression after injury suggested that the *Acomys* genome is poised to initiate and sustain regenerative wound healing. Among the 843 differentially regulated genes between *Acomys* and *Mus* were metabolic enzymes, transcription factors, and nephrogenic genes such as Orxl, 1/2 and Cdh6. Analysis revealed 6 clusters of genes that were differentially regulated with injury between *Mus* and *Acomys*. Clusters 1 and 4 represented Mus-specific genomic responses to UOL injury whereas the response to injury in *Acomys* is to maintain expression at homeostatic levels. In contrast, clusters 2 and 3 represent *Acomys*-specific kidney response gene sets which are unchanged or downregulated in *Mus*. Early after injury, a cluster 3 gene, Cdh6 appeared in rapidly expanding renal tubular mosaic patches throughout the injured *Acomys*, but not *Mus*. The repression of nephrogenesis was functionally translated by cell cycle arrest and DNA replication in tubular and glomerular cells, including podocytes and endothelial cells.

**Conclusions:** Our findings have important implications for an evolutionary solution to mammalian regenerative repair of the kidney, and by extension, to the heart and coronary vessels, lungs, liver and other internal organs similarly prone to organ failure as a result of progressive tissue fibrosis.

**Funding:** NIDDK Support, Other NIH Support - DiaComp

PO2477

Graphene Quantum Dots Protects Against Renal Fibrosis After Restoring Mitochondria Function in Rat 5/6 Nephrectomy

Kyu hong Kim,1 Soie Kwon,2 Semin Cho,1 Kyung Don Yoo,3 Yong Chul Kim,1 Jae Wook Lee,1 Dong Ki Kim,1 Yong Su Kim,1 Seung Hee Yang,1 Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea; 2Ulsan University Hospital, Ulsan, Republic of Korea; 3National Cancer Center, Goyang, Gyeonggi-do, Republic of Korea.

**Background:** Graphene Quantum Dots (GQDs) are carbon-based nanoparticles and are attractive in biological application due to their biocompatibility, quantum confinement, and low toxicity. Rat subtotal 5/6 nephrectomy exhibit mitochondrial dysfunction mediated by TRPC5 channel, a core calcium channel in podocytes and tubular cells. With current limited understanding of the interaction on between nanomaterials and renal cells, we show GQDs as a potential therapeutic nano-sized material in 5/6 nephrectomy rat model.

**Methods:** To evaluate GQDs therapeutic effect on 5/6 nephrectomy Sprague Dawley (8-week; male) rat model, GQDs (4mg/kg) was administered by intraperitoneal for 3 times per week up to 3 weeks. In vitro stimulation process that co-express macrophage TGF-beta (2mg/mL) and myofibroblast (a-SMA). Thus, in vitro study after TGF-beta induction showed similar results. GQDs-treated group in rats have increased potential cell viability by downregulating the collagen kinase inhibitors after decreasing Bax-2, P53, P21 but increasing BCL2 expression.

**Funding:** NIDDK Support, Veterans Affairs Support - DiaComp

PO2478

Critical Role of Histone Demethylase JMD3 in the Regulation of Macrophage Polarization and Renal Fibrosis

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**Background:** Chronic kidney disease is characterized by macrophage infiltration and fibrosis. Macrophage infiltration and polarization play an important role in the development of renal fibrosis. However, the mechanisms underlying macrophage polarization and development of renal fibrosis are not fully understood. In this study, we examined the role of histone demethylase JMD3 in the regulation of macrophage polarization and renal fibrosis.

**Methods:** To examine the role of JMD3 in vivo, we generated mice with global or myeloid cell-specific deletion of JMD3, and we treated wild-type mice with vehicle or GSK-J4, a selective JMD3 inhibitor. Unilateral ureteral obstruction (UUO) model was used to induce renal fibrosis.

**Results:** JMD3 expression was increased in the kidneys during the development of renal fibrosis. Mice with tamofoxen-inducible deletion of JMD3 (CAG-Cre, floxed JMD3) or myeloid cell specific deletion of JMD3 (LysM-Cre, floxed JMD3) were born normal and had no obvious morphological abnormality in the kidney. Compared with Cre negative, floxed JMD3 mice, mice with global or myeloid cell-specific deletion of JMD3 displayed fewer F4/80-positive macrophages, CD206-positive M2 macrophages, and myofibroblasts, and expressed less α-SMA protein in the kidneys following UUO. Furthermore, global or myeloid cell-specific deletion of JMD3 significantly reduced total collagen deposition and ECM protein production in the kidneys after UUO injury. Real-time RT-PCR showed that global or myeloid cell-specific deletion of JMD3 attenuated M2 macrophage polarization, fibroblast activation, and extracellular matrix protein production. Moreover, genetic deletion of JMD3 increased histone Lys 27 dimethylation. Wild-type mice treated with GSK-J4 exhibited fewer macrophages and myofibroblasts and produced less amounts of extracellular matrix proteins in the kidney following UUO.

**Conclusions:** Our study identifies JMD3 as a critical regulator of macrophage polarization and development of renal fibrosis. Therefore, JMD3 may represent a novel therapeutic target for chronic kidney disease.

**Funding:** NIDDK Support, Veterans Affairs Support - DiaComp

PO2479

DNA Methylation in Repeated Low-Dose Repeated Cisplatin-Induced CKD

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**Background:** DNA methylation is an epigenetic mechanism that regulates gene expression by adding methyl groups to DNA molecules via DNA methyltransferases (DNMTs). Recent DNA methylation changes have been implicated in the pathogenesis of kidney diseases. Recent work indicates that DNA methylation protects against cisplatin-induced acute kidney injury partially through hypomethylation of interferon regulatory factor 8 (IRF8). However, little is known about DNA methylation in chronic kidney disease following cisplatin exposure.

**Methods:** Mice and HK2 cells were subjected to repeated low-dose cisplatin treatment (RLDC). We analyzed the expression of DNMTs and the methylation marker 5-methyl-cytosine following RLDC. We further conducted representation bisulfite sequencing (RRBS) to analyze the genome-wide DNA methylation changes. To explore the pathogenic role of DNA methylation, we initially tested the effects of 5-aza, a pharmacological DNMT inhibitor. We further established and tested a conditional knockout mouse model in which DNMT3a is specifically ablated from kidney proximal tubule (GSK-J4, DNMT3a-KO).

**Results:** RLDC induced notable increases in DNMT1 and DNMT3a (but not DNMT3b) expression, which were accompanied by an overall increase in DNA methylation as shown by 5-methyl-cytosine staining. Genome-wide DNA methylation changes were identified by RRBS in 171 genes after RLDC.

**Conclusions:** Five of these genes (Oxgr1, Smuin2, Sc6a1a2, 1h1, Ntld) had hypermethylation in their promoter regions, which was associated with decreased mRNA expression, suggesting the regulation of these genes by DNA methylation. Functionally, 5-aza reduced the expression of these genes and proteins in acute stimulation model including collagen I and CTGF. In vivo, 5-aza and ablation of proximal tubule DNMT3a both alleviated the decline of renal function, kidney atrophy, and renal fibrosis after repeated cisplatin treatment.

**Funding:** NIDDK Support, Veterans Affairs Support, National Institute of Diabetes and Digestive and Kidney Diseases - Diacomp

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

**Underline represents presenting author.**

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PO2480
Targeting Histone Demethylase LSD1 Inhibits Renal Epithelial-Mesenchymal Transition and Attenuates Renal Fibrosis
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Background: Lysine-specific histone demethylase 1 (LSD1) as the first identified protein demethylase plays a special role in the regulation of gene expression by removing methyl groups from mono- and di-methylated lysine 4 and 9 on histone H3 and functions as an oncogenic factor in cancers. However, its role in renal fibrosis is unknown.

Methods: To evaluate the role and mechanisms of LSD1 in the development of renal epithelial-mesenchymal transition (EMT) and renal fibrosis, we inhibited LSD1 with its inhibitor, ORY1001, in mouse unilateral ureter obstruction (UUO) model and rat kidney fibroblasts (NRK-49F) and rat kidney proximal tubular (NRK-52E) cells stimulated by TGF-β1.

Results: We found that the expression of LSD1 was increased and the methylation of its histone targets were decreased in mouse kidneys with unilateral ureteral obstruction and NRK-52E cells undergoing EMT. Inhibition of LSD1 with ORY1001 decreased the deposition of extracellular matrix proteins and the expression of fibrotic markers, including α-smooth muscle actin (α-SMA) and fibronectin, which was associated with preserving E-cadherin expression and inhibiting N-cadherin upregulation in the obstructed kidney. Injury to the kidney enhanced the phosphorylation and activation of Smad2/3, AKT and Stat3, and that could be prevented by ORY1001 administration. Targeting LSD1 with ORY1001 and siRNAs inhibited TGFβ1 induced the activation of renal fibroblasts, NRK-49F, and EMT of NRK-52E cells. The expression of Snail family transcriptional repressor 1 (Snail-1) was upregulated in UUO kidneys and cultured NRK-52E cells treated with TGFβ1. Snail-1 repressed the expression of E-cadherin via the interaction of its N-terminal SNAG domain with LSD1. LSD1 inhibition with ORY1001 or siRNA silencing prevented the upregulation of Snail-1 and disrupted Snail/LSD1 interaction, resulting in the expression of E-cadherin. ORY1001 was also effective in suppressing TGF-β1-induced renal epithelial cells arrest at the G2/M phase.

Conclusions: This study indicates that LSD1 participates in the expression of profibrotic genes and contributes to renal EMT and fibrosis through activation of diverse signaling pathways, and places an emphasis that LSD1 has potential as a therapeutic target for the treatment of renal fibrosis.

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PO2481
Does Senescence Induce Muscle Wasting in CKD?
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Background: Muscle wasting is a common complication of CKD and associated with higher mortality and morbidity. The mechanism of muscle wasting in uremia has been widely studied; however, uremic stress-induced senescence might be a missing connection between chronic kidney disease and muscle wasting. Senescent cells are capable of producing and secreting various growth and proinflammatory factors, cytokines, and chemokines, which is known as the S-ASP. We hypothesized that senescence and senescence associated secretory phenotype (S-ASP) play important roles in the CKD-induced muscle loss.

Methods: CKD mice were induced by 5/6 nephrectomy. Senescence was confirmed by using senescence associated beta gal (SA-βgal). The levels of S-ASP (interleukin 6, TNFα, and IL-8) were measured by immunohistochemistry and ELISA. Senescence pathway markers p16, p21, and p53 were measured by Western blot. To limit senescence, dasatinib (5 mg/kg BW) + quercetin (50 mg/kg BW) (D&Q) were given by oral gavage 2 days per week for 8 weeks. Muscle function was measured with a grip force detector.

Results: CKD stress-induced premature senescence phenomena have been evidenced in the skeletal muscle of uremic mice by 1) the increases in senescence pathway indicators p21 and p16, but not p33 protein; 2) phosphorylated histone H2AX (γH2AX, DNA damage marker); 3) the level of the senescence biomarker SA-β-gal; and 4) S-ASP components present in the uremic muscle, which include high levels of interleukin 6 (IL-6), TNFα, TGFβ, and IL-8. The D&Q treatment eliminated CKD-induced elevation of p21, p16 and γH2AX, abolished positive SA-β-gal, and depressed the high levels of S-ASP cytokines. The muscle cross-sectional area was increased by D&Q treatment compared with the vehicle treatment in 5/6 nephrectomy mice. Skeletal muscle function was also improved with D&Q treatment in uremic mice.

Conclusions: Senescence and S-ASP are important factors in development of muscle wasting during CKD progression. Limiting senescence with D&Q ameliorates muscle wasting and improves muscle function. These results provide new approaches for developing therapeutic strategies to improve muscle health in chronic kidney diseases.

Funding: Veterans Affairs Support

PO2482
 Chronic Aristolochic Acid Administrations Induce Renal Senescence in Mice
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Background: The kidneys are one of the most susceptible organs to age-associated impairments. Recently, although renal aging research has been extensively performed, appropriate models of renal aging are still limited. Generally, renal aging is strongly associated with renal fibrosis, which is the final common pathway of chronic kidney disease. Aristolochic acid (AA), a renal toxic agent, causes aristolochic acid nephropathy (AAN) characterized by progressive renal fibrosis and functional decline. Here, we examined the potential of AAN as a model of renal senescence using chronic AA administrations into C57BL/6 mice.

Methods: 8-week-old male C57BL/6 mice were assigned to AA or vehicle control group after 1 week acclimatization. Mice were intraperitoneally administered with AA (3mg/kg) or vehicle (75% dimethyl sulfoxide) twice a week for 4 weeks, followed by a 4-week recovery period.

Results: Compared to controls, the AA group showed aged kidney-like phenotypes such as renal atrophy, renal functional decline, and tubulointerstitial fibrosis. In addition, AA provoked cellular senescence specifically in the kidneys, concomitant with an increase in renal p16 mRNA expression and senescence-associated β-galactosidase activity. Additionally, AA-induced mice exhibited proximal tubular mitochondrial abnormalities, followed by accumulation of reactive oxygen species.

Conclusions: Collectively, the results of the present study indicates that AAN partially mimics aged kidney and could become a useful mouse model for kidney aging research.

PO2483
Hypervitaminosis A Contributes to Kidney Injury Through Excessive Endoplasmic Reticulum Stress in CKD
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Background: Endoplasmic reticulum (ER) stress is activated upon the accumulation of misfolded proteins in the ER. PERK signaling, one of the downstream pathways of ER stress response, mediates some transcription factors such as activating transcription
factor 4 (ATF4) and C/EBP-homologous protein (CHOP). It has been known CHOP induction/accumulation and leads to chronic kidney disease (CKD) via apoptosis. ATF4 promotes transcriptional activation of DNA damage-inducible protein 34 (GADD34/ Ppp1r15a), which is the negative-feedback protein of PERK signaling and essential for cell survival. It is reported that the levels of plasma vitamin A and its metabolites, all-trans retinoic acid (ATRA), increased in CKD patients during the CKD stage. One recent report shows excessive vitamin A in CKD patients induces renal dysfunction, however, the effects of ATRA on ER stress have been unclear. In this study, we investigated the role of ATRA on ER stress in the kidney of CKD.

**Methods:** To determine the effect of CKD on circadian rhythm in the kidney, oscillation of several peripheral clock gene (Bmal1, Per1, CLOCK and Rev-erba) as well as physiologic parameters (GFR, transporter protein expression and urine output) were compared between control and adenine induced CKD mice. To determine the role of circadian disruption on CKD progression, renal function and fibrosis were compared between WT and Bmal1 knockout mice. In addition, adenine-induced CKD mice were given either a 24-hour ad libitum diet or a TRF for 8 weeks and the effect of TRF on CKD progression as well as oscillation of peripheral clock genes were measured.

**Results:** Adipine induced CKD mice showed disrupted oscillation of peripheral clock genes (Bmal1, Per1, CLOCK and Rev-erba) and this was associated with loss of rhythmic oscillations of glomerular filtration rate, tubular functions and urine output. Meanwhile, more severe fibrosis and lower GFR were observed in Bmal1 (principal driver of molecular clock) knockout mice compared to WT mice, showing a bidirectional relationship between disturbed circadian rhythm and CKD progression. TRF in adenine induced CKD mice significantly suppressed interstitial inflammation as well as cell cycle arrest and ultimately ameliorated worsening of renal function and fibrosis. These results were accompanied by partial restoration of disturbed oscillation of peripheral clock genes, suggesting that renoprotective effect of TRF is partially mediated by restoration of peripheral clock.

**Conclusions:** Our data demonstrated a unique bidirectional relationship between the circadian disruption and CKD and suggest that disruption of peripheral clock might contribute to CKD progression. The renoprotective effect of TRF might be mediated via resynchronizing disrupted peripheral clock in the kidney.

**PO2487**

D-Serine Promotes Kidney Remodeling via an mTOR-Related Pathway

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**Background:** D-Serine is a long-term undetected endogenous of serine, is a biomarker that reflects kidney function and disease activity, whereas the physiological functions of D-Serine have been unclear. Here, we investigated the physiological functions of D-Serine in human living kidney donors and in unilateral nephrectomy (UNX) mice model.

**Methods:** Dynamics of D-serine was assessed by measuring D-serine in human samples of living kidney donors using two-dimensional high-performance liquid chromatography before and after UNX. Effects of D-serine on kidney from UNX mice and genetically modified cells were examined by gene expression profiling and histological studies.

**Results:** Human living kidney donors after UNX decreased urinary excretion and thus increased the blood level of D-serine. The plasma ratio of D-serine correlated well with glomerular filtration rate (GFR). Treatment of D-serine at physiological dose promoted the enlargement of remnant kidney in UNX mouse model. Profiling of pathway enrichment analysis using RNAseq in the kidney of UNX mice revealed dominant activation of the cell cycle and inhibition of mTOR signaling. Mechanistically, D-serine activated the cell cycle for tissue remodeling through an mTOR-related pathway, and inhibition of mTOR suppressed D-serine-induced cellular proliferation.
Conclusions: D-Serine is a physiological molecule that promotes kidney remodeling. Besides its role as a neurotransmitter, D-serine has a physiological activity that influences kidney function.

Funding: Commercial Support - Shiseido Company, Limited, Government Support - Non-U.S.

PO2488
First-in-Class PRS Inhibitor DWN12088 Ameliorates Folic Acid-Induced Kidney Fibrosis

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Background: Fibrosis is characterized by the upregulated extracellular matrix (ECM), which drives organ damage and abnormal cell proliferation. According to recent studies, PRS (prolyl- tRNA synthetase) is known to play a role in synthesizing collagen during ECM components. It has been reported that PRS is greatly increased in the lung and liver fibrosis animal model, but the role of PRS in the renal fibrosis model has not been elucidated.

Methods: In this study, we investigated the protective effect of novel PRS inhibitor (Daewoong Pharmaceutical Co., Ltd., Korea), in folic acid (FA)-induced kidney fibrosis and aimed to determine whether this role depends on the inhibition of mitochondria dysfunction and the STAT3 signaling pathway. Renal fibrosis was induced by FA (250 mg/kg) intraarterial injection in C57BL/6 mice. DWN12088 (10, 30 mg/kg) was administered by intraperitoneal daily injection for 4 weeks. Histological changes were examined by Masson’s trichrome staining. The expression of ECM markers was evaluated by immunohistochemistry, western blot analysis and real-time-PCR. Mitochondria was also examined by electron microscopy.

Results: FA induced renal fibrosis and mitochondria dysfunction and upregulated PRS expression. When the FA induced decreased weight in mice, there was an effect on body weight by administering the DWN12088. We also examined the blood urea nitrogen (BUN), serum creatinine (Cr), creatinine clearance (CCR) and urine protein creatinine ratio (UPCR) levels. DWN12088 attenuated the levels of clinical data of renal injury (it decreased BUN and Cr levels and UPCR levels, and increased the CCR levels). The administration of DWN12088 decreased the PRS levels and improved FA-induced renal fibrosis and mitochondria. Moreover, DWN12088 effectively inhibited the ECM markers (FN and Collagen 1A1) and the levels of SIRT1/STAT3 induced by TGF-β1 induced fibroblast condition in HK-2 cells. DWN12088 also improved mitochondria function in HK-2 cells.

Conclusions: This study provides evidence for the detrimental role of upregulated PRS in the pathogenesis of renal fibrosis. The findings highlight a DWN12088 that may potentially be a therapeutic intervention to prevent renal fibrosis (NRF-2020R1A2C2003438).

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PO2489
AIM2 Modulates Renal Metabolic Profile and Inflammation in Acute and Chronic Kidney Injury

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Background: The absent in melanoma 2 (AIM2) is cytosolic double-stranded DNA receptor expressed in the kidney. AIM2 activation initiates the assembly of the inflammasome, culminating in inflammatory response. Inflammamsoes cause metabolic dysregulation and drive pathology in a wide variety of human diseases. So far, the function and how AIM2 affects inflammatory and renal metabolic profile in acute and chronic injury is poorly described.

Methods: We used wild-type (WT) and AIM2 KO mice were submitted to cisplatin-induced acute kidney injury or unilateral ureter obstruction (UUO), a chronic kidney disease model. We evaluated renal structure and function, fibrictic molecules, fibronectin (FN) and type 1 collagen (COL1) and inflammation (IL-1β, IL-6). The expression of carnitine palmitoyltransferase 1 (CPT1a), involved in fatty acid oxidation (the main energy source of kidneys), and glycolytic enzyme expression, pyruvate kinase M2 (PKM2) were used as an indicative of metabolic alteration. The AIM2 activation was also investigated in proximal tubular cells (PTCs).

Results: The severe tissue injury induced in WT mice by cisplatin was markedly attenuated in AIM2 KO mice, evidenced by reduction in tubular dilatation and amelioration of renal function. Moreover, AIM2 deletion impaired the reduction of CPT1a expression. In an in vitro model of UUO, we observed an increase of AIM2 expression, concomitantly with increase of IL-1β, IL-6, FN and COL1. Moreover, the animals presented reduced expression of CPT1a and increase of PKM2, suggesting a metabolic reprogramming in the kidneys. The AIM2 deficiency attenuated the renal injury, fibrosis, inflammation, and CPT1a levels, but did not change after kidney injury. In vivo study, the AIM2 activation caused metabolic reprogramming in PTCs, accompanied by increase of proinflammatory and profibrotic markers.

Conclusions: AIM2 activation drives acute e chronic kidney injuries. However, a better understand on how AIM2 affects PTCs metabolism and its connection with inflammation and kidney injury is needed.

Funding: Government Support - Non-U.S.

PO2490
Identification of Post-Translational Guanidinated Proteins in the Context of Systemic Lupus Erythematosus by Using Mass-Spectrometric Methods

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Background: With continuous identification of post-translational modified isoforms of proteins, it is becoming increasingly clear that post-translational modifications limit or modify the biological functions of native proteins are majorly involved in development of various chronic disease. This is mostly due to technically advanced molecular identification and quantification methods, mainly based on mass spectrometry. Mass spectrometry has become one of the most powerful tools for the identification of proteins and modifications.

Methods: In this study, we used sophisticated high-resolution mass-spectrometric methods to analyze the soluble ligand of receptor Notch-3, namely the Y-box protein (YB-1), in serum from system lupus erythematosus (SLE) patients. In addition, kidneys of lupus-prone (MLR, pr) mices were analyzed by mass-spectrometric imaging techniques to identify the underlying pathomechanisms. Serum YB-1 was isolated by chromatographic methods, afterwards digested by trypsin and analyzed by matrix assisted laser desorption/ionization mass spectrometry (MALDI-MS). The kidneys were fixed in paraffin, then kidney sections were deparaffinized, trypsin digested and analyzed by mass-spectrometric imaging techniques.

Results: Mass-spectrometry of extracellular YB-1 in SLE patient serum revealed post-translational guanidination of two lysine’s within the highly conserved cold shock domain (CSD) of the YB-1 protein (YB-1-2G). Patients with increased disease activity and those with active renal involvement (lupus nephritis, LN) had a higher degree of dual-guanidination within the CSD. Of note, at least one of these modifications was present in all analyzed LN patients, whereas single-guanidinated YB-1 was present in only one and double modification in none of the control individuals. Mass-spectrometric imaging analyses specifically localized YB-1-2G and increases Notch-3 expression in kidney sections from MRL-lpr mice.

Conclusions: The data from this study clearly demonstrate the high potential of high-resolution mass spectrometric methods as well as mass spectrometric imaging techniques to identify pathomechanisms of diseases like SLE/LN.

PO2491
Deletion of Tubular Cpt1a Does Not Worsen Kidney Aging or Response to Injury

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Background: Proximal tubules (PT) preferentially use fatty acid oxidation to generate the energy necessary to support their high reabsorptive capacity. Carnitine palmitoyltransferase 1 (CPT1) is required for long chain fatty acids to enter mitochondria, and CPT1a deletion would exacerbate kidney aging and injury. However, this has not been examined in an aged mouse model.

Methods: We analyzed renal function and histological changes in CPT1a-Cre mice and confirmed robust recombination. Mice were aged for 2 years or injured by unilateral ureteral obstruction (UUO). Primary PT-enriched cell populations were generated from aged mice, and fatty acid-dependent respiration and glycolysis were measured using Seahorse bioflux analyzer.

Results: Old mice lacking tubular Cpt1a (Cpt1aKO) had increased intracellular fatty acid oxidation (Oil Red O staining) and inflammation (IL-6) staining, but there were no significant differences in oxidative stress, fibrosis or renal function (GFR, proteinuria) compared with aged floxed controls. Similarly, Cpt1aKO mice had no differences in tubular injury or fibrosis after either AAN or UUO-induced injury. Palmitate-dependent respiration was reduced but not blocked in primary cells from Cpt1aKO aged mice, and glycolytic capacity was significantly increased. RNAseq from aged Cpt1aKO revealed significantly upregulated genes in several pathways including PPARGs that may compensate for Cpt1a loss.
**Conclusions:** Surprisingly, tubular deletion of Cpt1a did not worsen aging or response to injury, suggesting that compensatory responses can partially counter the metabolic impairment. A better understanding of these compensatory responses may inform future treatments for kidney injury.

**Funding:** NIDDK Support, Veterans Affairs Support

**PO2492**

**Multi-Omic Analysis of Mouse Renal Tubule Cell Responses Following Unilateral Nephrectomy**

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**Background:** The kidney increases in size following resection of the contralateral kidney. Modern -omics' methods provide an opportunity to understand this response at a cellular level.

**Methods:** Experiments were done in mice after unilateral nephrectomy (UNx) or sham nephrectomy. MRI was used to measure kidney volume. The earliest portion of the kidney proximal tubule (PCT) and the cortical collecting duct (CCD) were microdissected at different time points (24 hours and 72 hours). Microdissected tubules were analyzed by quantitative immunofluorescence microscopy to determine cell size and number, and by RNA-seq to identify gene expression changes. Quantitative protein mass spectrometry was used to identify proteomic changes.

**Results:** Increased kidney volume was already detectable at the 24-hour-time point after UNx (versus sham), and was increased further at 72 hours. Morphometry of microdissected PCT and CCD, labeled with apical and basolateral markers and DAPI, revealed a marked increase in total cell volume per unit length, but no significant change in mean cell volume in both PCT and CCD, revealing that the increase in total cell volume was due to cellular proliferation rather than hypertrophy of individual cells. Consistent with this observation, RNA-Seq at 72 hours after surgery showed significant increases in the abundance of transcripts associated with cell cycle regulation and regulation of both proximal and distal nephron function. In both PCT and CCD, many mRNAs were highly upregulated that predict increased free fatty acid levels in proximal tubule cells. Lipid mediators, including those derived from the fatty acid arachidonic acid, may be involved in cellular proliferation.

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**PO2493**

**Calponin 2 Determines AKI to CKD Transition Through Alternating Fatty Acid Oxidation**

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**Background:** Calponin 2 (CNN2) is an actin filament-associated regulatory protein that plays a central role in numerous fundamental biological processes, including cell proliferation, motility, and adhesion to substrates and other cells. Emerging evidence suggests that cell mechanics can have direct, non-transcriptional influences on cell metabolism. The kidney is a highly metabolically active organ. Fatty acid oxidation is one of the major metabolic processes that occurred in the kidney under pathophysiological conditions. It remains unknown whether CNN2 plays a role in mediating kidney disease progression from the perspective of cell metabolism.

**Methods:** We constructed ischemic reperfusion injury (IRI) and unilateral ureter obstruction (UUO) animal models in this study. It remains unknown whether CNN2 plays a role in mediating kidney disease progression from the perspective of cell metabolism.

**Results:** Increased kidney volume in response to UNx was due to cellular proliferation rather than hypertrophy of individual cells. Many lipid-metabolism related mRNAs were highly upregulated that predict increased free fatty acid levels in proximal tubule cells. Lipid mediators, including those derived from the fatty acid arachidonic acid, may be involved in cellular proliferation.

**Funding:** Private Foundation Support, Government Support - Non-U.S.

**PO2494**

**Decreased Renal Gluconeogenesis Is a Hallmark of CKD**

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**Background:** Chronic kidney disease (CKD) is associated with alterations of tubular function. Renal gluconeogenesis is responsible for 40% of systemic gluconeogenesis during fasting, but how and why this process is affected by CKD and the repercussions of such regulations are unknown.

**Methods:** We used data from more than 200 renal biopsies performed in CKD patients and from 43 kidney allograft patients. We studied three complementary mice models of chronic kidney disease in vivo and ex vivo. We analyzed a cohort of patients having benefited from renal catheterization and a retrospective cohort of patients hospitalized in the intensive care unit (ICU).

**Results:** Renal biopsies of CKD and kidney allograft patients revealed a stage-dependent decrease in the renal gluconeogenic pathway. Three different animal models of CKD confirm a proximal tubular cell-specific gluconeogenic down-regulation. This resulted in an alteration of renal glucose production and lactate clearance during an exogenous lactate load. Decreased renal glucose production and lactate clearance were confirmed by the isolated perfused kidney technique in animal models, and by renal venous catheterization in CKD patients. In CKD patients hospitalized in the ICU, systemic alterations of glucose and lactate levels were more prevalent and associated with increased mortality and worse renal prognosis at follow-up. Decreased expression of the gluconeogenesis pathway and its regulators predicted faster histological progression of renal disease in kidney allograft biopsies.

**Conclusions:** Renal gluconeogenesis function is impaired during CKD. Altered renal gluconeogenesis leads to systemic metabolic changes with a decrease in glucose and increase in lactate level, and associates with a worse renal prognosis.

**Funding:** Private Foundation Support, Government Support - Non-U.S.

**PO2495**

**Localization of Metabolites in Tubulointerstitial Disease**

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**Background:** Tubulointerstitial (TI) disease plays a critical role in the outcome of patients with chronic kidney disease, however the basic biochemical pathways that generate the TI damage remain unclear. The application of metabolomics in chronic kidney disease (CKD) studies provide researchers the opportunity to gain new insights into metabolic profiling and pathophysiological mechanisms. Mass spectrometry imaging (MSI) is a promising approach that has the potential in reveal spatially-resolved metabolic information within kidney tissue across different disease states.

**Methods:** In the current study, we employed a high-resolution matrix-assisted laser desorption/ionization (MALDI)-MSI approach to characterize small molecules in human kidney biopsy core samples (n=6) were received from KPMP recruitment sites (CCF, JOS, UTSW, CLU, JHMI, YLE, UPMC, BMC, CIN-HRT and UMI-CBR). The data output was uploaded to METASPACE for molecular annotation, and SCILS Lab, Metaboanalyst, and Cytoescape were utilized for data processing and statistical analyses.

**Results:** In total, 600 small metabolites (m/z 80-1000) were annotated by METASPACE using the human metabolome database (20% FDR) in human kidney biopsy core sections. MALDI-MSI of human kidney biopsy core sections exhibited different spatial distributions of intermediates in the tricarboxylic acid cycle, glutamate-glutamine cycle, malate-aspartate shuttle, and phospholipid metabolism, simultaneously. Specifically, D-4-phosphopantetheine (m/z 298.0867) was identified as a new glycolytic enriched marker and was also present in atrophic tubule. The glycolytic metabolite glucose-6-phosphate (m/z 259.0224) was enriched in normal tubules and not over expressed in atrophic tubule.
Conclusions: MALDI MSI is potentially an effective tool for small molecule in situ analysis in MALDI-MSI biopsies. A coupled MALDI-MSI readout of kidney tissue coupled with MS/MS enabled the identification of novel metabolic... shed new light on omics data integration studies. In summary, from an individual patient with CKD, we found spatial restrictions of metabolites to normal tubule and potentially with atrophic tubule.

Funding: NIDDK Support

PO2498
Association of Metabolic Syndrome with Hyperfiltration in a General Non-Diabetic Population: The Renal Iohexol Clearance Survey

Background: Metabolic syndrome (MS) affects approximately one quarter of the world, making it a global epidemic. Although MS has been associated with increased risk of rapid decline in the glomerular filtration rate (GFR), only a few studies have investigated the association of MS with abnormally elevated GFR, known as hyperfiltration. Previous studies of MS and hyperfiltration were limited by the use of estimated GFR and the results were divergent. As there are promising treatment options for hyperfiltration, establishing the relationship between MS and hyperfiltration is of clinical importance.

Methods: In the Renal Iohexol Clearance Survey (REINS) we included 1551 subjects from the population based Tromso survey (2007–2009). The participants were 50–62 years old without known diabetes, cardiovascular disease or kidney disease. The GFR was measured using iohexol clearance. The aim was to investigate the relationship between MS and RHF. The dichotomous variable for RHF was defined as an absolute mGFR (ml/min) above the 90th percentile after adjusting for gender, age and height.

Results: Metabolic syndrome was associated with increased absolute GFR (ml/min) and renal hyperfiltration (yes/no) independent of age, sex and height (OR 2.44 95% CI: 1.71 – 3.46, p<0.001). All risk factors except for hypertension were independently associated with RHF and increased absolute GFR. The risk of renal hyperfiltration was highest in subjects fulfilling 5 of out 5 criteria (OR 4.06, 95% CI, 1.54-10.67, p<0.005) compared to those fulfilling 0 or 1 criteria. Conversely, MS was not associated with higher estimated GFR based on creatinine or cystatin C.

Conclusions: Subjects with MS have a higher absolute GFR and increased risk of renal hyperfiltration compared to subjects without MS. RCTs are needed to explore whether treatment of hyperfiltration can prevent accelerated GFR decline and CKD in persons with MS.

PO2499
Hydrogen Sulfide Ameliorates High Fat Diet-Induced Hypertension and Kidney Injury in Mice
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Background: The role of hyperinsulinemia caused by high fat diet (HFD) in kidney injury is not known. Employing kidney proximal tubule specific insulin receptor (IR) KO mice, we have shown recently that HFD-induced kidney injury requires hyperinsulinemia-induced IR activation (Lee et al., JCI insight, 2021, 6(3): e143619). Furthermore, HFD reduced kidney hydrogen sulfide (H2S) generation in an IR-dependent manner. We tested if HSD administration ameliorates HFD-induced kidney injury in mice and cell models.

Methods: 5 month-old C57BL/6 male mice were placed on normal fat diet (NFD) or HFD for 2 months followed by randomization to receive for 2 months, H2S as sodium hydrosulfide (NaHS) 30 μmol/L in drinking water or water alone (n=5-6 in each group).

Results: HFD or NaHS did not affect blood glucose level. HFD increased body weight, and induced systolic hypertension (NFD: 118 ± 5 mmHg; HFD: 144 ± 10 mmHg), albuminuria (25.5 ± 16 vs. 139.7 ± 48 μg/mg), and kidney accumulation of matrix proteins. NaHS reduced these HFD-induced changes (systolic hypertension: 112 ± 7 mmHg, urinary ACR: 76.1 ± 29 μg/mg) without affecting body weight. In the renal cortex, HFD reduced level of H2S, which was restored by NaHS administration. HFD stimulated IR phosphorylation and inhibited AMPK activity, which promotes synthesis of proteins including matrix proteins. NaHS did not affect IR phosphorylation but increased AMPK activity. We employed proximal tubule cells to test the effect of H2S on insulin-induced matrix synthesis. Insulin increased fibronectin synthesis likely through stimulation of its mRNA translation by inhibiting AMPK and activating mTORC1. This effect of insulin was abolished by NaHS.

Conclusions: Taking in vivo and in vitro data together, we conclude: (1) HFD induces kidney IR activation and reduces H2S generation in an IR-dependent manner. We tested if HSD administration ameliorates HFD-induced kidney injury in mice and cell models. (2) H2S acts as a signaling molecule to activate AMPK, downstream of IR, and inhibits mTORC1 to ameliorate HFD-induced kidney injury. (3) H2S could be a therapeutic agent for obesity-related kidney injury.

PO2500
Proximal Tubule Cyclophilin D Mediates Kidney Fibrogenesis in Obstructive Nephropathy
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Background: Proximal tubule (PT) is highly vulnerable to acute injury, including ischemic insult and nephrotoxins, and chronic kidney injury. It is established that PT injury is a primary cause of development of chronic kidney disease, but the underlying molecular mechanism remains to be defined.

Methods: Here, we tested whether PT cyclophilin D (CypD), a mitochondrial matrix protein, is a critical factor to cause kidney fibrosis progression. To define the role of CypD in kidney fibrosis, we used an established mouse model for kidney fibrosis, unilateral ureteral obstruction (UUO) model in global and PT-specific CypD knockout (KO).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: Global CypD KO blunted kidney fibrosis progression with inhibition of myofibroblast activation and fibrosis. UUO-induced tubulointerstitial fibrosis was suppressed in kidneys of global CypD KO, but not tubular dilatation or apoptotic cell death. PT cell cycle arrest was highly increased in WT-UUO kidneys, but markedly attenuated in global CypD KO-UUO kidneys. The number of macrophages and neutrophils was less in UUO kidneys of global CypD KO than those of WT. The pro-inflammatory and fibrotic factors were all inhibited in global CypD KO. In line with those of global CypD KO, PT-specific CypD KO also blunted kidney fibrosis progression, along with less tubular atrophy, renal parenchymal loss, cell cycle arrest in PT and inflammation, indicating a critical role for PT CypD in fibrosis.

Conclusions: Collectively, our data demonstrate that CypD in PT is a critical factor contributing to kidney fibrosis in UUO, providing a new paradigm for mitochondria-targeted therapeutics of fibrotic diseases.

Funding: NIDDK Support

PO2501
Reduction of Hnf4α Expression in CKD Accelerates Disease Progression
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Background: Renal mitochondrial dysfunction is a common feature of Chronic Kidney Disease (CKD) and is associated with cardiovascular disease. HNF4α is highly expressed in proximal tubules and controls the expression of genes involved in various metabolic pathways. Mutations in Hnf4α are associated with mitochondrial defects. We tested the hypotheses that renal Hnf4α decline in CKD contributes to mitochondrial dysfunction and renal fibrosis via study of cardiovascular outcomes and that Hnf4α reduction in CKD is result of hyperphosphatemia.

Methods: We confirmed Hnf4α expression was reduced in the kidneys of Col4a3 KO mice, model of progressive CKD. Next, we performed RNA sequencing (RNAseq) on kidneys collected from WT and Col4a3 KO mice to identify genes and molecular pathways altered by HNF4α reduction in CKD. We treated mice with a continuous administration of Hnf4α antagonist (BI-6015, 3mg/g/day) for 8 weeks to study the effects of Hnf4α suppression on renal and cardiac functions. To further evaluate the role of Hnf4α reduction in CKD progression, we injected 30 mg/g BI-6015 to Col4a3 KO mice for 5 days. We also generated WT and Col4a3 KO mice with a Hnf4α deletion in kidney proximal tubules (Hnf4αfl/fl and Col4a3 KO/Hnf4αfl/fl). Finally, to demonstrate that hyperphosphatemia reduces Hnf4α expression in the kidney, we fed WT mice a control and a high phosphate diet (25% P) for 4 weeks.

Results: RNAseq of Col4a3 KO mice kidneys showed impaired molecular pathways regulated by HNF4α, including increased mitochondrial dysfunction and reduced oxidative phosphorylation. Inhibition of Hnf4α in WT mice led to kidney interstitial fibrosis and left ventricular hypertrophy, while in Col4a3 KO mice a shorter administration of HNF4α antagonist accelerated the decline in kidney function (+450% serum creatinine vs. Col4a3 KO-Ctr mice), demonstrating the crucial role of HNF4α in CKD progression. Similarly, Hnf4α deletion in proximal tubules impaired kidney function in WT mice and further worsened it in CKD animals. WT mice fed a HPI diet showed a 70% reduction in renal Hnf4α expression, suggesting that hyperphosphatemia contributes to renal HNF4α suppression.

Conclusions: Our results suggest that HNF4α is a master regulator of kidney mitochondrial function and might represent a novel therapeutic target to improve renal and cardiovascular outcomes in CKD.

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PO2502
Wasp Homologue Associated with Membranes and Microtubules Is a Kidney Disease Risk Gene
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Background: Genome-wide association studies identified hundreds of risk variants that are associated with kidney function traits. More than 90% of these variants are located in non-coding regions of the genome and therefore their target genes, target cell types and biological processes remain not known.

Methods: Here we used human kidney expression and methylation of quantitative trait (QTL and/or mQTL) information and complex computational integration to identify target cell types for genetic variants. We obtained mice with genetic loss of WHAMM. We induced acute kidney injury by cisplatin injection and chronic kidney disease by bleomycin injection. Kidney function was analyzed by serum creatinine and blood urea nitrogen, real time PCR, western blotting, and histology analyses. We cultured primary kidney tubule epithelial cells, in addition, autophagy was assessed by p62-LC3B GFP-RFP plasmid and quantified as colocalization of microtubule-associated proteins (m-tub) -GFP-RFP plasmid.

Results: Using Bayesian colocalization, summary mendelian randomization, and transcriptome-wide association studies we prioritized WHAMM as a kidney disease risk gene. Risk variant rs12903411 was associated with higher WHAMM expression. WHAMM is an ATG7 complex activator protein that is associated with mitochondrial dynamics by utilizing microtubules. WHAMMM heterozygous and knock-out mice subjects to cisplatin and bleomycin injection presented with improved kidney function (BUN, creatinine) and lower expression of injury markers (Kim1, N-gal) and fibrosis markers. Primary tubular cells with WHAMM loss showed increased autophagy flux compared to wild type. Furthermore, WHAMM heterozygous and knock-out mice and cells showed improved mitophagy and reduced expression of inflammatory markers such as IL-6 and TNFα. Moreover, WHAMM was associated with lower pyroptosis indicated by cleaved caspase1 and gasdermin D levels compared to WT mice in the follic acid model.

Conclusions: In summary, this study identified WHAMM as a new kidney disease risk gene.

Funding: NIDDK Support

PO2503
Autophagy Gene ATG7 Regulates Albumin Transcytosis in Renal Tubule Epithelial Cells
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Background: Receptor-mediated albumin transport in renal proximal tubule epithelial cells (PTECs) is important to control proteinuria. Autophagy is an evolutionarily conserved degradation pathway and its role in intracellular trafficking through interaction with the endocytic pathway has recently been highlighted. In this study, we determined whether autophagy regulates albumin transcytosis in PTECs and suppresses albumin-induced cytotoxicity.

Methods: Human tubular epithelial cell line (HK-2) was used for all experiments. The cells were exposed to 10 mg/ml BSA for 6 h or 24 h as required. For autophagy related 7 (ATG7) knockdown (KD), cells were transfected with ATG7 siRNA. The intracellular trafficking of FcRn was examined by biotin-labeled recycling assay. Immunofluorescence of FcRn and Rab7 or Rab11 was observed by confocal microscopy. The transcytosis of albumin in HK-2 was evaluated using FITC-HSA-based transcytosis assay. The release of IL-8 and KIM-1 caused by excess albumin were measured by ELISA, and mitochondrial damage was measured by MitoTrackerCMXRos.

Results: FcRn partially co-localized with autophagosomes. FcRn was accumulated and recycling of FcRn was attenuated in ATG7 KD cells. Colonization of FcRn with RAB7-positive late endosome or RAB11-positive recycling endosomes were reduced in ATG7 KD cells. In ATG7 KD cells, albumin transcytosis was significantly reduced, and albumin accumulated in the cells. Exposure to excess albumin reduced autophagic flux in HK-2. Consequently, excess albumin-induced mitochondrial damage is enhanced in ATG7 KD cells. The release of IL-8 and KIM-1 from ATG7 KD cells increased in response to excess albumin.

Conclusions: In PTECs exposed to excess albumin, autophagy is decreased and intracellular transport of FcRn is impaired, resulting in decreased albumin transcytosis. The resulting accumulation of albumin induces cytotoxicity in tubules. Preventing dysfunctional autophagy in PTECs might be beneficial in the clinical management of nephrinopathies with proteinuria.

Funding: Government Support - Non-U.S.

PO2504
Leveraging High-Content Imaging Platforms for Drug Discovery

Background: Disruption of the structure and function of the glomerular filtration barrier, leading to proteinuria, is a hallmark of several podocyteopathies. Efficacy in translatable in vitro models is a critical first step to develop new therapies. For example, free fatty acids such as palmitic acid and protonate sulfate are well characterized in vitro models to model DN and FSGS. However, these models are low throughput, making them unsuitable for target and compound screening.

Methods: We used immobilized murine podocytes and adapted the readouts of in vitro assays to a high content imaging (HCI) platform. Readouts in response to Palmitic Acid (PA) included: apoptosis and cell viability by annexinV and propidium iodide staining or MTI, mitochondrial membrane potential by JC-1 and Mitotracker Deep Red; and mitochondrial and cytosolic reactive oxygen species by MitoSOX andDCF. Actin cytoskeleton dynamics were assessed by quantification of actin aggregation that was partially rescued by cyclosporin A, a known positive control. We established a reliable and semi-automated high-content imaging assay. We developed a validated imaging pipeline to quantify 9 fields per well of a 96-well plate. We showed that there was a dose- and time-dependent increase of Phalloidin aggregation, and is usually assessed by confocal microscopy, but capacity was increased by at least 4x. We observed a dose-dependent, incremental increase of DCF. Actin cytoskeleton dynamics were assessed by quantification of actin aggregation data.

Results: Podocyte apoptosis and cell death was comparable to the readout by FACS, but capacity was increased by at least 4x. We observed a dose-dependent, incremental increase of DCF. Actin cytoskeleton dynamics were assessed by quantification of actin aggregation that was partially rescued by cyclosporin A, a known positive control.

Conclusions: We established a reliable and semi-automated high-content imaging platform, which will facilitate a better mechanistic understanding of podocyte injury, as well as drug discovery, including target validation and compound screening in podocytes.

Funding: Commercial Support - Goldfinch Bio

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PO2505

The eNOS–NO Pathway Attenuates the Progression of Age-Related Kidney Diseases via Suppression of C/EBPβ–Associated Inflammation

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Background: Chronic kidney disease (CKD) is a very common clinical problem in elderly patients and is associated with increased mortality. As life expectancy continues to improve worldwide, the prevalence of comorbidities and risk factors, such as hypertension and diabetes, that predispose this population to a high burden of CKD is rising. Chronic inflammation (inflammaging) is also an important cause of age-related organ damage, such as kidney disease, and we hypothesized that endothelial dysfunction accelerates the progression of age-related kidney injury.

Methods: We evaluated the anti-inflammatory effects of nitric oxide (NO) as an endothelial function in bone marrow–derived macrophages (BMDM) using in vitro experiments. BMDM derived from Wild Type (C57BL/6); W) were stimulated through NLRP3 inflammasome activation using LPS-ATP, and the IL-1β secretion was examined. To determine the importance of inflammasome activation in age-related kidney diseases, we used mice deficient in apoptosis-associated speck-like protein containing CARD (ASC)—which is an essential molecule for inflammasome activation—in vivo. We evaluated those mice (ASCKO), eNOS knockout (eNOSKO) mice, and eNOS-ASC double-knockout mice (eNOS-ASC-DKO).

Results: S-nitrosoglutathione (GSNO) attenuated the NLRP3 inflammasome activation that followed treatment with LPS-ATP. This indicates that NO directly inhibits NLRP3 inflammasome activation. GSNO also decreased the expression of inflammasome-related genes. To investigate the detailed mechanisms (epigenetic regulation), we performed ATAC-seq using BMDM. The binding region of the transcription factor CCAAT/enhancer-binding protein (C/EBP) was significantly closed in the LPS–GSNO, compared with the LPS group. Interestingly, we recently reported that C/EBP is associated with NLRP3 inflammasome and is activated in aging kidneys. These mice were sacrificed at 15 months of age; the glomerular injury was found to be exacerbated, and serum Cn was elevated in the eNOSKO-15M, but not in the WT-15M. These changes were improved in the eNOS-ASC-DKO-15M.

Conclusions: The eNOS–NO pathway ameliorated the progression of renal injury by regulating the inflammasome of the aging kidney. NO directly inhibits NLRP3 inflammasome activation via the suppression of C/EBPβ activation.

PO2506

Symmetric Dimethylarginine Inhibits Renal Fibrosis in Obstructive Kidneys

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Background: Symmetric dimethylarginine (SDMA) is regarded as an independent cardiovascular risk factor in patients with chronic kidney diseases. Renal interstitial fibrosis is a common pathway of all kinds of chronic kidney diseases progressing to the end stage of renal diseases. In this study we investigated the role of SDMA in renal fibrosis and its underlining mechanisms.

Methods: Normal saline (NS) and SDMA (2.50 µmol/kg) were administered into the kidney through the left ureter in a mouse model of unilateral ureteral obstruction (UUO). UUO was performed at day 7. Western blotting and Masson’s trichrome staining were performed to evaluate renal fibrosis. Moreover, human kidney (HK2) cells were treated with various concentrations of SDMA (0.01 µM to 10 µM) in the presence of 2.5 ng/ml TGF-β. Protein samples were collected from cells to measure the expression of fibrotic markers.

Results: We observed that intrarenal administration of SDMA attenuated renal fibrosis as shown by Masson staining and Western blotting analysis of the expression of fibrotenin, collagen-1 and α smooth muscle actin (αSMA). In parallel, SDMA dose-dependently reduced the expression of pro-fibrotic proteins in TGF-β stimulated HK2 cells. Phosphorylation of Smad3 protein was analyzed in vivo and in vitro, which showed that SDMA inhibited phosphorylation of Smad3 in UUO kidneys and TGF-β stimulated HK2 cells.

Conclusions: Thus, our data suggest that renal SDMA exerts direct anti-fibrotic effects in fibrictic kidneys probably through inhibition of Smad3 signaling pathway.

PO2507

Targeting ARG1+ Macrophages Slows the Progression of AKI to CKD

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Background: Recently, ARG1+ myeloid cells were defined as a new subgroup that express a large number of pro-inflammatory and pro-fibrotic genes. However, its function and clinical application in kidney disease has not yet been identified.

Methods: We clarified the source of ARG1+ macrophages via the bone marrow transplantation and the parabiosis, and constructed macrophage-specific ARG1 knockout mice (ARG1fl/fl; CX3CR1creERT2) and CX3CR1CreERT2–DTR mice. Kidney samples were harvested at day 7. Western blotting and Masson’s trichrome staining were performed to evaluate renal fibrosis. Moreover, kidney 2 (HK2) cells were treated with various concentrations of SDMA (0.01 µM to 10 µM) in the presence of 2.5 ng/ml TGF-β. Protein samples were collected from cells to measure the expression of fibrotic markers.

Results: Most of the intrarenal ARG1+ macrophages were from bone marrow. Knockdown of Arg1 in macrophages alleviated ischemia-induced AKI and the subsequent chronic fibrosis, and reduced the infiltration of macrophages in the kidney, while depletion of CX3CR1+ cells aggravated ischemia-induced renal injury. GSEA analysis revealed that the function of ARG1+ macrophages was highly enriched in the regulation of the release of inflammatory factors, activation of immune inflammatory response, and secretion of extracellular matrix. More biological macrophage ligand–mesenchymal receptor pairs expressed in ARG1+ macrophages between mesenchymal cell (MC)–ARG1+ macrophages compared to ARG1+ macrophages. Inhibiting ARG1 activity alleviated the proliferation of ARG1+ macrophages and reduced ischemia-induced renal fibrosis. The application of RNAI lentiviral vector of ARG1 via the tail vein injection alleviated the renal fibrosis, reduced ARG1 expression and macrophage infiltration.

Conclusions: ARG1+ macrophages accelerated the development of AKI to CKD by promoting inflammation response, activating fibroblasts and secreting extracellular matrix proteins. Inhibiting the activity or expression of ARG1 in macrophages alleviated IR-induced renal fibrosis.

PO2508

UBE-1099, a Novel Non-Covalent Keap1–Nrf2 Inhibitor, Protects Against Renal Ischemia-Reperfusion Injury via Nrf2 Activation

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Background: Patients with chronic kidney disease (CKD) showed a decline in renal function, as presented by glomerular filtration rate (GFR), as the disease progresses. A cavelos K-Like ICH-1-associated protein 1 (Keap1) – Nuclear factor erythroid 2-related factor 2 (Nrf2) inhibitor, bardoxalone methyl, has been reported to increase the estimated GFR in patients with advanced CKD. However, it is unclear how the Nrf2 activator improved GFR. Previous studies have shown that bardoxalone imidazole suppressed renal fibrosis in mice and improved renal function in Nrf2–/– double-knockout mice (eNOS-ASC-DKO-15M).

Methods: A fluorescence polarization-based (FP) assay and NADPH-inducible flavin oxidase (NQO1) enzyme activity-inducting assay on murine Hepa1c1c7 hepatoma cell were used to investigate a non-covalent Keap1-Nrf2 inhibitor. U-IR model was established using 10 week old male C57BL/6 mice. These mice were orally administered either the inhibitor (30 mg/kg, 10 mL/kg, once a day) or vehicle for 14 days. Renal damage was then evaluated by histopathological analysis and measurement of GFR using a percutaneous GFR measurement system (MediBeacon, St. Louis, Missouri).

Results: A novel non-covalent Keap1–Nrf2 inhibitor UBE-1099 improved the atrophic pathology, including renal tubular damage. More surprisingly, UBE-1099 also showed an increasing trend in GFR in that model.

Conclusions: A novel non-covalent Keap1–Nrf2 inhibitor UBE-1099 improved the atrrophic pathology and reduced tubular damage resulting from Nrf2 activation in U-IR model mice. UBE-1099 has been suggested to be a promising drug for renal diseases associated with oxidative stress.

PO2509

Peroxiredoxin 5 Regulates Cyst Growth and Ciliogenesis via Modulating Aurora A and Plk1 Stability and Wnt Signaling Activation

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Background: Peroxiredoxin 5 (Prdx5) is an antioxidant enzyme that catalyzes the reduction of H2O2 and alkyl hydroperoxide and plays a protective role in neurological and cardiovascular disorders. However, the role and mechanism of Prdx5 in autosomal dominant polycystic kidney disease (ADPKD) is unknown.

Methods: To investigate the role and mechanism of Prdx5 on cyst growth and ciliogenesis biogenesis in ADPKD, we knocked down Prdx5 in mIMCD3 and RPE cells with siRNA and shRNA, and performed Western blots, qRT-PCR and immunostaining analysis in renal epithelial cells and tissues. A 3D culture cell system was used to evaluate the effect of Prdx5 knockdown on cyst growth.

Results: We found that Prdx5 was downregulated in cystic renal epithelial and cells. Knockdown of Prdx5 resulted in: 1) abnormal centrosome amplification and multipolar spindle formation in mIMCD3 cells; 2) the upregulation of Polo-like kinase 1 (Plk1) and Aurora kinase A (AurA), essential in cell division and checkpoint regulation of mitosis; 3) the formation of cysts in a three-dimensional matrigel culture system using IMCD3 cells, which correlated with the phosphorylation and activation of PKD associated proliferation signaling, including ERK and mTOR; and 4) impaired primary cilia formation in mIMCD3 and RPE cells, which could be rescued by inhibition of Plk1 activity. In addition, we show that Pldx5 plays a crucial role in the regulation of Wnt signaling pathway activity in renal epithelial cells. Stimulation of Wnt3a ligand had no effect on ciliogenesis in Prdx5 knockdown cells. In contrast, stimulation of Wnt5a exacerbated ciliogenesis defect in Prdx5 knockdown cells. Consistent with Wnt5a activity on regulating primary cilia biogenesis, knockdown of Prdx5 decreased the recruitment of centriolar satellites PCM1 and CEP290, to the centrosome/basal body.
Conclusions: This is the first study to show that Pkd5 regulates cyst formation and cell death via affecting the stability of clearfix, and the activation of cytokines associated signaling pathways. Pkd5 could also control noncanonical Wnt5a-dependent regulation of ciliogenesis, a cascade of events that regulate the recruitment of centriolar satellites necessary for, primary cilia biogenesis.

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PO2510
Comparison of the Renal Effects of Heme-Dependent and Independent Soluble Guanylate Cyclase Targeting Drugs in 5/6 Nephrectomized Rats on High-Salt Diet
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Background: Soluble guanylate cyclase (sGC) targeting drugs were reported to have beneficial renal effects in chronic kidney disease (CKD). The sGC stimulators bind to reduced, heme-containing sGC, while sGC activators bind to oxidized, heme-free sGC and their actions are heme-independent. Regarding renal outcomes, the potential differences between these two classes of drugs are unknown so far. This study aimed to provide a head-to-head comparison of the renal effects of BAY 41-8543 (sGC stimulator) and BAY 60-2770 (sGC activator) in 5/6 nephrectomized rats on high salt diet as a model of CKD.

Methods: Rats were allocated to the following groups: Sham + normal diet + placebo (PBO); 5/6Nx + 2% high salt diet (HSD) + PBO; 5/6Nx + HSD + Telmisartan (5mg/kg/day); 5/6Nx + HSD + BAY 60-2770 (1mg/kg/day); 5/6Nx + HSD + BAY 41-8543 (1mg/kg/day). The treatment period was 8 weeks.

Results: Blood pressure was significantly decreased by BAY 60-2770 and BAY 41-8543 versus placebo (-32.52-27.20 mmHg, p<0.001; -23.83/29.90 mmHg, p=0.001, respectively), which was also comparable to the effects of telmisartan (-24.24-31.90 mmHg, p=0.001). Plasma creatinine was not altered by any of the three drugs, however, renal fibrosis was significantly decreased by BAY 60-2770 (44.76%, p<0.05) and telmisartan (43.96%, p<0.05) versus placebo. On the other hand, BAY 41-8543 did not ameliorate renal fibrosis. RNA-sequencing in renal tissues revealed that 144 genes were differentially regulated among the groups. Interestingly, 23 genes including collagen type VI alpha 5 (Col6a5), phospholipase C eta 1 (PLCeta1) and claudin 19 (Clnd19) were exclusively differentially regulated by BAY 60-2770 and these genes might explain anti-fibrotic renal effects.

Conclusions: Only the sGC activator BAY60-2770 ameliorated renal fibrosis comparable to the gold-standard treatment of CKD with an ARB (telmisartan). These effects were blood pressure independent since blood pressure was similar in all treatment groups. Inactivation of the sGC by oxidative stress in our CKD model may explain the failure of the sGC stimulator in reducing kidney fibrosis. The mechanisms underlying the renal anti-fibrotic effects of BAY60-2770 might involve the differential regulation of Col6a5, Plch1 and Clnd19.

PO2511
In-Depth Proteomic Analysis to Identify the Cellular Proteins and Secretome of Human Tubular Epithelial Cells with Fibrotic Injury
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Background: Fibrosis is the major pathophysiology in the development of chronic kidney disease. While there are several proteomic studies to reveal the mechanism of renal fibrosis. Seventeen proteins including STRAP and EIF3B were significantly decreased in same manner in both cell and secretome analysis, suggesting overall decrease in expression of these proteins with fibrosis. Seventeen proteins including STRAP and EIF3B were significantly decreased in cells while increased in secretome, representing the possible extracellular release of proteins with the response to fibrosis injury. There were 25 proteins including SERPIN1 and CTGF significantly elevated in both cell and secretome identified. And the other 15 proteins including Piegzo1 and ABCD4, which are presumably translocated into the cells with damage.

Conclusions: We identified different protein expression changes in cells and secretome following fibrotic injury. Further studies are needed to validate the pathophysiological role of these proteins on kidney tubulointerstitial fibrosis.

PO2512
Hyaluronan Synthase-2 Antisense (HAS2-AS1) Is a Novel Long Non-Coding RNA That Regulates Pro-Fibrotic Cell Responses in the Kidney
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Background: Renal interstitial fibrosis drives CKD and increased synthesis of hyaluronan (HA) in the tubulointerstitium correlates with fibrosis and renal outcomes. Our work shows that of the three HA synthases, HAS2 expression is causally linked with fibrosis in vivo, a pro-fibrotic cell phenotype in vitro, and is regulated by a long non-coding RNA, HAS2-AS1. Here we investigated the mechanisms that regulate HAS2-AS1 expression and function and influence HA-dependent regulation of pro-fibrotic cell phenotype.

Methods: Primary human fibroblasts were used to test effects of siRNA-mediated HAS2-AS1 knockdown on TGFβ1-driven myofibroblast differentiation and HA levels by ELISA, RT-qPCR and immunofluorescence. CHIP-Seq determined binding of HYAL2 to HAS2-AS1 and HAS2 promoters. Alterations in HAS2-AS1 expression were assessed from acute to chronic kidney injury and in fibrosis prevention using kidneys from a rat-model of lethal loop diuretic-induced acute renal failure (IRI) or from rats that underwent ischemic preconditioning prior to IRI (prevention model).

Results: In fibroblasts, TGFβ1 increased HAS2-AS1 expression concomitantly with HAS2. HAS2-AS1 knockdown resulted in significant attenuation of HAS2 expression demonstrating that HAS2-AS1 is a positive regulator of HAS2. HAS2-AS1 knockdown led to a decrease in soluble and cell-surface HA, attenuated TGFβ1-driven expression of pro-fibrotic markers, and modified expression of the principal HA receptor, CD44 and its variant isoforms suggesting a link between HAS2-AS1 and CD44 alternative splicing related to renal fibrosis. HAS2-AS1 knockdown decreased plasma creatinine in rats sacrificed before and after IRI. Kidneys with progressive fibrosis had significantly increased HAS2-AS1 expression versus kidneys that were protected from fibrosis through IPC, suggesting an in vivo role for HAS2-AS1 in modulation of pro-fibrotic renal responses.

Conclusions: HAS2-AS1 is a novel lncRNA causally-linked with pro-fibrotic responses both in vitro and in vivo and a new potential therapeutic target for intervention in fibrosis.

PO2513
Renoprotective Effects of Soluble Guanylate Cyclase (sGC) Activation vs. ACE Inhibition in a CKD Model with Volume/Salt-Dependent Hypertension
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Background: BP control using renin-angiotensin systen (RAS) blockade is the current standard of care for CKD. However, outcomes remain suboptimal in part because adequate BP reductions are difficult to achieve in the volume expanded CKD states with RAS blockade even with additional antihypertensives. Given that endothelial dysfunction and/or NO loss accelerate the progression of both diabetic and non-diabetic CKD, sGC activators represent potential novel therapeutic interventions in CKD.

Methods: Two weeks after 3/4 nephrectomy and instrumentation for chronic BP radiotelemetry, male Sprague-Dawley rats were switched to a 4% NaCl diet after 1 week of normal saline. The rats started receiving vehicle only (5 ml/kg), the ACE inhibitor, enalapril (50 mg/kg), the sGC activator (BR-11257) (10 mg/kg), or the combination of BR11257 + enalapril by daily gavage. After 6 weeks of therapy and final proteinuria measurements, the rats were sacrificed for a blinded histologic assessment of % glomerular fibrosis (GS).

Results: In this CKD model with volume (salt) dependent hypertension (HTN), BR-11257 alone or in combination with enalapril but not enalapril alone, significantly lowered BP, ameliorated proteinuria and reduced the development of GS (Table). Linear regression analysis showed a strong correlation between individual systolic BP (SBP) and % GS (r=0.69, n=63, p < 0.0001), without a significant difference in the slope of the relationship (0.3 ± 0.04) between treatment groups.

Conclusions: These data strongly support the therapeutic potential of sGC activators alone or in combination with RAS blockers in hypertensive and proteinuric CKD states.

Funding: Commercial Support - Bayer AG.
PO2514

Oxysterol-Binding Protein Like 7 in CKD

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Background: ATP-binding cassette transporter A1 (ABC1A)-mediated, cholesterol ester-induced podocyte injury plays a major role in the progression of glomerular disease and pharmacological inducers of ABC1A (ABC1A-blockers) are sufficient to partially rescue glomerular injury in proteinuric mice. Interestingly, these ABC1A’s compete specifically with oxysterol binding to a novel oxysterol-binding protein (OSBP) like 7 (OSBPL7), a member of a group of lipid-binding proteins involved in lipid transport between intracellular membranous. OSBPs are implicated in cholesterol transfer from the endoplasmic reticulum (ER) to the Golgi, in cholesterol efflux, and in the regulation of ABC1A expression. However, if OSBPL7 is expressed in the kidney and if it is important in the preservation of ER function has not been explored.

Methods: In this study, we utilized podocytes and tissues obtained from wildtype and Col4a3+/− mice, an experimental model of CKD. siOSBPL7 Podocytes and HEK293 cell lines were established using siRNA yielding cells deficient in OSBPL7. HEK cells do not express ABC1A making them a valuable tool to study the ABC1A independent effects of OSBPL7. OSBPL7 levels were determined from kidney cortex and isolated podocytes from WT and Col4a3+/− mice by western blot, immunohistochemistry, and RT-PCR. siOSBPL7 podocytes and HEK cells were analyzed for changes in ER stress markers, reactive oxygen species (ROS), cytotoxicity, and apoptosis.

Results: OSBPL7 is expressed in podocytes isolated from wildtype and Col4a3+/− mice, an experimental mouse model of chronic kidney disease. Western blot analysis revealed that OSBPL7 protein levels are reduced in kidney cortex of Col4a3+/− mice. siRNA knockdown of OSBPL7 in HEK293 cells showed increased levels of ER stress, ROS, cytotoxicity, and apoptosis. Overexpression of OSBPL7 in Col4a3+/− podocytes lead to a reduction in apoptosis levels further indicating a beneficial role of OSBPL7 in podocytes.

Conclusions: This study represents the first time that OSBPL7 has been implicated in CKD. OSBPL7 deficiency in podocytes leads to ER stress and ultimately apoptosis suggesting that OSBPL7 levels are beneficial to podocyte function. Future studies will address the role of OSBPL7 in podocyte lipid trafficking in chronic kidney disease that may lead to the identification of novel therapeutic targets for the treatment of this prevalent and costly disease.

Funding: NIDDK Support

PO2515

Determinants of Serum Phosphate Concentration in CKD

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Background: The serum phosphate concentration (SP) is the sum of rates of P excretion and reabsorption per volume of filtrate (EP/Cr) and TRP/Cr. EP/Cr is calculated as UPxScr/Ucr (U-urine, S-serum, P-phosphorus, cr-creatinine). In a steady state, EP/Cr rises as P intake rises or Ccr falls. TRP/Cr, calculated as SP – EP/Cr, is hormonally regulated. We aimed to analyze the evolution of SP and its determinants over CKD stages G1-G5 (dialysis excluded).

Methods: This was a retrospective study involving 200 US veterans followed in the nephrology clinic of the Army VAMC from 1/2000 to 4/2021. CKD stages were based on 4-variable MDRD eGFR. There were 293 simultaneous random measurements of SP, UP, Scr, Ucr, PTH, and eGFR. Means of these parameters were plotted against CKD stage. Correlations among variables were determined by linear regression models.

Results: The mean age (SD) of the cohort was 73 (10) years. 96% were male, and 48% had diabetes. In comparison to stages G1-2, EP/Cr rose and TRP/Cr fell significantly starting at stage G3b (Figure). EP/Cr correlated with eGFR (R² = 0.28, p < 0.001), but TRP/Cr and SP did not. SP correlated with EP/Cr (R²=0.24, p<0.001) and TRP/Cr (R²=0.36, p<0.001). PTH correlated with EP/Cr (R²=0.32, p<0.001), and TRP/Cr correlated with [PTH] (R²=0.10, p<0.001).

Conclusions: EP/Cr rises consistently as eGFR falls. At stage G3b, the decrement in TRP/Cr equals the increment in EP/Cr, and SP remains stable. In stages G4 and G5, the rise in EP/Cr is greater than the fall in TRP/Cr, and SP ascends accordingly. As eGFR declines, PTH rises, but its apparent effect on TRP/Cr is blunted. As CKD progresses, maintenance of stable SP depends primarily on reduction of intestinal P absorption.

Funding: Veterans Affairs Support
with low oxalate diet and calcium supplements a 24-hour urine collection showed improvement of oxaluria to 62 mg/day. Her renal function remains stable.

**Discussion:** Patients who undergo malabsorptive weight loss surgery are at risk for AKI, CKD and nephrolithiasis from hyperoxaluria. Kidney damage can continue years after the surgical procedure. Treatment involves low oxalate diet and aggressive oxalate binding with use of calcium supplements. Bariatric surgery reversal is the definitive treatment if conservative management fails. Bariatric patients should be referred promptly to a nephrologist if change in renal function is noted.

**PO2518**

**Increasing Acid Retention with Progressive GFR Decline Is Associated with Decreasing Urine Ammonium Excretion**

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**Background:** Our laboratory showed that acid (H+) retention without metabolic acidosis increased as eGFR declined while plasma total CO2 (PTC02) remained within normal range (AP 314, 1998-2018) but the mechanisms for this potential acceleration of GFR decline were not explored. We now examine if changes in urine net acid excretion (UNAE) or its components associated with changes in H+ retention in longitudinally followed patients with CKD 2 (eGFR 60-89 ml/min/1.73 m2) without metabolic acidosis.

**Methods:** One hundred twenty macroalbuminuric, non-diabetic patients with CKD 2 (eGFR=75±6.1 ml/min/1.73 m2), 40 treated with 0.5 mEq/kg bw NaHCO3, 40 with 0.5 mEq/kg bw NaCl, and 40 with usual care (UC) were evaluated annually for 5 years. We assessed H+ retention by comparing observed to expected increase in plasma [HCO3-] in response to retained HCO3- (expected retention) 2 hours after (dose-urine excretion) 2 hours after an oral load of NaHCO3 bolus (0.5 mEq/kg bw), assuming 50% body weight HCO3 space of distribution. Specifically, H+ retention = (retained HCO3- × 0.5 × body weight) – observed increase in plasma [HCO3-] (× 0.5 × body weight). We measured 8-hour urine NAE as the sum of ammonium (8h UNH-V), titratable acidity (8h UTAV) and bicarbonate (UHICO V).

**Results:** While acid retention in our study was not different for any group and was not different among groups at baseline or at 5 years. Nevertheless, longitudinal change in 8h UNH-V was inversely associated with change in H+ retention for UC (p=0.01, R2=0.82), NaCl (p=0.01, R2=0.71), and NaHCO3 (p=0.01, R2=0.20). Combining all three groups, the change in 8h UNH-V was also inversely associated with the change in H+ retention (p=0.01, R2=0.48) but the longitudinal change in 8h UTAH-V was directly associated with change in H+ retention (p=0.01, R2=0.19).

**Conclusions:** These longitudinal data support that less ability to maintain UNH-V as eGFR declines contributes to worsening H+ retention, despite maintenance of overall UNAE. Further studies are needed to determine reasons for individual variability in UNH-V with progressive eGFR decline and the apparent greater importance of UNH-V than greater UTAH-V in avoiding increasing H+ retention.

**Funding:** Private Foundation Support

**PO2519**

**Kidney Function and Renin-Angiotensin-Aldosterone System in Hypouricemia**

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**Background:** Uric acid (UA), the end product of human purine catabolism, is produced using xanthine dehydrogenase (XDH) and xanthine oxidase enzymes. Both enzymes are encoded by the XDH gene. Disruption of UA homeostasis has been implicated in chronic kidney disease for many years. However, the mechanisms behind the correlation remain unclear. Increased level of UA (hyperuricemia) has been shown to activate the intrarenal Renin-Angiotensin-Aldosterone system (RAAS) in many studies.

**RAAS in the decreased levels of UA (hypouricemia) has not been studied adequately.**

**Methods:** We have created a new rat model with genetic ablation of the Xdh gene in the Dahl salt-sensitive rat background (SS+/+) to study hypouricemia. RAAS components were quantified using liquid chromatography-tandem mass spectrometry. Rats were kept on a standard diet, and their plasma, urine, and kidneys were collected when they were 8 weeks old. Mean arterial blood pressure (MAP) was measured by using radio telemetry. Results: The rat model is hypouricemic (UA in plasma 0.25±0.03 mg/dl & not detectable for SS-/- & SS+/+ respectively). Histology of SS-/- kidneys shows severe damage. The SS-/- rats show renal function decline with different parameters. They demonstrate significantly higher diuresis (2.7±0.9 & 14.4±5.1 ml; N=9 & 8 for SS-/- & SS+/+), lower creatinine clearance (0.51±0.19 & 0.12±0.04 ml/min; N=7 & for both SS-/- & SS+/+) and Na retention (136±1.8 & 150±3.7 mmol; N=10 & 9 for SS-/- & SS+/+). The SS-/- rats have significantly lower levels of Angiotensin II and Renin and an increased level of Aldosterone compared to SS+/+ rats (Table 1). The 10-week-old SS-/- compared to SS+/+ rats did not have a difference in MAP on the standard diet. When they were challenged with a 4% NaCl diet, they failed to survive.

**Conclusions:** These results show that the Xdh enzyme is crucial for kidney function and lack of the enzyme can lead to electrolyte imbalance and changes in RAAS.

**Funding:** Other NIH Support - NHHLBI R35 HL133749

**Table 1: RAAS in plasma**

**PO2520**

**Angiotensin II Type 2 Receptor Agonist C21 Acutely Prevents the Loss of Megalin in the Kidney Cortex and the Onset of Proteinuria in Obese Zucker Rats Fed with High-Sodium Diet**

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**Background:** The appearance of protein in the urine (i.e. proteinuria) is a function of the glomerular filtration rate of protein and the reabsorption of protein from the post-glomerular filtrate by the endocytic receptors, megalin and cubulin, localized in the renal proximal tubules. We have shown that treatment with the angiotensin-II type 2 receptor (AT2R) agonist C21 for 2 weeks reduces proteinuria in obese Zucker rats (OZR) fed HSD. The consumption of sodium-rich diet (HSD) can acutely precipitate proteinuria which is a risk factor and indicator of kidney injury. Therefore, the objective of this study was to identify the acute and chronic mechanism that may have been involved in proteinuria upon consumption of HSD and to identify the anti-proteinuric mechanism upon AT2R activation in obesity.

**Methods:** Male OZR were treated acutely (2 days) or chronically (14 days) without or with AT2R agonist C21 (1mg/kg/day) while fed with normal salt diet (NSD 0.4%) or HSD (4%).

**Results:** The effects of HSD feeding on the expression of endocytic receptor megalin was biphasic. The HSD feeding for 2 days decreased, but for 14 days, increased megalin expression (p=0.05 vs. OZR). However, at 2- and 14-days, HSD feeding caused significant proteinuria (p=0.05 vs. OZR). The expression of cubulin remain unaffected.

The AT2R agonist treatment significantly prevented the HSD-associated changes in the expression of megalin at 2-days and 14-days, and prevented the onset of proteinuria. The expression of glomerular proteins, nephrin and podocin, which are part of the renal filtration apparatus, in the kidney cortex remains unaffected at 2-days, which suggest that glomerular filtration of protein due to the loss of these glomerular proteins, per se, is not affected by HSD intake and that altered tubular reabsorption is involved in the initiation of proteinuria.

**Conclusions:** Collectively, these data suggest that AT2R activation protects against HSD induced proteinuria in obese rats by preventing the early loss of endocytic receptor megalin.

**Funding:** NIDDK Support

**PO2521**

**Revealing the Antifibrotic Mechanism of Finerenone in the DOCA-Salt Nephropathy Rat Model Using Single Nuclei and Bulk Transcriptomics**

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**Background:** Finnenone is a nonsteroidal mineralocorticoid receptor antagonist (MRA) that has been proposed to possess pronounced antifibrotic efficacy with a reduced risk to develop hyperkalemia in comparison to steroidal MRAs. However, the exact mechanism of this investigational medication has not been revealed. Single nuclei RNA-sequencing by determining the transcriptional signature at single cell level is an emerging method for elucidating the molecular mechanism of drug action.

**Methods:** Uninephrectomized, Sprague-Dawley rats were treated with DOCA and salt with an equivalent antihypertensive dose of finerenone (10mg/kg/d), spironolactone (50mg/kg/d), or vehicle. Kidney interstitial fibrosis was considered as outcome. Single nuclei RNA-seq using 10X Genomics Chromium platform in 11 and bulk RNA-seq in 14 specimens were generated.

**Results:** Interstitial fibrosis was significantly lower in the finerenone group than rats who received DOCA or spironolactone. Unbiased clustering was performed on 85’561 nuclei. All kidney cell types were represented in the final dataset. Comparison of cell type fractions in each group demonstrated that injured and proliferative proximal tubule (PT) cells as well as principal cells of the collecting duct and immune cells were significantly different. Single nuclei RNA-sequencing by determining the transcriptional signature at single cell level is an emerging method for elucidating the molecular mechanism of drug action.

**Trajectory analysis on the PT cells indicates that PT cells in DOCA and spironolactone treated rats are more susceptible to the injury and transforming to injured PT cells.** The results of bulk RNA-seq analysis is consistent with single nucleus transcriptomics indicating the normalization of the genes enriched in metabolic processes and immune responses by finerenone.

**Conclusions:** Overall, our results demonstrate that treatment with finerenone protects the kidney from interstitial fibrosis. Using single nuclei and bulk transcriptomics revealed that the protection of the PT cells via normalizing the expression of genes which are enriched in metabolic processes and immune response could be a putative further protective mechanism of finerenone in renal diseases.
PUB001
Regional Citrate and Systemic Heparin Are Adequate to Maintain Filter Half-Life for COVID-19 Patients on CRRT
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Background: The aim of our study is to compare clotting of CRRT filters in patients with COVID-19-associated AKI vs. septic shock-associated AKI.

Methods: Retrospective single center study of adult patients with COVID-19 infection compared to those with septic shock admitted to the ICU at a tertiary university hospital April-October 2020. We used independent t-test and chi square test to determine statistical significance of CRRT filter clotting and related factors in COVID-19 patients compared with septic shock patients in the ICU. Time to event data was analyzed with Kaplan-Meier curves. Analyses were performed on Microsoft Excel and MedCalc.

Results: A total of 27 ICU patients with AKI requiring CRRT were included in the study, 13 with COVID-19 infection and 14 with septic shock. The mean half-life of CRRT hemofilter was similar in COVID-19 patients compared to non-COVID-19 patients (27.4 hours vs 27.5 hours, p=0.79). The number of CRRT hemofilter changes per day were also similar in both groups (0.6 filter changes per day, p=0.84) (fig. 1). However, significantly more patients with COVID-19 were on systemic heparin compared to the non-COVID-19 patients (69% vs 13%, p=0.02) (fig. 2).

Conclusions: We found that COVID-19 patients with AKI requiring CRRT had similar CRRT hemofilter half-life compared with sepsis-associated AKI patients with use of regional citrate anticoagulation and systemic heparin use. Further studies are needed to find which methods of anticoagulation is optimal in patients with COVID-19 infection with AKI requiring CRRT.

Figure 1. Details about CRRT in COVID-19 and non-COVID-19 patients with AKI

Figure 2. Demographic and clinical data for COVID-19 and non-COVID-19 patients with AKI on CRRT

PUB003
Kidney Disease in the Aftermath of COVID-19 Infection
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Introduction: COVID-19-associated nephropathy (COVAN) is a known, but potentially missed cause of AKI. We present a case of COVAN presenting with a severe AKI in a previously healthy patient.

Case Description: A 48-year-old African American male with no known past medical history and a recent COVID-19 infection presented with hypertension and lower extremity edema. Initial work-up showed BUN 60, Cr 4.8. Urinalysis was significant for proteinuria. Urine protein to Cr ratio was 1.4. Renal ultrasound did not show any hydronephrosis. Initial management included blood pressure control and intravenous hydration, and his Cr downtrended to 3.1. Of note, his Cr was 1.2 weeks prior to admission. Given his acute renal failure and significant proteinuria, a renal biopsy was obtained which showed collapsing FSGS consistent with COVAN.

Discussion: Glomerular disease is a known complication of COVID-19. The most distinct presentation is the collapsing FSGS seen in this case (Image 1). This has primarily been reported in patients of African descent, specifically those with high-risk APO1 genotypes. Patients may recover kidney function, but some may also develop CKD. One reason for the hospitalization in this patient’s Cr was 4.3 and we suspect he will likely have significant CKD. COVAN can be a difficult diagnosis to make. Proteinuria can often be attributed to common co-morbidities, therefore confounding its diagnosis. The timing also complicates the diagnosis, as in our patient who presented a week after his COVID-19 symptoms resolved. With COVID-19 vaccines, perhaps COVAN may become more common, but the prevalence and incidence in the era of vaccines must be studied. The long-term repercussions of COVAN are unknown; COVAN should be considered in patients with recent COVID-19 infection presenting with proteinuria. We should make people aware of the possible renal consequences of COVID-19 and sharing this knowledge may help with vaccine hesitance.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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**PUB004**

Treatment Outcome of New-Onset Collapsing Focal Segmental Glomerulosclerosis in a Patient with COVID-19

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**Introduction:** COVID-19 has been shown to cause acute kidney injury (AKI) in as high as 46% of hospitalized patients. This case describes a patient who developed an AKI during her admission for COVID-19 pneumonia and was found to have collapsing focal segmental glomerulosclerosis (FSGS). Several cases of FSGS associated with COVID-19 have been described in the literature with varying outcomes. Unfortunately, the patient described in this case has not had significant recovery despite months of high-dose prednisone.

**Case Description:** A 57-year-old African-American female with a history of diabetes mellitus type 2, hypertension, and small cell lung cancer was admitted for intractable vomiting and found to be positive for COVID-19. Despite no history of kidney disease, patient developed an AKI over the first few days of hospitalization with creatinine 1.96mg/dL. (with no creatinine rise on admission). This case analysis, performed five months after admission, revealed onset high urine protein/creatinine ratio greater than 12 g/g. Renal biopsy demonstrated collapse of the glomerular tufts and associated hypertrophic podocytes, consistent with collapsing FSGS. No significant immunofluorescence staining was seen. Other serologies were negative, including HIV. Following discharge, she was started on prednisone 60mg daily. Despite several months of prednisone, patient’s creatinine remained elevated, mostly in the range of 2.5-3.5mg/dL, never returning to baseline. She continued to have nephrotic range proteinuria and no response to prednisone therapy was noted.

**Discussion:** As COVID-19 is a new and rapidly evolving disease, extrapulmonary disease is being newly identified, necessitating development of effective treatment strategies. Many of the cases that described collapsing FSGS in COVID-19 patients required initiation of dialysis. The patient in this case recovered from the respiratory symptoms of COVID-19, but continued to have impaired renal function despite several months of treatment. This case demonstrates prednisone failure for our patient, and further study is needed to determine more effective treatment regimens.

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**PUB005**

Incidence and Prognosis of COVID-19 in People with CKD

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**Background:** Coronavirus-disease-2019 (COVID-19) disproportionately affects people with chronic diseases such as chronic kidney disease (CKD). We assessed the incidence and outcomes of COVID19 in people with CKD.

**Methods:** We searched MEDLINE, EMBASE and PubMed through February 2021 for cohort and case-control studies measuring the incidence or outcomes of COVID19 in people with CKD. We extracted data on COVID19 incidence, death, respiratory failure, dyspnoea, COVID19 recovery, intensive care admission, acute dialysis, and acute kidney injury. Certainty evidence was adjudicated using GRADE.

**Results:** We included 348 studies (382407 participants with COVID19, 1139979 people with CKD). In low-certainty evidence, the incidence of COVID19 was higher in people with dialysis-dependent CKD (105/10000-person-weeks [pw]; 95% confidence interval [CI] 91-120; 95% prediction interval [PrI] 23.9-23.9; 59 studies; 46233 participants) than pre-dialysis CKD (16/10000-pw; CI 4-33; PrI 0-92; 5 studies; 70683 participants).

**Conclusions:** The incidence of COVID19 may be higher in people with dialysis-dependent CKD compared to pre-dialysis CKD or CKRs. People with CKD and COVID19 may have a higher incidence of death than those without COVID19.

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**PUB006**

Safety and Efficacy of Bedside Insertion of Tunneled Hemodialysis Catheters in Critically Ill Patients with COVID-19

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**Background:** Critically ill patients with coronavirus disease-2019 (COVID-19) and kidney dysfunction often require tunnelled hemodialysis catheter (TDC) placement for kidney replacement therapy (KRT), typically under fluoroscopic guidance to minimize catheter-related complications. This entails transportation of patients outside the intensive care unit (ICU) to a fluoroscopy suite, which may potentially expose both healthcare providers to COVID-19. One potential strategy to mitigate the risk of viral transmission is to insert TDCs at the bedside, using ultrasound (US) and anatomic landmarks only, without fluoroscopic guidance.

**Methods:** We reviewed all COVID-19 patients in the ICU who underwent right internal jugular (RIJ) TDC insertion at the bedside utilizing anatomic landmarks under US guidance between April-December 2020. Outcomes included procedural complications such as bleeding, arterial puncture, venous air embolism, arrhythmias, pneumothorax, hemotherox and catheter tip malposition. TDC insertion was considered successful if the catheter was able to achieve blood flow sufficient to perform a single hemodialysis treatment.

**Results:** We collected data on 25 patients with COVID-19 who had RIJ TDCs placed at the bedside, 10 of whom underwent simultaneous insertion of small-bore (5 Fr) RIJ tunnelled central venous catheters (T-CVC). The median age and body mass index of the cohort were 62 years (interquartile range [IQR]:55-70) and 28.8 kg/m² (IQR:25.2-33.2) respectively; comorbid conditions included chronic kidney disease (n=14), diabetes mellitus (n=12) and hypertension (n=18). Continuous veno-venous hemodialysis was the KRT modality employed in all patients. A median catheter blood flow rate of 200 ml/min (IQR:200-200) was achieved in all patients without any deviation from the dialysis prescription. No catheter related complications were observed and none of the catheter tips were mal-positioned on post-insertion chest radiographs.

**Conclusions:** Bedside RIJ TDC placement in COVID-19 patients, using US and anatomic landmarks without fluoroscopic guidance, may potentially reduce the risk of COVID-19 transmission amongst health care workers without compromising patient safety or catheter function. Continuous dialysis via bedside TDC insertion may also be safely accomplished and further help limit personnel exposure to COVID-19.

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**PUB007**

Irreversible Damage from a Pandemic Outbreak: A Rarely Described Case Report

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**Introduction:** Renal cortical necrosis (RCN) is a rare cause of acute kidney injury (AKI) in developed countries with frequency of 1.9%-2% of all patients with AKI. Drugs especially non-steroidal anti-inflammatory drugs (NSAID’s) are very rarely described to cause cortical necrosis. It happens due to permanent occlusion of afferent arteriole and interlobular arteries in the cortical vasculature, either by prolonged vasospasm or primary vascular damage with thrombosis.

**Case Description:** We present the case of a 20-year-old black man who was admitted to the hospital due to abdominal pain and decreased urine output. He had been symptomatic with severe toothache due to a dental abscess. Since it happened during the pandemic outbreak of COVID-19 he was unable to contact any dentist and he was given regular oral paracetamol and ibuprofen in doses he could not quantify (ibuprofen exceeded 600 mg per day every 8 hours daily in a week). Initial laboratory tests revealed anemia (Hb 11 g/dL), slight increase in inflammatory parameters and acute renal failure (sCreatinine 12.7 mg/dL, sUrea 109 mg/dL) and a urine protein-to-creatinine ratio of 1.8 g/g. Renal ultrasound excluded obstruction. Viral serologies were negative, clonal gammonorphs were excluded, autoimmune study and serum complement levels were normal. Blood and urinary cultures were also negative. He underwent tooth extraction and completed 10 days of amoxicillin-clavulenate and metronidazole with resolution of...
infection. Despite proper fluid replacement the patient showed no clinical improvement and presented with anuria, so hemodialysis was started. Abdominal and pelvic CT scan showed no positive findings. A renal biopsy was obtained showing extensive cortical necrosis. At that moment we concluded renal cortical necrosis probably secondary to NSAIDs intoxication. Unfortunately, the patient did not recover and became dependent on renal replacement therapy.

Discussion: This case illustrates the need to be aware of the effect of NSAIDs. Despite being readily available, a subset of individual is susceptible to serious renal toxicity and caution should be exercised when these drugs are used. Our patient presented with bilateral renal cortical necrosis with irreversible renal failure secondary to prolonged use of over-the-counter NSAIDs in the setting of pandemic outbreak of COVID-19.

PUB008

Challenges in Conducting a Clinical Trial During the COVID-19 Pandemic

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Background: The COVID-19 pandemic has caused a global upheaval in daily life, economics, clinical care, and research. We report challenges faced and addressed based on our experiences conducting an NIH-funded randomized controlled clinical trial during the pandemic.

Methods: Combination of Novel Therapies for CKD Comorbid Depression (CONCORD) is an ongoing multi-center randomized trial comparing two novel 16-week treatment strategies for depression, vs. a placebo and attention control group, in 200 patients with stages 3b-5 non-dialysis CKD. One strategy is to deliver bupropion antidepressant drug for 8 weeks, with augmentation to combination bupropion and behavioral activation teletherapy (BAT) for an additional 8 weeks if depression did not remit. The second strategy is to deliver BAT for the first 8 weeks, with addition of bupropion for 8 more weeks for non-remitters.

Results: Since October 2020 to-date, 690 patients were screened at the University of Texas Southwestern, Dallas, and at the University of Washington, Seattle, of whom 151 (21%) met the screening cutoff for depression. Despite the ongoing pandemic, this percentage was similar to previously reported rates for CKD patients. Thirty-one (80%) of the 39 target to-date were randomized, and 22 (71%) have completed the trial. Only 2 exited before 16 weeks. The national shift away from in-person visits to telehealth slowed screening from outpatient clinics. A lower number of screening surveys were conducted due to unavailability of patients via telephone. Because CKD patients have a high burden of healthcare contact and barriers to accessing in-person care, CONCORD was designed prior to COVID-19 to use teletherapy instead of in-person visits to minimize burdens. Telehealth intervention delivery has been especially beneficial in minimizing in-person contact during the pandemic. Blinded assessments of primary outcome were also conducted by computer-assisted telephone interview. Thus, the protocol allowed minimization of in-person visits, which were further decreased from every 4 to every 8 weeks only for phlebotomy and drug dispensation.

Conclusions: Despite challenges posed by COVID-19, CONCORD successfully upped its near-target recruitment, due to perseverance of staff, use of teletherapy to minimize in-person visits, and patients’ willingness to participate.

PUB009

Mortality and Evolution Between Community and Hospital-Acquired COVID-AKI (CA-AKI and HA-AKI)

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Background: Differences between HA-AKI and CA-AKI are not well established.

Methods: Retrospective cohort. We included 877 patients hospitalized with COVID in two hospitals in Mexico. Primary outcome was all-cause mortality at 28 days compared between COVID with CA-AKI and HA-AKI. Secondary outcomes included the need for KRT, and risk factors associated with the development of CA-AKI and HA-AKI.

Results: A total 33.7% developed AKI. CA-AKI occurred in 59.9% and HA-AKI in 40.1%. Patients with CA-AKI had more comorbidities than those with HA-AKI. Patients’ survival with CA-AKI it was 75.4%, and with HA-AKI 69.6%. Age > 60 years (OR 1.12), COVID severity (OR 1.09), mechanical ventilator (OR 1.67), and HA-AKI 3 (OR 1.16) increase mortality. The presence of CKD (OR 1.48), serum lymphocytes < 1000 µL (OR 1.03), the need for mechanical ventilator (OR 1.06), and CA-AKI stage 3 (OR 1.37) were the only variables associated with a KRT start.

Conclusions: We found that COVID complicated by CA-AKI have more comorbidities and worse biochemical parameters than HA-AKI patients, but despite these differences, their probability of dying is similar.

PUB010

Predictors of Short- and Longer-Term Mortality After COVID-19 Presentation Among Dialysis Patients in the Americas

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Background: We aimed to build machine learning (ML) models to understand the predictors of short- and longer-term mortality among hemodialysis (HD) patients affected by COVID-19 in four countries in the Americas.

Methods: We used data from adult HD patients treated at regional institutions of a global provider in Latin (LATAM) & North America (NA) who had COVID-19. We used data on 96 variables from Jul-2019 through Dec-2020 to develop XGBoost models (60%-20% random split for training, validation, & testing) to predict the likelihood of death in 0-14, 15-30, >30 days after COVID-19 presentation, and identify importance of predictors. Models were developed in a side-by-side manner and used same programming for datasets in LATAM (Argentina, Columbia, Ecuador) & NA (United States) countries.
Results: Among HD patients with COVID-19 in LATAM (n=12,121) and NA (n=21,624), 15.8% and 7.3% died within 0-14 days, 8.2% and 4.6% died within 15-30 days, and 4.8% and 6.8% died >30 days after presentation, respectively. Models in LATAM & NA had area under (AUC) in testing datasets of 0.64 & 0.70 for death within 0-14 days; top predictors at presentation were diabetes, lower interdialytic weight gain, age, and lower dry weight in NA.

Conclusions: Profiles of mortality in HD patients after COVID-19 were distinct in LATAM & NA. Mortality more often occurred within 0-14 or 15-30 days after COVID-19 in LATAM versus NA. About 5% to 9% of COVID-19 patients died >30 days after presentation. Comorbidities, demographics, weight, and BP appear risk factors for death after presentation. Use of underexplored follow-up timeframes along with ML modeling techniques that account for collinearity and missingness provide novel insights related to mortality in COVID-19.

Funding: Commercial Support - Fresenius Medical Care

PUB011
SARS-CoV-2 Breakthrough Infection in a Fully Vaccinated Hemodialysis Patient
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Introduction: End-stage kidney disease (ESKD) is associated with immunosuppression manifesting as both increased infection rates & impaired vaccine immunoresponsiveness. Nonetheless, COVID-19 vaccines have proven highly effective in dialysis-dependent ESKD patients, with reported seroconversion rates as high as ~96%. Herein, we describe a case of breakthrough SARS-CoV-2 infection in a fully-vaccinated hemodialysis patient.

Case Description: A 69 year-old white male with dialysis-dependent ESKD presented for routine rural in-center hemodialysis with a new intermittent nonproductive cough following known COVID-19 exposure. He tested positive for COVID-19 via both rapid antigen testing & RT-PCR despite full mRNA-1273/Moderna SARS-CoV-2 vaccination ~2 mo prior, & was admitted for inpatient management pending availability of isolated outpatient dialysis. He was afebrile, normoxemic, & clinically stable at presentation & throughout his subsequent hospital course. Following 10 d of uneventful isolation, during which he received thrice-weekly hemodialysis but no COVID-19-specific therapies, he resumed maintenance outpatient dialysis. Of note, he was current on all recommended vaccinations for dialysis patients, but had required multiple courses of hepatitis B vaccination for a documented history of impaired seroconversion. The patient ultimately developed both anti-nucleocapsid IgM & anti-spike IgG antibodies directed against SARS-CoV-2, & viral genome sequencing revealed a novel SARS-CoV-2 variant of interest (B.1.526).

Discussion: While breakthrough COVID-19 is rare – reported in <0.001% of the fully vaccinated U.S. population as of 20 Apr 2021 – incidence rates may be higher in specific immunosuppressed subgroups such as ESKD patients. This case illustrates the potential for fully-vaccinated ESKD patients to contract COVID-19, particularly following known exposure(s) or in the setting of viral variants. It is also consistent with accumulating anecdotal clinical experience suggesting that breakthrough infections are generally milder phenotypically than primary infections in vaccine-naïve individuals. As such, high levels of suspicion may be required for identification & proper isolation. Constrained local resources in rural settings may also require different risk mitigation & management strategies for in-center hemodialysis patients with breakthrough COVID-19.

PUB012
Membranous Nephropathy in a Patient with Recent COVID-19 Infection
Weiven Guo, Shashidhar Baikunje. Songklang General Hospital, Singapore, Singapore.

Introduction: Membranous nephropathy (MN) associated with COVID-19 infection is rare and most reported cases are anti-phospholipase A2 receptor (PLA2R) negative. We report a case of PLA2R seropositive MN with COVID-19 infection.

Case Description: A 29-year-old Asian male presented with fever, myalgia and lower limb swelling for 3 days. 4 weeks prior, he was treated symptomatically for COVID-19 infection. He was diagnosed with acute kidney injury and nephrotic syndrome. Immune markers, virology and imaging of kidneys were normal.(Table 1) MN was diagnosed on renal biopsy (Figures A & B). PLA2R was negative in the glomeruli by immunofluorescence, but serum PLA2R antibodies was positive at 139RU/ml. Workup for other causes of secondary MN was unrevealing. Due to increasing COVID-19 infections at that time, immunosuppression was deferred. ACE inhibitor was titrated to the highest tolerated dose.

Discussion: Seropositive but biopsy-negative PLA2R associated MN is uncommon, and occurs rarely in patients with possible secondary MN. PLA2R positivity on renal biopsy has been reported in viral hepatitis and some cases had circulating serum PLA2R antibodies. To our knowledge, there are no reported cases of circulating PLA2R antibodies with COVID-19 infection. Our case illustrates the diagnostic and management challenges of MN in the era of widespread COVID-19 infection. Clinical course and PLA2R antibody titres remain useful guides for consideration of immunosuppressive treatment.
SARS-CoV-2 Antibody Dynamics in Chronic Hemodialysis Patients

Ohnmar Ohnmar, Jie Ouyang, Yasmin N. Mahmoud, Felicia Mckoy, Moro O. Salifu, Okwudili Nnaji, Angelica C. Gresser. SUNY Downstate Health Sciences University, New York, NY.

Background: Detrimental impact of COVID-19 on renal function unvaried over time. Nephrology community was in a dilemma whether transplantation should continue under such circumstances. We investigated which States within the US continued to perform kidney transplantation despite such odds.

Methods: Retrospective data from Organ Procurement and Transplantation Network (OPTN) regions for kidney transplant alone (KTA) performed across the US from 2019 to 2020, reflecting the peak of the first wave of COVID-19 pandemic were analyzed. To address whether the COVID-19 had an impact on transplanted kidneys, we analyzed graft survival at 3- and 6-months post-transplant during that era. We further investigated the statewide variation of KTA in both deceased donor (DD) transplants and living donor (LD) transplants.

Results: There was a 3.1% decrease in KTA from 2019 to 2020 (22,429 to 21,731). There was an overall trend of a decrease in number of transplants across all states with a peak decline in March-April 2019 era and rebound in May 2019 onwards. Statewide regional decline or variation of DD KTA was most significant in region 9 (NY, Vermont) while regions 4 (Oklahoma and Texas) continued to perform transplants unabated. In 2019, 30.6% of KTA were from LD while in 2020 the rate decreased to 24.1%. The transcription of DD increased from 15,562 to 16,497 in 2020. Overall, 3-month graft survival was significantly negatively impacted for DD KTA performed between February and May. The decrease in KTA in the southern regions was less compared to the northern-eastern regions.

Conclusions: The COVID-19 pandemic had a major impact on kidney transplantation with a significant reduction within all OPTN regions. While LD transplantation could presumably be rescheduled, DD organs must be procured immediately, or they are lost. Therefore, the number of DD transplants decreased initially between March and May but recovered afterwards. Transplanted kidneys during COVID-19 first wave pandemic era performed reasonably well but with an increase rate of injury and rejection.

Incidence and Risk Factors for SARS-CoV-2 Infection in Patients with Lupus Nephritis

Bogdan Obrisca, Alexandra Vornicu, George Dimofte, Valentin Mocanu, Bogdan M. Sorohan, Roxana A. Jurubita, Andreea G. Andronesi, Achim Camelia Adrian, Gener Ismail. Fundeni Clinical Institute, Bucharest, Romania.

Background: Patients with lupus nephritis (LN) are known to be at higher risk for severe infections due to both an underlying immune dysfunction and as a consequence of immunosuppressive therapy (IS). We sought to investigate the impact of COVID-19 pandemic in patients with LN.

Methods: A total of 95 patients with LN actively monitored in our department were included in the study. Demographics, comorbidities, clinical and laboratory characteristics, current IS therapy, COVID-19 symptoms and outcome were collected. A COVID-19 diagnosis was made if clinical symptoms were accompanied by a positive SARS-CoV-2 PCR.

Results: Fifteen patients (15.8%) were diagnosed with COVID-19 at a median 279 days (IQR:218-341) since the first case was diagnosed in Romania, and 1st May 2021 were included in the study. Demographics, comorbidities, clinical and laboratory characteristics, current IS therapy, COVID-19 symptoms and outcome were collected. A COVID-19 diagnosis was made if clinical symptoms were accompanied by a positive SARS-CoV-2 PCR.
symptoms were fatigue (73.5% of patients), followed by loss of taste and/or smell (53.3%) and fever (46.7%). Overall, 40% of patients were hospitalized for a median of 11.5 days (IQR:3.75-14). Of these, 2 patients needed supplemental oxygen and 1 patient non-invasive ventilation. There were no COVID-19-related deaths during the study period. Of the clinical variables associated with infection development, fewer patients with COVID-19 were on hydroxychloroquine (46.7% vs. 89%; p<0.04) or were on clinical remission during the study period (40% vs. 67.5%; p=0.04), while the median maintenance oral corticosteroid dose was significantly higher in those with SARS-CoV-2 infection compared to those without [16 mg (IQR:7.2-21) vs. 6 mg (IQR:4-10); p=0.007].

In multivariable Cox regression analysis, use of hydroxychloroquine (HR, 0.23; 95%CI, 0.04-1.26) and oral corticosteroid dose (HR, 1.11; 95%CI, 1.01-1.22) remained the most important predictors of COVID-19.

Conclusions: The burden of SARS-CoV-2 infection in patients with LN seems to be low. Use of hydroxychloroquine seems to be associated with a lower risk for COVID-19, while from different immunosuppressive agents corticosteroid dose was identified as an independent risk factor for infection development.

PUB017

Long-Term Mortality Risk of Hemodialysis Patients Surviving Initial COVID-19: A Report from the Quebec Renal Network COVID-19 Study

Methods: We included patients with SARS-CoV-2 PCR tests performed between March 1st 2020 and February 28th 2021 from 7 dialysis centers in Quebec. Patients alive at 30 days after SARS-CoV-2 diagnosis were matched by age, sex, center and PCR test date to patients negative for SARS-CoV-2 and followed for up to one year, starting at 30 days after initial infection (or negative test). We assessed mortality risk in unadjusted and adjusted multivariable Cox regressions.

Results: Ninety-eight patients with SARS-CoV-2 infection alive 30-day after diagnosis were matched to 166 SARS-CoV-2-negative patients. Baseline characteristics between dialysis patients who survived 30-day after a SARS-CoV-2 infection and dialysis patients negative to SARS-CoV-2 were similar between the two groups. Patients were followed for a median of 331 (301-347) days. Overall, 32 patients died during the study period (15 [15%] in the SARS-CoV-2-positive group and 17 [10%] in the SARS-CoV-2-negative group, p=0.22). There was no statistically significant association between mortality risk and previous SARS-CoV-2 infection (HR 1.5, 95% CI 0.8-3.1), even after adjustment for residual imbalance (aHR 1.4, 95% CI 0.7-3.1). Results remained similar after exclusion of 4 patients who died of infection (HR 1.5, 95% CI 0.8-3.1), even after adjustment for residual imbalance (aHR 1.5, 95% CI 0.8-3.1). Results remained similar after exclusion of 4 patients who died of infection (HR 1.5, 95% CI 0.8-3.1), even after adjustment for residual imbalance (aHR 1.5, 95% CI 0.8-3.1). Results remained similar after exclusion of 4 patients who died of infection (HR 1.5, 95% CI 0.8-3.1).

Conclusions: One-year survival of dialysis patients surviving SARS-CoV-2 infection was similar to those never infected.

Funding: Government Support - Non-U.S.

PUB019

Impact of COVID-19 on Hemodialysis Patients: The Quebec Renal Network (QRN) COVID-19 Study

Background: Hemodialysis patients had to face numerous challenges during the COVID-19 pandemic. They are at increased risk of severe complications of COVID-19 and continued to visit hospitals thrice weekly, increasing their risk of being infected. The objective of this study was to document the impact of the COVID-19 in patient’s experience in hemodialysis in Quebec.

Methods: Between November 2020 and May 2021, we conducted semi-structured interviews with 20 patients who were undergoing dialysis treatments in six hemodialysis units in Montreal. Interviews were transcribed and analyzed using thematic content analysis.

Results: Patients were satisfied by the measures implemented within their units in order to prevent COVID-19 outbreaks, such as making masks mandatory, restricting access to the dialysis ward, and even limiting the number of accompanying persons allowed. Participants reported that following the public health guidelines (social distancing, wearing a mask and washing hands) was easy and important in order to ensure their own and their family members’ safety. Because of this, participants were more likely to refuse to see their family resulting in feeling of isolation. This was particularly relevant for Indigenous patients who were having their hemodialysis treatment away from their home and family. This sub-group experienced particular issues due to the prolonged remoteness from their loved ones, change in their hemodialysis center and with the measures put in place by the hotel they were residing at. Even though their usual routine outside of dialysis might have changed due to the pandemic, hemodialysis treatments allowed patients to keep a certain normality in their lives. Positive consequences were mentioned such as frequent contact through telemedicine and the existing solidarity between patients during the pandemic.

Conclusions: Patients undergoing hemodialysis faced particular challenges due to the COVID-19 pandemic. Nonetheless, they showed great resilience in their capacity to adapt to the new reality of their hemodialysis treatments.

Funding: Government Support - Non-U.S.
AKI-D in Ventilated Critical Patients with COVID-19

Background: Acute Kidney Injury (AKI) is a frequent complication in critical patients with Coronavirus Disease 2019 (COVID-19) and has been associated with a poor prognosis, especially when it is necessary to implement renal replacement therapy (KTR). The mortality reported in COVID-19 patients with AKI and KTR (AKI-D) is variable according to studies published today.

Methods: In this retrospective cohort study, we analyzed the clinical characteristics, comorbidity and prognosis of 87 COVID-19 patients, older than 18 years, ventilated and AKI-D between March 2020 and February 2021. We divided our patients into two groups: Group 1: Patients who start KTR in the period of time between the onset of COVID-19 symptoms and day 21. Group 2: Patients who initiate KTR after day 21 of the onset of COVID-19 symptoms. The Charlson Comorbidity Index and SOFA Score were calculated on the day of admission to hemodialysis.

Results: Our cohort of 87 patients had a mortality 95%, Group 1: 98%, Group 2: 82%. We found no significant differences in age, SOFA before KTR, Charlson score, AKI at admission and survival after the start of KTR between the two groups. Of the total patients, 10 recovered kidney function; four patients were discharged from hospital without KTR (1 from group 1 and 3 from group 2), the other six died during hospitalization. 29 patients (33,3%) died within 48 hours of starting dialysis, with a median pre-KTR SOFA: 15 (IQR: 13–16).

Conclusions: In this study, a high mortality is reported, particularly in ventilated patients with the need for KTR in the first 21 days from the onset of COVID-19 symptoms (Group 1). We observed an excess of mortality compared to Group 2. We assume that it may be due to the severity of the underlying viral condition during the initial days of infection, a matter that would become less relevant as time goes by.

Cardiac Troponin and AKI in COVID-19 Sepsis-Related Patients
Beatriz V. Woffort, Marcelo R. Bacci. Faculdade de Medicina do ABC, Santo Andre, Brazil.

Background: The COVID-19 pandemic became the major reason of hospitalization of patients in ICU worldwide. AKI is a major disease and continue closely related with sepsis and COVID-19 infection. Cardiac injury is frequent in patients with septic shock and higher levels of cardiac troponin are expected in AKI patients however whether this is related with a poor outcome in the pandemic scenario still remain unknown. The objective of the study was evaluate the impact of the occurrence of AKI and cardiac troponin levels in patients with severe SARS-CoV-2 infection and their major outcomes.

Methods: We conducted an observational study during COVID-19 pandemic in 2020 first wave outbreak in Brazil. The research was approved by IRB and patients of a Sao Paulo major public hospital. The main inclusion criteria were the occurrence of COVID-19 infection confirmed by oropharyngeal swab in the last 3 days of admission and the need of permanence of at least 3 days. Patients with a poorer expectancy of survival in the next 24 hours of inclusion were not considered eligible. Blood sample at admission was used to confirm sepsis and AKI and the patients were followed daily until discharge of the unit or dead. AKI occurrence was seen as the rise of serum creatinine happened according KDIGO AKI guideline. Patients were divided in groups regarding the development of AKI and major outcome (mechanical ventilation or dead).

Results: A total of 86 patients with sepsis were included. Female patients represented 58.3% of the patients. About 96,51% of the patients had at admission a level of d-dimer above 500 ng and 77.91% of patients had a cardiac troponin 1 above 20 ng in AKI patients group with a p level of 0,003. About 44 patients had AKI due to COVID-19 sepsis and 28 patients by admission in the ICU Median serum creatinine at admission was 2.44 mg/dL (1.64-4.02). There was a higher proportion of patients in mechanical ventilation with development of AKI after admission (14) than those without AKI during the whole hospitalization (11) with a p of 0.299. The mortality of patients with higher cardiac troponin were significantly higher in AKI patients than the non AKI patients.

Conclusions: In patients with COVID-19 sepsis related disease, there is a positive correlation between AKI and higher levels of cardiac troponin and higher days with mechanical ventilation.

COVID-19 and Kidney Disease: A Follow-Up Study
Marta De Filippo, Marco Simonini, Lorenza Citterio, Simone Fontana, Teresa Arcidiacono, Paolo Betti, Elena Cinel, Rebecca De Lorenzo, Paolo Manunta, Patrizia Rovere Querini, Chiara Lanzani. IRCCS Ospedale San Raffaele, Milano, Italy.

Background: Immunization against COVID19 has become the cornerstone in prevention of Sars-CoV-2. Maintenance Hemodialysis (HD) patients are at higher risk of both exposure and mortality. This study aims to describe humoral immunogenicity and suggest risk factors for low or absent response to Pfizer BNT162b2 in an HD cohort.

Methods: Observational prospective study including a group of HD patients followed in a Portuguese Nephrology Center who received BNT162b2. Anti-Spike IgG measured as arbitrary units per milliliter (AU/mL) was obtained on two separate occasions, corresponding to the first and second doses’ humoral response. Absolute IgG value, rate of Non-Responders (NR), IgG<1AU/mL after each dose, and Weak-Responders (WR), under Percentile 25 after each dose, were evaluated for risk factors that included demographic and analytical variables.

Results: IgG anti-Spike levels showed a strong correlation with CCI and PTH after each inoculation (p=0.64; 0.66; p=0.56;0.65, respectively; p<0.01). Higher CCI and lower PTH was observed in NR subgroup after the 1st (p=0.01), whereas with the 2nd there was a lower albumin and PTH (p=0.01) and an association with female sex (p=0.01). Similarly, WR also showed higher CCI and lower PTH after the 1st (p=0.02) and 2nd doses (p=0.01), adding older age (p=0.03) and lower albumin (p=0.05) to the 2nd. After both inoculations, WR subgroup was associated with age over 75 yo (p=0.03); female sex (p=0.01), CCI over 8 (p=0.01), CVC over AVF/AVG (p=0.01), dialysis vintage under 24 mo (p=0.01) and PTH under 150 μg/l (p<0.01). A model combining CCI, sex (male) and vascular access (CVC) as a regression model associated those factors to WR after the 2nd dose with OR (95% CI): 1.81 (1.06-3.08); 0.05 (0.01-0.65); 13.55 (1.06-174.18), respectively (p=0.01).

Conclusions: Older age, high CCI, low PTH and albumin, CVC over AVF/AVG and recently started dialysis (less than 2 years) relate to lower response. High comorbidity burden is suggested as a more significant risk factor than age alone. The role of PTH as a marker of low immunogenicity in the HD population should be target of further investigation. Signalization of HD patients at risk of low response may play a key role in policy making, namely the necessity for booster doses, follow-up measurements and isolation methods.

COVID-19 and Kidney Disease: A Follow-Up Study
Marta De Filippo, Marco Simonini, Lorenza Citterio, Simone Fontana, Teresa Arcidiacono, Paolo Betti, Elena Cinel, Rebecca De Lorenzo, Paolo Manunta, Patrizia Rovere Querini, Chiara Lanzani. IRCCS Ospedale San Raffaele, Milano, Italy.

Background: It is well known that SARS-CoV-2 infection is associated with the development of acute kidney disease; however, not much is known about the long-term kidney effects of this pathology.

Methods: We analyzed kidney function data during hospitalization and subsequent follow-up (6 months) of 150 (of which 51 with CKD) patients hospitalized for COVID-19.

Results: 28% of subjects developed AKI during hospitalization; proteinuria and microhematuria were present in 53% and 45% respectively (p=0.01) whereas with the 2nd dose the prevalence was 17.08 ml/min vs 62.43 ml/min (p=0.004; figure 1). This result was confirmed even after exclusion from the analysis of those patients already being admitted (73.30±14.28 vs 66.17±16.99; p=0.004; figure 1).

Conclusions: Starting from these data, we can assume that COVID-19 patients, with intra-hospital AKI development, have an accelerated loss of renal function during follow-up. Further studies are needed to identify pathogenic mechanisms and the long-term evolution of kidney damage after Sars-Cov-2 infection.
COVID-19 and Kidney Transplantation in a Colombian population
Carlos F. Duran, Mayra A. Estacio, Daniela Espinosa, Fredy S. Lozano, Juan Posada, Liliana Mesa, Johanna Schweinberg, Fundacion Valle del Lili, Cali, Colombia.

Background: Patients with kidney transplants seem to be at particularly high risk for severe COVID-19 disease due to their impaired immune responses and comorbidities.

Methods: We performed an observational study of kidney transplant recipients with SARS-CoV2 infection admitted at Fundación Valle del Lili from June to December 2020. To be eligible for this study, patients have symptoms compatible, a positive RT-PCR and inpatient management. Asymptomatic patients were excluded.

Results: We enrolled a total of 50 patients. 64% were male, and the median age was 53.5 years (range 46-60). The comorbidities were: 36(70%) hypertension, 16(32%) diabetes mellitus, 5(10%) obesity. The most common immunosuppressive regimen was tacrolimus 76% and prednisone 88%. The median time from symptoms onset to the positive RT-PCR was 7 days. The most common initial symptom was fever (64%), and fatigue (44%) and dyspnea (36%). Baseline levels of CRP was 6.43 mg/dL (3.25-11.22). The median lymphocyte count was 785 mm3/uL (550-1230). Baseline D-Dimer was 0.767 ug/ml (0.484-1153.5), ferritin median level was 1011ng/ml (670-2145). Clinical outcomes are shown in Table 1. Six of the patients died (12%), 0/6 were by sepsis-related multi-organ failure and 2/6 were by ARDS.

Conclusions: Major complications such as acute kidney injury, acute respiratory distress syndrome and mortality related to COVID-19 infection observed in our study are lower than those reported in other countries.

Clinical outcomes of the hospitalized patients

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No (N%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deceased</td>
<td>12 (24)</td>
</tr>
<tr>
<td>Arrive</td>
<td>14 (28)</td>
</tr>
<tr>
<td>ICU admission</td>
<td>18 (36)</td>
</tr>
<tr>
<td>Intubation or mechanical ventilation</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Days of NIV, median (IQR)</td>
<td>12 (8, 27)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>13 (26)</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>12 (24)</td>
</tr>
<tr>
<td>Days of hospital stay, median (IQR)</td>
<td>11 (6-40)</td>
</tr>
<tr>
<td>Wilms tumor, immunosuppressive</td>
<td>28 (56)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Hydroxychloroquine</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Prednisone</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>19 (38)</td>
</tr>
<tr>
<td>Iloprost</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

PUB024

| Table 1: Univariate and Multivariate Analysis of Predictors of In-hospital Mortality Among Hospitalized Patients with COVID-19 and AKI

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate Analysis (Odds Ratio, 95% CI)</th>
<th>Multivariate Analysis (Odds Ratio, 95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.03 (1.01-1.05)</td>
<td>1.03 (1.01-1.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex Male</td>
<td>1.09 (0.95-1.25)</td>
<td>1.09 (0.95-1.25)</td>
<td>0.52</td>
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<td>Race White</td>
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<td>1.00 (0.99-1.02)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.00 (0.99-1.02)</td>
<td>1.00 (0.99-1.02)</td>
<td>1.00</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>1.00 (0.99-1.02)</td>
<td>1.00 (0.99-1.02)</td>
<td>1.00</td>
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<tr>
<td>Baseline CRP</td>
<td>1.00 (1.00-1.01)</td>
<td>1.00 (1.00-1.01)</td>
<td>0.49</td>
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<tr>
<td>Baseline D-Dimer</td>
<td>1.00 (1.00-1.01)</td>
<td>1.00 (1.00-1.01)</td>
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<tr>
<td>Baseline Ferritin</td>
<td>1.00 (1.00-1.01)</td>
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<tr>
<td>Baseline Albumin</td>
<td>1.00 (1.00-1.01)</td>
<td>1.00 (1.00-1.01)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Conclusions: Age, dialysis requirement, severity of AKI, and ICU admission are predictors of mortality among patients with COVID-19 and AKI at our institution.

PUB025

Predictors of In-Hospital Mortality Among Hospitalized Patients with COVID-19 and AKI: A Single-Center Study
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Background: AKI and COVID-19 infection are both independently associated with high mortality rates and those with COVID-19 who develop AKI have higher mortality rates. We investigated the predictors of mortality in patients admitted to our hospital with COVID-19 who developed AKI during their hospital stay.

Methods: We conducted a retrospective analysis of all patients hospitalized at University of Virginia Medical Center for COVID-19 infection who developed AKI from March 2020 through April 2021. In-hospital mortality was defined as death during admission or within 7 days of discharge to hospice. Data on patients’ demographics, comorbidities, AKI stage, dialysis requirement, admission to ICU, serum albumin, ferritin, d-dimer, fibrinogen, hemoglobin, as well as mortality at hospital discharge and 90 days were collected through chart review. Univariate analysis and a multivariate logistic regression model were used to identify factors associated with in-hospital mortality.

Results: 219 patients qualified for study inclusion criteria. The average age was 66.2 years and 56.6% of patients were men. The in-hospital mortality rate was 27.9%. An additional 1.37% died in the 90-day follow-up period. Age (p = 0.049), AKI-D (p < 0.001), AKI stage (p = 0.001), serum albumin (p < 0.001), and ICU admission (p < 0.001) were associated with mortality in the univariate analysis (Table 1). After adjustments for covariates, age (p < 0.001), AKI-D (p < 0.001), ICU admission (p < 0.001) were predictors of mortality in our multivariate analysis [AUC: 0.863, 95% CI (0.815-0.911)].

Conclusions: Age, dialysis requirement, severity of AKI, and ICU admission are predictors of mortality among patients with COVID-19 and AKI at our institution.
Impact of COVID-19 in Quebec Hemodialysis Units: Health Care Providers’ Experiences
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Background: Chronic kidney disease is a risk factor for the severe form of COVID-19 and the hemodialysis unit represents a high-risk setting for virus transmission. Healthcare providers (HCPs) have the duty to keep patients safe and healthy, and also to protect themselves from the virus. The objective of this study was to gather health care provider’s experiences working in hemodialysis units.

Methods: We conducted semi-directed interviews by phone or video with 21 HCPs working in 6 hemodialysis units - nurses, nephrologists, pharmacists, social workers, security agent and housekeeping attendant - between November 2020 and May 2021. The content of the interviews was analyzed using thematic content analysis.

Results: Participants identified positive and negative impact of COVID-19 pandemic. In their professional life, HCPs declared undergoing a more collaboration, creativity and mutual support. However, due to the pandemic restrictive measures and lack of resources, HCPs felt a lot of distress not being able to provide adequate care for patients’ needs. Participants also reported disruption in communication between HCPs and patients because of physical distancing and wearing a mask. They also described problems associated with patient transportation leading to delays or even absence of patients to their treatments. In their personal life, some HCPs declared being concerned by these new challenges at work and reported difficulties balancing work and family life. Also, most of them feared to contaminate their family and adopted certain routine cleaning to alleviate this fear.

Conclusions: HCPs working in hemodialysis units faced multiple challenges during the Covid-19 pandemic that impacted their wellbeing. However, they have shown high level of resilience and dedication to ensure health care delivery and to support hemodialysis patients.

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Renal Manifestations and Their Association with Mortality in COVID-19 Patients at a Safety-Net Hospital
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Background: Renal involvement in COVID-19 leads to severe disease and higher mortality. We study additional previously not studied renal parameters in COVID-19 patients and their association with mortality.

Methods: A retrospective study (n=340) of confirmed COVID-19 patients with renal involvement determined by the presence of acute kidney injury. Multivariable analyses of logistic regression for mortality and linear regression for length of stay (LOS) were calculated adjusted for relevant demographic, comorbidity, disease severity, and treatment covariates.

Results: Mortality was 54.4% and mean LOS was 12.9 days. For mortality, creatinine peak (OR:3.52, 95% CI:2.81, 4.42, P < 0.01) and persistent renal involvement at discharge (OR:4.47, 95% CI:1.99,10.06, P < 0.001) were each significantly associated with increased odds for mortality. Increased blood urea nitrogen peak (OR:0.98, 95%CI:0.97,0.996, P < 0.05) was significantly associated with decreased odds for mortality. For LOS, increased blood urea nitrogen peak (B0.001, SE < 0.001, P < 0.01), renal replacement therapy (B0.19, SE:0.06, P < 0.01), and increased days to acute kidney injury (B0.19, SE:0.05, P < 0.001) were each significantly associated with increased length of stay.

Conclusions: As persistent renal involvement at discharge is associated with increased odds for mortality, this suggests that early identification of renal involvement characteristics in COVID-19 patients is useful for treatment management. Clinicians should focus on renal parameters of blood urea nitrogen peak, renal replacement therapy, and days to acute kidney injury for predicting patient length of stay.

COVID-19 and Vitamin D in an Urban US Hemodialysis Population
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Background: Due to logistical constraints of in-center hemodialysis (HD) ESKD patients, we endeavored increased risk during the COVID-19 pandemic. Minorities are overrepresented in ESKD, making this group more susceptible to poor outcomes given existing racial disparities. Studies have emerged spotlighting vitamin D’s effects on autoimmune regulation of immune function and the relevance of extra-renal one alpha hydroxylase. Many studies describe links between vitamin D deficiency and severity of SARS-CoV-2 infection in high-risk patients, but there is a paucity of data specific to ESKD patients. This study explored the association between vitamin D status and COVID-19 infection in a primarily black HD population.

Methods: Emory Dialysis patients’ vitamin D levels [25(OH)D] were collected November 2020 as part of a quality improvement project. All SARS-CoV-2 positive HD patients were identified (October 2020 to April 2021). Retrospective chart review including baseline data and labs were collected. An unpaired t-test was used to compare vitamin D levels between COVID-19 positive and negative patients.

Results: 620 patients were included. All patients enrolled in-center HD three times per week. Patient identified race makeup included black (n=570) and non-black n= 50. Average age was 59 years. Gender: males (n=324) and females (n=296). 73 patients died in COVID-19 and 447 patients survived. As defined as black race. Average vitamin D levels for COVID-19 positive patients 27.33 and COVID-19 negative patients 26.2 (P = 0.55).
Average FTH in COVID-19 positive patients 507.3±371 and COVID-19 negative patients 557.57±371 (p=0.04). The mean level in COVID-19 positive patients 8.7±0.66 and COVID-19 negative patients 8.73±0.72 (p=0.48). Relative risk of developing COVID-19 in black HD patients was 1.14 compared to others (p=0.75).

**Conclusions:** Our study showed no statistically significant correlation between Vitamin D level and COVID-19 acquisition. The role of vitamin D deficiency as a risk factor and the role of Vitamin D supplementation for prevention or treatment COVID-19 in this population is unclear. Further studies investigating the relation between Vitamin D levels and severity of COVID-19 infection in this population should be explored.

**PUB034**

Impact of Different COVID-19 Vaccines on Platelet Count Changes in a Dialysis Cohort

**Methods:** We undertook a retrospective analysis of routine dialysis bloods, examining any significant changes in platelet count pre and post vaccine in our dialysis cohort, prior to offering 2nd doses. **Results:** For 780 hemodialysis patients with platelet count pre and post first dose COVID-19 vaccine were analysed. Of these, 471 patients received the Oxford/AZ vaccine, 145 received Pfizer, and the remainder were vaccinated elsewhere, therefore data on vaccine type not available. Mean platelet count for the whole cohort pre-vaccine was 215±10/L, and post was 218±10/L. 126 patients had a platelet count below 150±10/L pre-vaccine, and the number was the same post vaccination. No difference was observed based on vaccine type (see table).

**Conclusions:** No signal of vaccine-induced thrombocytopenia was detected in this cohort, though the numbers were small to detect such a rare event. The benefits of using these vaccines outweigh the small risk of vaccine-associated thrombocytopenia and thrombosis in this clinically extremely vulnerable cohort.

Results of platelet count changes pre and post COVID-19 vaccination by Vaccine type

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Pre-Vaccine</th>
<th>Post-Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxford/AZ</td>
<td>215±10/L</td>
<td>218±10/L</td>
</tr>
<tr>
<td>Pfizer</td>
<td>209±10/L</td>
<td>218±10/L</td>
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</tbody>
</table>

Platelet count values given as 10^9/L.
The Tale of Two Collapsing Glomerulopathies Associated with COVID-19 in Stamford Hospital
Mariana A. Chang, Revekka Babayev. Stamford Hospital, Stamford, CT.

Introduction: One pattern of kidney injury seen in COVID 19 is collapsing glomerulopathy (CG), a type of Focal Segmental Glomerulosclerosis (FSGS). It has been hypothesized that direct viral effect or increased circulating cytokines from the inflammatory response of the virus, or both, can lead to CG especially in patients with high-risk alleles of APOL1 gene.

Case Description: Patient 1: 63-year-old man, COVID-19 positive, who received only supportive care while hospitalized (Results in table 1). Patient 2: 62-year-old man, COVID-19 positive, who required brief treatment with dialysis and received high-dose steroids (Results in table 1).

Discussion: We present 2 cases who achieved partial renal recovery despite different treatments, raising the question of the role of steroids in patients with COVID associated CG.

Table 1
Renal biopsy (Patient 1) showing glomerular collapse

Impact of First vs. Second COVID-19 Surge in Dialysis Patients in San Antonio
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Background: San Antonio, Texas witnessed a COVID-19 surge during July and December 2020. COVID-19 had disproportionately severe impact on dialysis population during first surge; however, experiences from second surge is not known. The aim of our study is to compare the effect of two surges on prevalence and outcomes of COVID-19 infections in dialysis patients within University Health System

Methods: First surge was from April 20 to Sept 20; second was from Oct 20 to Mar 21. Over12-month period, we recorded COVID-19 infections and outcomes for adult patients receiving dialysis at three centers (1st surge n=359 including 25 home and 2nd surge n=362 including 37 home). Demographic, clinical, laboratory, treatment and outcomes data were analyzed

Results: COVID-19 infection were similar during surges (36 [10%] vs.43 [12%]). There was no difference in age, sex, ethnicity, smoking, co-morbidities, cause of ESKD, access and medications. However, patients during second surge were more obese (28±4.5 vs 30.4±7.5 kg/m² p=0.015), less dialysis vintage (6.2±4.5 vs. 5.7±3.1 yr, p=0.006), higher WBC (6.5±2.2 vs. 7.3±3.6 x 10³/ml, p=0.016), ferritin (939±719 vs. 1227±1621 µg/L, p=0.048), and D-dimer (2285±2120 vs. 5670±12410 IU ng/ml, p=0.02). No infection occurred in home dialysis patients during first surge compared to 6 (14%) during second surge (p=0.02). Table shows outcomes

Conclusions: Incidence of COVID-19 infections in our dialysis population were similar in the two surges. Hospitalization rates were similar, but more patients required ICU admission, ventilation and longer stay during second surge, although non-significantly. Death was significantly higher during second surge. Home dialysis patients more frequently affected than first surge suggesting change in health behaviors

Table 1
Renal biopsy (Patient 1 & 2): Tubular microcyst formation; also seen in HIV-associated nephropathy
A Single-Center Experience: SARS-Cov-2 in ESKD and Kidney Transplant Patients
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Background: A new strain of coronavirus was first recognized in late 2019 resulting in a worldwide pandemic by early 2020. This pandemic challenged health care systems worldwide. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), resulted in a spectrum of illnesses ranging from asymptomatic, mild, and self-limiting to severe disease. To this date, there are no clear treatment guidelines or protocols for the management of patients in general and for hemodialysis and transplant patients in particular. The Centers for Disease Control and Prevention (CDC) lists patients with chronic kidney disease and immunocompromised patients as high risk for severe disease from SARS-CoV-2.

Methods: Our study is a single-center retrospective study. We conducted an observational, retrospective study in ESKD and kidney transplant recipients hospitalized and diagnosed with COVID-19 disease at Advocate Christ Medical Center admitted between March 1 to May 31, 2020, a 3-month period. We describe our experience in patients with ESKD and kidney transplants during the COVID 19 pandemic. With particular attention to the treatments used, prognosis, and kidney outcomes in these patients.

Results: From the aggregate total of patients diagnosed with SARS-COV 2 between March 1 to May 31, 2020, there were 34 patients with ESKD on KRT and 3 kidney transplants. The median age of our ESKD cohort was 63.5 years while the KT cohort was 69 years. For both patient populations were predominantly male with 52.9% for ESKD and 66.7% for KT. With 64.7% of ESKD being composed of African Americans, while our KT patients were predominantly Caucasian at 66.7%. The average length of hospital stay was longer for KT patients at an average of 22 days. The incidence of in-hospital death was significantly higher in ESKD patients at 27.8% while we had no mortality for KT pts. For in-patient mortality serum Na, K and BUN were not statistically significant from those who survived. D-dimer peak was significantly higher in mortality.

Conclusions: COVID-19 infection is associated with a high rate of mortality. D-Dimer levels were correlated with disease severity as a single criterion for the decision of admission to ICU.
The Relevance of Urinalysis in the Hospitalization of Patients with COVID-19 and Nephrology Early Intervention
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Background: Multidisciplinary management of the COVID’s patients is essential for their evolution, and the early detection of AKI is a significant role to avoid morbidity.

Methods: In a retrospective, observational analysis of all the patients >18 Y that were hospitalized at the Hospital Universitario de Monterrey, in the COVID area, from March to August 2020, we notice how the urinary sedimentation examination from the beginning could detect patients who could develop AKI or the need of RRT. All data were analyzed using SPSS statistical software (version 25; IBM Corporation, Armonk, New York).

Results: A total of 344 patients hospitalized from March to August 2020. 220 patients with EGO since the beginning (obtained when our nephrology team take place on the presentia evaluation from AEMI) 102 did not have proteinuria, and, on the other hand, the rest (61 or 37%) reported it. 95 patients (41.7%) had hematuria. Hematuria were more likely to be treated with KRT. Patients with hematuria demonstrated an increased tendency to require RRT: 38.2% of patients with hematuria versus 11.6% without hematuria, the greater chance that needs RRT (P<0.001).

Conclusions: The presence of active sedimentary urinary on COVID patients is frequent. The patients who present the combination of hematuria and proteinuria develop severe AKI (KDIGO 3 without RRT) or the need for RRT. Factors in patients such as to be on their upper edge of 40 years old, the presence of hyperkalemia, metabolic acidosis, also the hematuria and proteinuria, suggest the AKI risk that required RRT.

PUB043
Algorithm for Predicting AKI
Shivangi Patel. Morristown Medical Center, Morristown, NJ.

Background: Current detection of AKI relies on acute rise in serum creatinine (sCr) and/or a decline in urine output over given time interval. However, biomarkers for AKI have been shown to be elevated prior to change in sCr, suggesting that the time to intervene and prevent AKI is before the change in sCr occurs, when irreversible damage has already occurred. The purpose of the present study was to identify variables that would predict patients at risk for developing AKI without relying on sCr or urine output.

Methods: Retrospective chart review was conducted on all patients admitted from Jan. 1 to Jul. 31 of 2019. The present data was made between those that developed AKI and those that did not develop AKI, a change of sCr ≥0.3mg/dL. After exclusion criteria, the final data set consisted of a total of 547 patients and was basis to detect variables that are readily available.

Results: Data showed that the higher the rise in sCr the worse the renal injury requiring renal replacement therapy and worse the patient outcome. sCr ≥ 1.5x baseline correlated with prerenal or mild AKI, while contrast induced nephropathy correlated with ≥ 2x baseline sCr and acute tubular injury and need for renal replacement therapy correlated with ≥ 3x baseline sCr. 20 specific variables were identified in differentiating those that will develop AKI and those that did not develop AKI. Individually some variables weighed more than others in differentiating between AKI and no AKI, however same variables were present across any severity of AKI. Using the 20 variables a specific algorithm was developed to identify any patient admitted and their risk to develop AKI in any inpatient clinical setting. To confirm the accuracy of the data, the same variables were extracted via computer (instead of manually) on a new pool of 769 patients with retrospective admissions yielding same result as the clinician with 81% sensitivity, 80% specificity and 80% accuracy in detecting AKI.

Conclusions: The variables are readily available without need to change patient management or increasing cost. Further study is being conducted to answer the following: How early and accurately will this algorithm predict AKI? Will this prevent AKI by altering management of clinicians when alerted? This could potentially be integrated into hospitals’ electronic health records for real time patient monitoring and detection of early AKI and modify patient care outcomes.

PUB044
Not Everything Is About COVID-19: An Unusual Case of Rhabdomyolysis and AKI After Physical Activity
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Introduction: Rhabdomyolysis is the breakdown of striated muscle, leading to systemic manifestations that typically include myoglobinuria, being responsible for 5 to 7% of non-traumatic acute kidney injury(AKI). It can be caused by trauma, status epilepticus, metabolic myopathies, drugs, infections, thyroid disease and hemoglobinopathies.

Case Description: We report a case of 31 year old woman who was admitted with muscle pain and choloria 12 hours after physical exercise for a public contest, having mild SARS-CoV2 infection 3 weeks before. She was previously healthy, without regular use of any medication, in training for a physical test, with no family history of blood or muscle diseases. At admission she was dehydrated. Exams are shown in table 1. During hospitalization she was conducted with vigorous hydration, diuretics when necessary and urine alkalization, without hemodialysis. After 12 days, she was discharged. In outpatient follow-up, although the history fits as rhabdomyolysis as exerting physical activity in a post-covid patient, additional tests were performed: TSH 2.41 mU/L, negative serology for HIV, normal CRP and ESR. Despite negative family history of hemoglobinopathy, hemoglobin electrophoresis was compatible with sickle cell trait (Hb A 97.8%, Hb S 3.1%, Hb C 3.8%, Hb F 8.8%).

Discussion: Sickle cell disorder(SCD) is a genetic disease where hemoglobin (Hb) S mutation is present on at least one beta chain. When both β chains of HbA carry HbS mutation, the patient exhibits phenotypic features of SCD. If a mutation affects only one β globin chain and the other is normal, the patient is said to have sickle cell trait (SCT), which is a relatively benign carrier state and does not have the classic phenotypic features of SCD. It is estimated that affects 1 million to 3 million americans, and 8 to 10 percent of African Americans, configuring a serious public health problem. SCD does not appear to be associated with increased overall mortality, but studies demonstrate that it is associated with a significantly higher risk of severe exertional rhabdomyolysis, and this case is a reminder to perform this assessment.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PUB045
Kidney Involvement in Hantavirus Infection: The Importance of Kidney Biopsy
Gabriela Lupusoru,1,2 Ioana Ilinciu,1 Georgiana Fratila,1 Mirea Lupusoru,2 Andrea G. Andronescu,1,2 Achim Camelia Adriana,1,2 Mihaela A. Banu,2 General Ismail,1,2 Institutul Clinic Fundeni, Bucuresti, Romania;1 Universitatea de Medicina si Farmacie Carol Davila, Bucuresti, Romania.

Introduction: Hantavirus infection, a rare zoonosis, associates two major syndromes: hemorrhagic fever with renal syndrome (HFRS) and cardiopulmonary syndrome (CPS). We present two cases of HFRS in which kidney biopsy (KB) was the key in guiding diagnosis.

Case Description: Case 1: 26-year-old female (no medical history) presented with acute kidney injury (AKI), nephrotic syndrome (NS), hematuria, high blood pressure (HBP), hepatic cytolysis, severe thrombocytopenia, anemia, leukocytosis, elevated LDH, normal haptoglobin, positive Coombs test, negative immunological and viral tests (C3/C4, ANA, ANCA, antiGBM, hepatitis B/C, HIV, Epstein-Barr, Cytomegalovirus), normal ADAMTS13 activity KB showed macroscopic features of hemorrhage in the renal medulla, light microscopy with normal glomeruli, proximal tubules with intratubular erythrocytes, interstitial hemorrhage in medulla, electron microscopy with endotheliosis and interstitial inflammation, features suggesting Hantavirus infection. Serological testing of IgM/IgG antibodies (Ab) for Hantaan serotype (HTNV) established diagnosis

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Methods: This is a prospective observational study with 62 NBs admitted to a tertiary hospital in Fortaleza, northeast Brazil, between August 2019 and September 2020. Using serum samples and urine, the biomarkers were measured by ELISA and compared to the determination of AKI by neonatal Kidney Disease: Improving Global Outcomes (KDIGO), by urinary output.

Results: No AKI was found by using the traditional biomarkers. CysC levels were 4.78 (1.9 – 25.63) ng/mg-Cr, uCysC 0.64 (0.2 – 2.29) ng/ml; NGAL 27.81 (14.29 – 58.98) ng/mg-Cr; sNGAL 0.85 (0.4 – 1.39) ng/ml; and uNGAL 3.14 (1.74 – 5.51) ng/ml. In the group of sick NBs, the levels of uCysC and uNGAL were associated with a longer period of hospitalization. As a consequence, after combining the two biomarkers, it was possible to observe a poor prognosis in NBs with neonatal infection or sepsis (AUC: 0.783; p = 0.016), Figure 1.

Conclusions: Our study evidenced that uCysC, uNGAL and sNGAL were associated with kidney injury in premature NBs with neonatal infection or early sepsis. Also, there was an association of uCysC and uNGAL with hospital stay time longer than 30 days and the prognosis of NBs.

Funding: Government Support - Non-U.S.
on the mortality of patients with AECOPD remains unknown. Therefore, the aim of this study is to investigate the joint effect of ARF and AKI on mortality in AECOPD patients.

Methods: We performed a retrospective, observational cohort study of data from Nanjing First Hospital. The effect of AKI and ARF on in-hospital mortality was assessed using a multivariate logistic regression model. Additive interaction was assessed with the relative excess risk due to interaction.

Results: 1647 participants were enrolled for analysis. Most (77%) patients were male, and the median age of the overall cohort was 78 years (IQR: 71 - 84). ARF and AKI occurred in 515 (31.3%) and 357 (21.7%) patients, respectively. Overall, in-hospital mortality was 35.3%. The in-hospital mortality rate of the none ARF nor AKI group, the ARF only group, the AKI only group, and the both ARF and AKI group were 0.8%, 7.0%, 7.5%, and 29.9%, respectively. After multivariate logistic regression analysis, the independent risk factors for in-hospital death included: albumin (OR 0.88, 95% CI 0.83-0.93, P < 0.001), ARF only (OR 8.53, 95% CI 3.64-19.99, P < 0.001), AKI only (OR 8.95, 95% CI 3.58-22.55, P < 0.001), and both ARF and AKI (OR 39.13, 95% CI 17.02-89.97, P < 0.001). The relative excess risk due to interaction was 22.62 (95% CI, 0.31 to 44.93), the attributable proportion due to interaction was 0.59 (95% CI, 0.36 to 0.79), and the synergy index was 2.46 (95% CI, 1.44 to 4.20), indicating ARF and AKI had a significant synergic effect on in-hospital mortality.

Conclusions: ARF and AKI were independent risk factors for in-hospital mortality in AECOPD patients. Moreover, those two complications had a synergistic effect on in-hospital mortality.

PUB053
Vanishing Vancomycin-Associated Acute Interstitial Nephritis
Nolan M. Giehl, Nilofoar Nobakht, Jonathan E. Zuckerman. University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA.

Introduction: Intravenous (IV) vancomycin is a ubiquitously used antibiotic for a variety of infections that can cause nephrotoxicity. We present a remarkable biopsy-proven case of acute interstitial nephritis (AIN) attributed to supratherapeutic vancomycin levels successfully treated with corticosteroids.

Case Description: A 44-year-old woman monitored by an outpatient parenteral antibiotic therapy (OPAT) program presented with a morbilliform rash 2 weeks after starting postoperative IV vancomycin (goal trough 15-20 mcg/mL) for mastoiditis. Baseline serum creatinine (SCr) was 0.92 mg/dL, which had increased to 3.8 mg/dL on labs through the OPAT program 3 days prior. Her vancomycin trough was notably >80 mcg/mL. Repeated values on admission were 5.27 mg/dL and 74.3 mcg/mL, respectively. Last vancomycin dose was 1 day prior. Urine microscopy showed 1% protein, 104 white cells and 36 non-dysmorphic red cells. Urine culture and eosinophils >80 mcg/mL. Repeated values on admission were 5.27 mg/dL and 74.3 mcg/mL, indicating ARF and AKI levels successfully treated with corticosteroids.

Conclusions: Case presentation of a remarkable biopsy-proven AIN case attributed to IV vancomycin and treated with corticosteroids. AIN is a rare adverse effect of vancomycin but should be on the differential in patients with marked increases in SCr. Corticosteroids should be considered in cases with uncontrolled proteinuria and eosinophils.

PUB054
N-acetylcysteine and Contrast-Induced AKI: An Umbrella Review of Systematic Reviews
Wan Peng,1,2 Emran Ruzicka, Edward G. Clark, Jennifer Kong, Swapnil Hiremath. University of Ottawa, Ottawa, ON, Canada.

Background: There have been numerous trials and metaanalyses of N-acetylcysteine (NAC) in contrast-induced acute kidney injury (CIAKI). The large trials do demonstrate the futility of NAC. In this umbrella review, we synthesize the evidence as collated from the systematic reviews and metaanalyses.

Methods: A literature search was done to identify all systematic reviews on NAC and CIAKI using databases from inception to end 2020. Two independent reviewers screened the studies and extracted data on including assessment of heterogeneity, publication bias and we used the A MeaSurement Tool to Assess systematic Reviews (AMSTAR 2) to appraise the included studies.

Results: The literature search retrieved 273 citations, of which 42 systematic reviews were eligible. The quality assessment using the AMSTAR-2 was variable (see table) with high quality noted for certain domains (eg explicit question, explanation of study designs), low for others (funding, reasons and list of excluded studies). All studies reported high heterogeneity; 39/42 (93%) performed a meta-analysis, all with an overall benefit with NAC (pooled relative risks range 0.38 - 0.84). 26/42 (62%) reported on the presence of publication bias, and 31/42 (74%) reported the risk of bias. Only 2/42 studies (9%) reported on efforts to resolve heterogeneity did not report a summary effect size as a result.

Conclusions: Systematic reviews can provide misleading results if heterogeneity and publication bias are not taken into account.

AMSTAR Checklist

PUB055
Nephrologist Interventions to Avoid Kidney Replacement Therapy in AKI
Jonathan Chavez,1,2 Jorge I. Michel gonzález,1,2 Andres E. De la torre quiroga,1,2 Andres Aranda,1,2 Alexia C. Romero,1,2 Bladimir Diaz Villavicencio,1,2 Guillermo Garcia-Garcia1.1 Universidad de Guadalajara, Guadalajara, Mexico; 2Hospital Civil de Guadalajara, Guadalajara, Mexico.

Background: We investigated the impact of 5 early nephrology interventions on starting kidney replacement therapy (KRT), AKI progression and death in AKI patients.

Methods: In a prospective cohort, we followed-up for 10 days AKI patients. We analyzed 5 interventions of the nephrology team (fluid adjustment, nephrotoxic withdrawal, antibiotic dose adjustment, nutritional adjustment and removal of hypercatabolic solutions) and multivariate analysis for the risk of starting KRT (primary objective), AKI progression to stage 3 and death (secondary objectives).

Results: We analyzed 288 AKI patients. The mean age was 55.3 years, 60.7% were male, AKI KDIGO stage 3 was present in 50.5% of them, sepsis was the main etiology 50.3%, and 72 (25%) patients started KRT. The overall survival was 84.4%. Fluid adjustment was the only intervention associated with a decreased risk for starting KRT (OR 0.58, 95% CI 0.48-0.70, p = <0.001) and AKI progression to stage 3 (OR 0.59, 95% CI 0.49-0.71, p = <0.001). Receiving vasopressors and KRT were associated with mortality. None of the interventions studied was associated with reducing the risk of death.

Conclusions: In this prospective cohort study of AKI patients, early nephrologist intervention and fluid prescription adjustment was associated with lower the risk of starting KRT and progression to AKI stage 3.
Acute Interstitial Nephritis (AIN): Current Presentation and Therapy Beyond Corticosteroids (CS)


Background: AIN is most often caused by drugs (DI-AIN) and autoimmune disease (AI-AIN). Many patients (PTS) are treated with CS. There are sparse data on management of relapsing disease.

Methods: 53 PTS with AIN followed at our center between 2010-2020. Median (IQR) are reported. T-Test, Fisher’s exact were used as appropriate.

Results: Median age was 55 years (31-64) at diagnosis and 28 (53%) were female. The cohort included 26 (49%) DI-AIN, 20 (38%) AI-AIN, 1 (2%) infection, and 6 (11%) unknown etiology. Antibiotics were the most common drug; Sjogren’s predominated AI-AIN. Table 1 summarizes the clinical course. Serum Creatinine (SCR) at biopsy was higher in DI-AIN. 4 (15%) DI-AIN were dialysis dependent at diagnosis vs. 0 AI-AIN. PTS (p=0.12). 44 (83%) PTS received CS as initial therapy, and DI-AIN PTS received shorter courses. 2 (8%) DI-AIN and 6 (30%) AI-AIN reached ESKD (p=0.06) after 66.5 months (33-97). Among AI-AIN cohort not reaching ESKD, the follow up SCR 1.8 (0.84 – 3.3) mg/dL, n=54, p=0.0001, t=6.4872, df=119. Nadir creatinine after drug discontinuation was 1.49 (0.66 - 2.7) mg/dL, n=70, P<0.0001, t=6.4872, df=135. Kidney function trajectory after stopping Olmesartan

Kidney function trajectory after stopping Olmesartan

Conclusions: The elective withdrawal of concurrent RAAS blockade in CKD patients who present with progressive worsening AI generally demonstrate clearly improved renal outcomes. We posit that in selected CKD patients with progressive AI such as in our study, RAAS blockade discontinuation indeed is the correct next step in their management for both improved renal and CV outcomes.

PUB058

A Case of Acyclovir Neurotoxicity Masquerading as Progression of Zoster Encephalitis


Introduction: We present a case of varicella zoster virus (VZV) central nervous system infection complicated by acyclovir neurotoxicity.

Case Description: A 53-year-old male with ESRD on hemodialysis presented with acute encephalopathy. He had been diagnosed with VZV laryngitis 10 days prior to presentation, and was discharged on oral valacyclovir. He now presents with altered mental status. As the CSF was positive for VZV IgM and his symptoms persisted, this raised concern that his VZV infection was progressing to encephalitis. He was therefore transitioned to intravenous acyclovir for better coverage. However, the patient’s encephalopathy did not improve. Acyclovir level was found to be elevated at 4.9 mcg/mL (normal <2 mcg/mL). Acyclovir was then held and he improved – demonstrating that his encephalopathy was most likely due to acyclovir. The diagnosis is clinical. Studies suggest a temporal association between symptoms and acyclovir administration as patients typically present within 24 to 72 hours; while VZV encephalitis patients present 1 week after the onset of skin eruptions. MRI findings for VZV encephalitis include clustered subcortical plaque-like lesions with mononuclear predominance and high protein. The pathophysiology for acyclovir neurotoxicity remains
under investigation. Currently the presumed mechanism is via high concentrations of 9-carboxy-8-deoxyguanosine methylguanine (CMGG), a metabolite of acyclovir. Large doses of CMGG may inhibit mitochondrial DNA polymerase and alter mitochondrial function. Hemodialysis serves as the only treatment as the half-life of acyclovir in patients with ESRD can reach up to 20 hours, as compared to 3 hours in patients with normal kidney function. Acyclovir neurotoxicity poses a diagnostic dilemma since VZV encephalitis carries a mortality rate of up to 20%. Recognizing the risk factors and the temporal relationship between acyclovir administration and symptoms will lead clinicians to a timely diagnosis.

PUB059
Severe AKI Leads to Worse Patient-Centered Outcomes in Survivors of Critical Illness
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Background: Acute kidney injury (AKI) is a detrimental condition that occurs in about half of critically ill patients. Survivors of critical illness are at high risk of persistent impairments in physical, cognitive, and emotional health, which may be worse in patients who suffered from AKI. The main objective of this study was to evaluate patient-centered outcomes of critical illness survivors who did and did not have severe AKI.

Methods: Retrospective observational study of adult patients surviving an ICU admission due to critical illness who attended outpatient follow-up in the ICU Recovery Clinic at the University of Kentucky. Patients with end-stage kidney disease were excluded. Patients were also excluded if they had an acute neurologic, traumatic, or orthopedic injury that prevented participation in outcomes testing at their follow-up visit. The primary outcomes were distance patient ambulated on the six-minute walk test (6-MWT) and self-reported health-related quality of life (HrQoL) in a visual analog scale ranging from 0 to 100 with higher scores indicating better quality of life at 3-month follow-up.

Results: A total of 105 patients were studied. Mean age (SD) was 54.6 (13) years, 53% were male, and 73% white. Sixty-eight (65%) patients had AKI, 46 of them severe AKI (KDIGO stage 2). ICU survivors that suffered from AKI stage 2 had lower HrQoL scores than those with AKI stage 1 or no AKI (69.1 ± 20.6 vs. 77.8 ± 14, p=0.015) and ambulated shorter distances on 6MWT (195.0 [153.8-285.0] vs. 300.0 [180.0-408.0], p=0.029) ± 153 meters, p=0.059. In multivariable regression analyses, older age, longer ICU length of stay, and AKI severity were associated with lower HrQoL scores; while older age and need for tracheotomy were associated with shorter distances achieved on 6-MWD.

Conclusions: Survivors of critical illness who suffered from severe AKI during their ICU stay had increased physical disability and worse quality of life compared to ICU survivors without severe AKI. Critical illness/AKI survivors may benefit from specialized post-ICU care and rehabilitation treatments. Future studies should focus on testing interventions that could ameliorate patient-centered outcomes in this special patient population.

Funding: NIDDK Support

PUB060
High Symptom Burden in Medical ICU Patients with Any Degree of AKI Sarah Ramee,1,2 Yulin Yang,2 Holly P. Grieger,2 Khaled Abdel-Kader,3 James J Peters VA Medical Center, Bronx, NY; 2Weill Cornell Medicine, New York, NY; 3Vanderbilt University Medical Center, Nashville, TN; 4Icahn School of Medicine at Mount Sinai, New York, NY.

Background: We know little about patients’ physical symptoms during acute kidney injury (AKI). Here we provide one of the first descriptions of symptoms in medical intensive care unit (MICU) patients with varying degrees of AKI.

Methods: This is a cross-sectional study from the MICU of an urban teaching hospital conducted 07/2016-01/2019. Study staff obtained informed consent from patients and a nephrologist ascertained the presence and KDIGO stage of AKI at the hospital conducted 07/2016-01/2019. Study staff obtained informed consent from patients about half of critically ill patients. Survivors of critical illness are at high risk of persistent impairments in physical, cognitive, and emotional health, which may be worse in patients who suffered from AKI. The main objective of this study was to evaluate patient-centered outcomes of critical illness survivors who did and did not have severe AKI.

Methods: Retrospective observational study of adult patients surviving an ICU admission due to critical illness who attended outpatient follow-up in the ICU Recovery Clinic at the University of Kentucky. Patients with end-stage kidney disease were excluded. Patients were also excluded if they had an acute neurologic, traumatic, or orthopedic injury that prevented participation in outcomes testing at their follow-up visit. The primary outcomes were distance patient ambulated on the six-minute walk test (6-MWT) and self-reported health-related quality of life (HrQoL) in a visual analog scale ranging from 0 to 100 with higher scores indicating better quality of life at 3-month follow-up.

Results: A total of 105 patients were studied. Mean age (SD) was 54.6 (13) years, 53% were male, and 73% white. Sixty-eight (65%) patients had AKI, 46 of them severe AKI (KDIGO stage 2). ICU survivors that suffered from AKI stage 2 had lower HrQoL scores than those with AKI stage 1 or no AKI (69.1 ± 20.6 vs. 77.8 ± 14, p=0.015) and ambulated shorter distances on 6MWT (195.0 [153.8-285.0] vs. 300.0 [180.0-408.0], p=0.029) ± 153 meters, p=0.059. In multivariable regression analyses, older age, longer ICU length of stay, and AKI severity were associated with lower HrQoL scores; while older age and need for tracheotomy were associated with shorter distances achieved on 6-MWD.

Conclusions: Survivors of critical illness who suffered from severe AKI during their ICU stay had increased physical disability and worse quality of life compared to ICU survivors without severe AKI. Critical illness/AKI survivors may benefit from specialized post-ICU care and rehabilitation treatments. Future studies should focus on testing interventions that could ameliorate patient-centered outcomes in this special patient population.

Funding: NIDDK Support

PUB061
Expanded Hemodialysis (HDx) May Improve Inflammation in AKI due to COVID-19 Disease Requiring Renal Replacement Therapy Giuseppe Gennone. ASL Bari, Bari, Italy.

Background: A baseline hyperinflammatory state afflict COVID-19 positive patients (pts). AKI as a final common pathway of systemic inflammation and increased immunologic response leading to uncontrolled circulating levels of pro-inflammatory mediators and direct cytokine-induced organ damage. Hemodialysis expanded (HDx) represents an innovative strategy to remove uremic toxins up to 50 Kd, thanks to the medium cut-off membrane (MCO) and internal convection. Transcription of pro-inflammatory cytokines in peripheral leukocytes is markedly reduced and removal of soluble mediators of inflammation is enhanced by HDx. In vitro studies confirm that HDx limit neutrophil activation by decrease of ROS, TNF-alfa and IL6 and increase of apoptosis. Aim of this study is to evaluate the response to treatment with HDx and HF-HD in AKI due to COVID-19 disease.

Methods: Six pts were enrolled in a retrospective observational study: 3 pts were treated with HF-HD (FX80-Fresenius) and 3 with HDx (Theranova 400-Baxter) during COVID-19 infection. 2 pts treated with HDx and 1 with HF-HD showed hemodynamic instability and need for vasopressors. They were daily assessed using the following: urea, creatinine, C-reactive protein (CRP), procalcitonin (PCT), D-Dimer and Albumin. The values have been reported as mean±SD.

Results: HDx (Qb=218±48 m/l/min) discovered in every patient a significant reduction for CRP (-59.7% average) and PCT (-11.2% average), whereas HF-HD (Qb=205±27 m/l/min) showed an opposite trend (+69.1% and +39.1% average). Moreover HDx induce a greater reduction of D-Dimer (51.4% vs 19.8% average), Urea and serum Creatinine in comparison to HF-HD (average), (Tab.1) and better hemodynamic stability (Pam 75 vs 67 mm/Hg).

Conclusions: HDx effectively impact on inflammation and renal markers, compared to HF-HD, in COVID-19 positive. HDx, due to the increased clearance of cytokines, has recently been confirmed as a support for COVID-19 positive treatment in some Italian dialysis centers. Our preliminary results have to be confirmed by enlarged studies but in the meantime could help to build a new scientific evidence.

PUB062

Background: Two of the components of ERAS protocol are the maintenance of euvolemia and the use of multimodal analgesia, which includes NSAIDs. Given the restrictive fluid therapy strategy and the potential use of nephrotoxic analgesics, it’s pertinent to assess the risk and potential consequences of acute kidney injury (AKI). The objectives of this study are to assess the incidence of AKI and its outcomes.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author. 783
Methods: Descriptive and single-center retrospective study. It included the first two hundred adult patients consecutively enrolled for colorectal surgery according to the ERAS protocol. AKI was defined according to KDIGO criteria.

Results: The median age was 71 years (IQ 62-78) and 64.5% of patients were male. The clinical follow-up time was 39 months (IQ 33.8-44.2). Compliance with the ERAS protocol was 81.5% (IQ 71.4-66.5). The median length of stay was 7 days (IQ 5-11). AKI occurred in 23% (46), mostly KDIGO 1 (71.7%). There was a need for renal replacement technique (TRRT) in 8.7%. Patients who developed AKI had a higher median age (76 vs. 70, p<0.001), incidence of diabetes (32.6% vs. 15.6%, p=0.011), hypertension (84.8% vs. 57.8%, p<0.001) and chronic kidney disease (65% vs. 48%, p=0.041). Weight loss in the first 24h was higher in patients who developed AKI (-1.9kg vs. -0.5kg, p=0.010). There was no statistical difference in the administration of NSAIADs. Patients who developed AKI had a greater need for postoperative amnogenic support (13% vs. 1.9%, p=0.001) and mechanical ventilation (13% vs. 0.65%, p=0.001). They were more often submitted to laparotomy (41%) vs. 25.3%, p=0.036) and exposed to intravenous iodinated contrast (34.8% vs. 17.5%, p=0.012). Patients with AKI had greater need for admission to intensive care (23.9% vs. 9.7%, p=0.019) and lower survival at follow-up (log rank 19.03, p=0.001). None of the patients were dependent of dialysis at discharge. In the first 2 years of follow-up, patients who developed AKI had a more pronounced decline in eGFR (6.3mL/min/1.73m2/year vs. 3.48mL/min/1.73m2/year, p=0.030).

Conclusions: AKI was associated with a worse clinical prognosis with reduced survival. Additionally, the development of AKI negatively influenced the reduction of glomerular filtrate in the first 2 years. Some clinical factors were identified, as age and comorbidities, that may help us to identify patients at higher risk.

PUB063
Renal Surgery and Postoperative AKI Risk in Normal Renal Function Patients: A Hidden Threat
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Background: Acute kidney injury(AKI) is a major postoperative complication in renal surgery, both in radical(RN) than in partial nephrectomy(PN). One of the most intriguing arguments is to understand if normal renal function patients(pts) can develop postoperative AKI after renal surgery, both in the oncological and in the living donors' assets. Aim of our study was to compare the AKI incidence in the two major renal surgeries approaches in a selected cohort of pts with normal renal function.

Methods: We enrolled a cohort-study of 214 pts who underwent RN or PN due to non-oncological pts. Serum creatinine (s-Cr) values were collected before surgery (t0). We divided our cohort in two groups: a group of 33 kidney living donors was also enrolled to measure the impact of RN in the first 2 years of follow-up, patients who developed AKI had a more pronounced decline in eGFR (6.3mL/min/1.73m2/year vs. 3.48mL/min/1.73m2/year, p=0.030).

Conclusions: AKI was associated with a worse clinical prognosis with reduced survival. Additionally, the development of AKI negatively influenced the reduction of glomerular filtrate in the first 2 years. Some clinical factors were identified, as age and comorbidities, that may help us to identify patients at higher risk.

PUB064
Mind the Gut: Gastric Complications of Immunosuppressive Therapy in a Patient with ANCA Vasculitis
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Introduction: Granulomatosis with polyangiitis (GPA) is one of three ANCA-associated vasculitides which frequently affects the small vasculature of the pulmonary and renal systems. Management has evolved due to several pivotal trials, and recent data from PEXIVAS trial suggests lower prednisone doses maybe just as effective as the higher doses, with fewer complications.

Case Description: A 76-year-old - previously healthy woman presented with shortness of breath and cough. She was treated as an outpatient for presumed atypical bacterial pneumonia without improvement. On admission, she had a RR of 24 and oxygen saturation of 87% on room air and examination revealed cr clacks in bilateral lung bases. Labs were remarkable for Hgb 7.1 mg/dL and Cr 4.2 mg/dL from a baseline of 1mg/dL. UA showed moderate blood and 100mg/dL protein. On day 2, she developed new-onset hemoptysis. Kidney function deteriorated over the next several days requiring temporary dialysis. She was started on empiric pulse dose steroids and kidney biopsy confirmed severe diffuse crescentic, necrotizing pauci-immune glomerulonephritis with anti-MPO antibody/P-ANCA sero-positivity. She was treated with steroids and rituximab. She continued to have hemoptysis, prompting initiation of plasmapheresis as well as discharge on a 6-month course of prednisone. She was also discharged with GI prophylaxis, which unfortunately she was not taking and she was readmitted 1-month later for gastric ulcer perforation likely as a complication of steroid use, and unfortunately expired.

Discussion: This case outlines the severity and high risk for mortality in patients with GPA. Not only can the associated inflammation itself be fatal but immunosuppression is not without risk; such as the risk for peptic ulcer disease with steroid use as highlighted in this case. Data from trials such as PEXIVAS should be considered.

PUB065
Magnetic Resonance Imaging Contrast Leads to Acute Tubular Damage and Accumulation of Gadolinium-Rich Nanoparticles in Renal Cortex
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Background: Intravenous administration of gadolinium-based contrast agents leads to long-term gadolinium retention in every vital organ, including the kidney and the brain, regardless of brand. The safety profile of gadolinium-chelate agents remains the subject of debate.

Methods: Male and female C57BL/6 mice were randomized by age and weight to GBCA-treatment (Omniscan, 2.5 mmol/kg, intraperitoneally, 20 doses over 4 weeks) or control (n = 20 each). Kidneys were isolated, fixed, sectioned at 200 nm, and supported with carbon holey grids. Scanning electron microscopy and multiple elemental analyses by energy-dispersive x-ray spectroscopy (EDS) were performed using JEOL 2010F FEGSTEM (200kV) microscope and the FEI Tecnai G(2) F30 S-Twin (300kV) transmission electron microscope.

Results: Renal proximal tubule cells of GBCA-treated animals exhibited lipid-laden vacuoles and extensive mitochondrial damage. Spiculated, electron-dense nanoparticles self-assembled in the tubular epithelia of gadolinium-treated animals. The electron densities were rich in gadolinium, phosphorous, and calcium. Gadolinium and phosphorous co-localized within the electron densities.
Conclusions: Systemic magnetic resonance imaging contrast treatment leads to the self-assembly of gadolinium-rich nanostructures in kidney tubular cells. These in vivo findings demonstrate that transmetallation is occurring (and this may be a mechanism for the resultant fibrosis) (Figure). Speciating the gadolinium-rich precipitates may aid in prophylactic strategies and therapies for gadolinium-induced diseases (including acute kidney injury, gadolinium deposition disease, gadolinium-associated plaques, ‘nephrogenic’ systemic fibrosis, and gadolinium-induced encephalopathy).

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PUB066
Scleroderma Renal Crisis Sans Scleroderma
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Introduction: Scleroderma renal crisis (SRC) is an uncommon autoimmune disease that can present with hypertension, acute kidney injury (AKI), proteinuria, hematuria. Rarely is SRC the initial manifestation of scleroderma (scleroderma renal crisis sans scleroderma). We report a case of a patient presenting with SRC complicated by malignant hypertension, thrombotic microangiopathy, and acute kidney injury (AKI).

Case Description: A 47 year old female with four months of headache, blurry vision, and chest palpitations who presented to an outside hospital in hypertensive crisis. Serum Creatinine (Scr) was 1.1 mg/dl initially, however steadily increased to a peak level of 4.46 mg/dl. Urinalysis showed small blood and protein, and spot urine protein to creatinine ratio was 1,412 mg/g. SSA antibody was positive, while SLC 70 antibody and centromere antibody were negative. Serum aldosterone was 60.3 ng/dl and plasma renin activity 43.4ng/ml/hr with aldosterone/renin ratio 1.4. Evaluation for renal artery stenosis was negative. A kidney biopsy showed thrombotic microangiopathy with scattered subendothelial immune complex deposits. The patient was transferred to our facility where her Scr continued to worsen. She was started on lisinopril 2.5mg when her creatinine level was 3.89 mg/dl. Scr stabilized after three days of ACE inhibition.

Discussion: SRC is a medical emergency requiring prompt diagnosis and treatment. Diagnosis can be challenging when this is the initial presentation of scleroderma. SRC should be considered in the differential diagnosis for patients presenting with AKI, new-onset microscopic hematuria, proteinuria, malignant hypertension and thrombotic microangiopathy. ACE inhibition is crucial for patient survival and can lead to renal recovery, which could take as long as 24 months after a renal crisis.

Fenofibrate-Induced AKI: An Underrecognized Adverse Effect
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Introduction: Fenofibrate is widely used as a second-line agent for hyperlipidemia refractory to statin therapy, especially in the setting of nephrotic syndrome and severe hypertriglyceridemia. There is growing evidence that fenofibrate can cause acute kidney injury (AKI) and that this might be occurring more often than previously thought.

Case Description: 42-year-old male patient with a history of hypertension and hyperlipidemia (predominantly hypertriglyceridemia in the 500-600 mg/dl range) had been on fenofibrate and angiotensin-II receptor blocker (ARB) for 18 months (no recent dose changes) and had a serum creatinine (Scr) 1.0 mg/dl at baseline. He developed sub-acute kidney injury with Scr peaking at 2.2 mg/dl over 6 months. He underwent kidney biopsy that showed tubular injury. Possibility of fenofibrate-induced AKI was entertained, as he was not on any other potential nephrotoxic medications. The drug was stopped and renal function returned to his prior baseline within a month. It remains normal and unchanged 9 months after stopping the drug.

Discussion: It is known that fenofibrate can cause fully reversible isolated elevations in serum creatinine by inducing increased metabolic secretion of creatinine. It causes a true AKI by means of rhabdomyolysis, often when used with a statin, and in patients who have other risk factors like chronic kidney disease (CKD). However, there are recent studies showing fenofibrate causing true AKIs evidenced by rise in cystatin C, an independent marker for kidney function, with subsequent decline in glomerular filtration rate (GFR). The exact mechanism of fenofibrate-induced AKI is still not fully understood but one hypothesis is that it impairs the production of renal vasodilatory prostaglandins, leading to renal vasoconstriction, and subsequently causing reduced renal plasma flow and glomerular pressure. Fenofibrate-induced AKI remains an under-recognized adverse effect of the drug. Although there is growing evidence and reports of these incidences, the exact mechanism remains unclear. Further studies showing the effects of fenofibrate on renal tissues at the molecular level are needed to better understand the pathophysiology of renal injury.

Serum creatinine (SCr) trend

PUB068
Granulomatous Interstitial Nephritis Unrelated to Drug Exposure in a Patient with Ulcerative Colitis
Josue O. Flores Santiago, Juan Carlos O. Velez, Muner Mohamed. Ochsner Medical Center - New Orleans, New Orleans, LA.

Introduction: Granulomatous interstitial nephritis (GIN) has been reported in patients with inflammatory bowel disease (IBD) treated with mesalamine but rarely as an inherent manifestation of IBD. Herein, we report a rare case of a young adult with a non-bloody diarrhea and acute kidney injury (AKI) caused by GIN and subsequently newly diagnosed with ulcerative colitis (UC).

Case Description: A 24-year-old man presented to an outside hospital with non-bloody watery diarrhea for 4 months, abdominal pain and unintentional weight loss. No report of voiding disturbance. He was taking no medications. Upon arrival, his vital signs and physical exam were normal. Laboratory data were pertinent for a serum creatinine of 8.0 mg/dl (baseline 0.6 mg/dl), and severe anemia. Urine studies were only relevant for sterile pyuria, no proteinuria. A kidney ultrasound showed no abnormalities. A kidney

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
biopsy was performed on the 9th day of hospitalization. He was discharged the next day. He presented to clinic 6 days after discharge with persistent diarrhea. His vital signs and physical examination remained normal. Serum creatinine was still elevated at 7.2 mg/dL. Microscopic examination of the urinary sediment only revealed coarse granular casts. The kidney biopsy specimen revealed a diffuse cellular infiltrate involving 80% of the interstitium, 70% interstitial fibrosis with atrophy, acute tubular injury and tubulitis. The presence of immune complexes in the glomeruli was present for immunofluorescence. Electron microscopy showed no deposits. Treatment of GIN with prednisone 60 mg qd was begun. After 3 weeks, his serum creatinine improved to 4.8 mg/dL. A colonoscopy showed severe pancolitis consistent with UC and addalimumab and dexamethasone were added. Six months later, his serum creatinine value remains at 4.8 mg/dL. (eGFR 16 ml/min).

Discussion: GIN is a rare histologic diagnosis that may be the first manifestation of a systemic disease or caused by drugs. GIN causing AKI has been rarely described in therapy-naïve patients with IBD, primarily in Crohn disease. Given the profound inflammation and young age and despite the severe chronicity in the biopsy specimen, the patient was treated with immunosuppressive therapy (IST). IST was later escalated to treat the UC lesion. Drug-naïve IBD should be listed as potential cause of GIN.

PUB069
Post Corangiography Angiography Cholesterol Embolism Syndrome Resulting in Atheroembolic Renal Disease
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Introduction: Cholesterol embolization syndrome (CES) has been characterized as being a multi-system disease resulting from embolization of cholesterol crystal from atheromatous plaque and its embolization to small arteries resulting in organ ischemia. A poorly recognized subgroup of CES is atheroembolic renal disease (AERD) or renal CES which accounts for a considerable subgroup. We present a case of a 69-year-old female who developed renal CES after undergoing coronary angiography.

Case description: Our patient was a 69-year-old female with past medical history of chronic kidney disease stage 3, diabetes mellitus, hypertension, and heart failure with ejection fraction 40-45%, coronary artery disease, and chronic obstructive pulmonary disease who presented with progressive dyspnea and lower extremity edema for several months. Two months prior to this admission she had undergone coronary angiography. Her initial creatinine was 1.28 mg/dL. Over the next two months her creatinine up trended to 2.93 mg/dL. The inciting factor was initially attributed to acute kidney injury secondary to over diuresis. On examination the patient looked euvoiclim but continued to have dyspnea and diuresis. Right heart catheterization was performed to better assess volume status which demonstrated normal filling pressures. Laboratory results were notable for persistent eosinophilia. In the context of recent contrast, rising eosinophilia, and normal filling pressures a renal biopsy was performed which demonstrated acute tubular injury, arterionephrosclerosis, and cholesterol emboli. Despite medical management, the patient’s renal function did not recover.

Discussion: Our patient’s initial presentation was concerning for decompensated heart failure with a possible cardioaortic insult. Post-diuresis instead of having improvement in her dyspnea and acute kidney injury, she continued to decompensate. Further complicating her presentation was recent contrast exposure for coronary angiography and rising eosinophilia. Biopsy ultimately showed cholesterol emboli that most likely dislodged post catheterization and caused acute tubular injury. The teaching point of our case is that renal injury irrespective of coronary angiography timing in patients with preexisting cardiac and kidney disease non-responsive to medical therapy.

PUB070
Checkmate! A Rare Case of Immune Checkpoint Inhibitor-Related AKI
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Introduction: With the advent of immune checkpoint inhibitors (ICPIs) used in cancer therapy, there has been improved prognosis in various malignancies; however, with the use of these novel class of drugs, there has been a rise in associated immune-related adverse events reported, including acute kidney injury (AKI). ICPI-associated AKI is an emerging entity and in this case we highlight one such ICPI, Nivolumab, an antibody directed against programmed death-1, causing renal dysfunction.

Case Description: An 80-year-old man with renal cell carcinoma with baseline creatine of .58 mg/dL (RCT) was referred to Nephrology services to evaluate AKI, with serum creatinine 2.3 mg/dL, found in routine labs. The patient received immunotherapy with Nivolumab every four weeks. Urinalysis revealed no active sediment and renal ultrasound remarkable for solid mass in the left kidney, consistent with previous imaging of his RCC. The patient was diagnosed with Nivolumab-induced immune tubulointerstitial nephritis. At the time of presentation, the immunosuppression was placed on hold, and he was started on steroids. His kidney function gradually improved to serum creatinine of 1.3 mg/dL, with the withdrawal of Nivolumab and initiation of steroid therapy.

Discussion: In this case, we highlight an instance of Nivolumab-induced AKI, which poses a unique diagnostic and management challenge to clinicians due to lack of clinical awareness in the account of the rarity of such immune-related side effects. With the rise in the use of new novel biologic agents, a multidisciplinary approach is essential so that clinicians can make a timely diagnosis when there is a high suspicion. Prompt discontinuation and early steroid therapy institution is crucial in management and can prevent further kidney injury or potential chronic kidney disease.

PUB071
Severe ESA Resistance Reversed by Cincalcet in a Hemodialysis Patient with Sickle Cell Anemia
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Introduction: Hematologic diseases such as sickle cell disease (SCD) complicate anemia of end-stage renal disease (ESRD). Hyperparathyroidism is another etiology of ESA resistance that can cause irreversible bone marrow fibrosis. We present a case of severe ESA resistance in a SCD patient on hemodialysis (HD) that dramatically improved with cinacalcet.

Case Description: The patient is a 28 year old Black man with SCD and ESRD from FSGS on thrice weekly HD. His anemia had been treated with hydroxyurea and high dose subcutaneous Aranesp (400 mg every 2 weeks) with a mean hemoglobin (Hgb) of 6.4 (1.4) mg/dL over several years. He developed worsening hyperparathyroidism on phosphatase binders and vitamin D. Despite stable Aranesp doses, Hgb decreased until a blood transfusion was needed. Aranesp was increased to 500 mg every 2 weeks with some increase in Hgb. After starting cinacalcet, parathyroid hormone (PTH) decreased (1390 to 593 pg/mL), and Hgb further increased (8.2 to 11.2 mg/dL). Intermittent nonadherence to cinacalcet led to PTH variability until hospital admissions for sickle cell crisis and then COVID-19. Afterwards, PTH was more consistently suppressed. Following day 500, supplemental Epogen was given in addition to Aranesp, but Hgb increased only when PTH was most suppressed. During the first year on cinacalcet, there was a strong inverse correlation between Hgb and PTH (r=0.67, p=0.01). Figure 1 shows the Hgb, phosphorus, and PTH (divided by 150 to simplify y-axis) where Hgb peaks correspond to PTH nadirs. We demonstrate a case of severe anemia from both ESRD and SCD where Hgb dramatically improved with cinacalcet. We acknowledge that Aranesp increases preceded the initial Hgb rise, but Hgb peaks following PTH suppression exceeded any prior levels. These Hgb peaks were reproducible and sustained whenever PTH suppression was achieved. This case demonstrates that some hyperparathyroidism-related ESA resistance may be reversible and supports how important control of bone mineral disease is in specific populations of HD patients that are susceptible to severe anemia.

Background: We present a case of severe ESA resistance in a hemodialysis patient with sickle cell disease. The patient presented with acute kidney injury secondary to acute kidney injury, arterionephrosclerosis, and cholesterol emboli. Despite medical management, the patient’s renal function did not recover.

Discussion: Our patient was a 69-year-old female with past medical history of chronic kidney disease stage 3, diabetes mellitus, hypertension, and heart failure with ejection fraction 40-45%, coronary artery disease, and chronic obstructive pulmonary disease who presented with progressive dyspnea and lower extremity edema for several months. Two months prior to this admission she had undergone coronary angiography. Her initial creatinine was 1.28 mg/dL. Over the next two months her creatinine up trended to 2.93 mg/dL. The inciting factor was initially attributed to acute kidney injury secondary to over diuresis. On examination the patient looked euvoiclim but continued to have dyspnea and diuresis. Right heart catheterization was performed to better assess volume status which demonstrated normal filling pressures. Laboratory results were notable for persistent eosinophilia. In the context of recent contrast, rising eosinophilia, and normal filling pressures a renal biopsy was performed which demonstrated acute tubular injury, arterionephrosclerosis, and cholesterol emboli. Despite medical management, the patient’s renal function did not recover.

Discussion: Our patient’s initial presentation was concerning for decompensated heart failure with a possible cardioaortic insult. Post-diuresis instead of having improvement in her dyspnea and acute kidney injury, she continued to decompensate. Further complicating her presentation was recent contrast exposure for coronary angiography and rising eosinophilia. Biopsy ultimately showed cholesterol emboli that most likely dislodged post catheterization and caused acute tubular injury. The teaching point of our case is that renal injury irrespective of coronary angiography timing in patients with preexisting cardiac and kidney disease non-responsive to medical therapy.

PUB072
Addition of Roxadustat to Erythropoiesis-Stimulating Agent (ESA) Effectively Corrects ESA-Hyporesponsive Anemia in Peritoneal Dialysis Patients
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Background: Erythropoiesis-stimulating agent (ESA) hyporesponsiveness is an important cause for the undertreatment of anemia. This study aimed to investigate the effectiveness and safety of adding HIF-PHI (roxadustat) to ESA for the treatment of ESA-hyporesponsive anemia in Peritoneal Dialysis (PD) patients.

Methods: This was a single-center prospective-designed study in PD patients of Huashan Hospital, Fudan University. Patients with ESA-hyporesponsive anemia were enrolled from January 2020 to April 2020 with a 24-week follow-up period. Patients were added a new roxadustat at a starting dose of 50 or 100 mg thrice weekly without changing the ESA dose. Roxadustat and ESA dose adjustments were made as needed to maintain Hb levels within 11.0–13.0 g/dL. Efficacy outcomes and safety were assessed.

Results: A total of nine patients were recruited in the study. Both the cumulative responsive rate and the maintenance rate of patients with Hb<11 g/dL were 100%. Six out of nine patients had ESA dose reduced from 15,000 IU/week or more to 7000 IU/week or less at week 24. No drug-related severe adverse event was reported in this study.

Conclusions: The present study showed that the addition of roxadustat not only overcome the ERA correction in patients who were resistant to ESA, but also reduced the dose of ESA.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
PUB073

Hypercalcemia Secondary to Silicon Injections (Granulomatous Disease): Case Report

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Introduction: Hypercalcemia is a relatively common clinical problem. Among all the causes of hypercalcemia, primary hyperparathyroidism and malignancy are most common. Other less common causes include granulomatous diseases (tuberculosis and sarcoidosis), milkalkali syndrome, immobility, medications and familial hypocalciuric hypercalcemia. We have seen a case of hypercalcemia secondary to silicon injections leading to granulomatous inflammation.

Case Description: 39 y/o F with a history of Sjogren’s disease (+ ANA 1:80 cytoplasmic, 1:2560 speckled, + SSA/SSB + sicca symptoms), recurrent hypercalcemia, malnutrition, history of silicone injections (gluteal), at age 19, who presented to the hospital with facial swelling and found to have hypercalcemia (calcium 1.17, ionized calcium 1.89, serum albumin 2.3). On examination she had severe soft tissue changes in her bilateral legs, ankles, buttokcs and hips. Initial differential was malignancy, primary hyperparathyroidism and soft tissue tumor. Work up consistent with elevated 1,25-Vit D(280), ACE (77; nml 9-67), PTHrP (11.3; nml 0-3.4) and PTH was found to be appropriately suppressed (<6.3; nml 15.8-88). CT scan revealed marked edema gluteal region bilaterally, pelvic wall, perineum and proximal thighs due to foreign body granulomatous/silicone injections. There was no evidence of malignancy on CT scans. She had no clinical signs of sarcoidosis. She has been treated with IVF, pamidronate, and calcitonin, with minimal improvement of her calcium levels. She continues to have recurrent hypercalcemia requiring steroids and repeat treatment with pamidronate, despite extensive excisional debridement of silicone implants.

Discussion: Our patient diagnosed with the granulomatous disorder secondary to silicon injections as the etiology of hypercalcemia. This is supported by her low parathyroid hormone (PTH) level and high (1,25) dihydroxy vitamin D level. Her Skin and soft tissue fragments from debridement/excision showed foreign body (silicone) granulomas, associated scarring and dystrophic calcification. Cosmetic filler injections are known to cause several acute and chronic effects, including local inflammation, nodule formation, and granulomatous reaction. Treatment includes steroids, bispophosphonates, and the removal of implants. Hypercalcemia may persist, and long-standing low dose steroid recommended to maintain calcium and kidney function.

PUB074

Lack of Testing, Urgency to Treat, Consensus, and Concrete Guidelines All Contribute to Subpar Management of Secondary Hyperparathyroidism and Vitamin D Insufficiency for Non-Dialysis Patients with CKD


Background: During October and November 2020, we conducted an independent, retrospective patient chart audit of 1,030 non-dialysis patients with CKD (gGFR<60) who were most recently seen by their nephrologist (n=183). The purpose of this study was to understand the real world patient presentation and treatment priorities for non-dialysis CKD patients as it pertains to the management of CKD-MBD.

Methods: Using a HIPAA-compliant, online chart audit tool, nephrologists submitted de-identified clinical and non-clinical demographic information beginning at the time of patient referral and concluding with details from the most recent visit. These data were then merged with the physician demographic profile and attitudinal responses. The full data set was analyzed in SPSS.

Results: When asked about their top interest in nephrology, only 6% selected bone and mineral metabolism (SHPT); respondents were most interested in glomerular diseases, AKI, and diabetic kidney disease. At the time of first referral, 38% of patients had a 25-D level in their chart and 36% had an iPTH level. At the most recent visit, only slightly more than half of the patients had at least one measure for 25-D and iPTH. Among patients treated with active vitamin D, 57% (57%) had more than a 25-D level and 7% had a level of at least 10.0ng/mL at last measure. Importantly, among patients currently prescribed AVD, 31% did not have a iPTH test in the past 12 months. Among treated patients with a iPTH test, 19% had a level >30pg/mL. Unlike the use of iPTH, which increases as renal function declines, treatment with nutritional vitamin D (NVD) is more consistent across stages, with 46% of patients being treated; at referral, more than one-in-five are already on NVD (vs. just 2% for AVD). Similar to iPTH testing patterns, there are gaps in follow-up testing. Further, treatment patterns reveal that NVD is often added to the AVD regimen instead of a switch, reasoning in about half of the AVD-treated patients also on NVD. Less than 10% of NVD-treated patients achieve a 25-D level of 50ng/mL, despite that, 28% have iPTH levels >100.

Conclusions: Improved monitoring of 25-D and iPTH among CKD-ND patients could lead to better outcomes.

PUB075

Use of Alkaline Phosphatase as a Bone Marker in Patients on Hemodialysis

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Background: Some patients on hemodialysis may suffer from high turnover bone disease despite having levels of parathormone (PTH) within the targets set by KDIGO. Recent international guidelines suggest the use of other bone markers, such as serum total and bone-specific alkaline phosphatase (TALP and BALP respectively). The caveat of using TALP to assess bone turnover status is that other conditions, such as hepatic cholestasis, also cause increases in BALP. We can, however, use it as an alternative to BALP as long as gamma-glutamyl-transferase (GGT) is normal. Though it would generally be expected that PTH and TALP move in the same direction with changes in bone turnover, these two markers can sometimes evolve in opposite directions. Our study aimed to evaluate the correlation between PTH, TALP and BALP.

Methods: Cross sectional study including all patients on hemodialysis at the Hôpital Maisonneuve-Rosemont from May 9, 2019 to June 7, 2019 (N=264 patients). We measured PTH, TALP and BALP in these patients and correlation coefficients were recorded. Regression analyses were performed for multiple potential confounding factors.

Results: The correlation between PTH and TALP was found to be positive and moderate (Rho 0.36; p-value < 0.0001). It was not statistically significant in patients having high GGT levels (above 60 IU/L) and was stronger in patients with normal GGT (Rho 0.40; p-value < 0.0001). The correlation between PTH and BALP was also positive and moderate, but stronger than with TALP (Rho 0.43; p-value <0.0001) and statistically significant even in patients having high GGT levels. The correlation between TALP and BALP was positive, strong and statistically significant (Rho 0.36; p-value <0.0001). It was stronger when GGT levels were normal compared to patients with high GGT levels (Rho 0.94 and Rho 0.71 respectively).

Conclusions: There is a positive correlation between PTH and TALP but it is only moderate. It is thus important to take into consideration TALP in patients with normal GGT levels when evaluating the bone status of patients on hemodialysis.

Correlation coefficients for all patients and stratified by GGT level

PUB076

Intravenous Paricalcitol Treatment in Chinese Hemodialysis Patients: A Real-World Database Analysis

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Background: The aim of this analysis based on the real-world database was to observe the effect of paricalcitol on blood calcium and phosphorus and the safety profile in Chinese hemodialysis patients with secondary hyperparathyroidism under routine clinical practice.

Methods: A total of 668 Chinese hemodialysis patients from 104 dialysis centers between 2015 and 2019 were included. Intact parathyroid hormone (iPTH), total serum calcium (Ca), phosphate (P), dosage of paricalcitol (Zemplar®) were analyzed via retrospective analysis of the database during the treatment.

Results: Patients were divided into five groups according to the duration of follow-up. Median iPTH levels decreased from 1183 pg/mL at baseline to 676 pg/mL at the final visit, or 30.88% (p < 0.0001). Serum Ca levels shown significantly increased just in the group of month 12–24 (P=0.0479). The incidence of hypercalcemia for three consecutive laboratory draws was significantly lower than the incidence of hypercalcemia for two consecutive laboratory draws in all groups (0.5-3 months 0.49% vs 2.96%, respectively,

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3-6 months 0.49% vs 4.88%, 6-12 months 4.00% vs 8.00%, 12-24 months 4.00% vs 20.00% and 24-48 months 2.10% vs 5.99%, respectively. Subgroup analysis of patients with hyperphosphatemia showed a rapid phosphate reduction, within the first few weeks, along with the reduction in the iPTH level.

Conclusions: This is the first national retrospective real-world observational study since intravenous paricalcitol is available in China since 2014. This study adds valuable information to real-world data investigating the use of paricalcitol in Chinese hemodialysis patients and demonstrated the use of paricalcitol as an effective and well-tolerated treatment for the control of PTH during its use in routine practice. The occurrence of hypercalcemia is mostly transient, followed by continuous treatment, the blood calcium level tends to be stabilized, and the blood phosphorus level will be improved with the control of PTH.

PUB077
Paricalcitol in Hemodialysis Patients with Secondary Hyperparathyroidism: A Long-Term Case Report
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Introduction: A case analysis of a HD patient with SHPT was performed, who was in paricalcitol treatment for 72 months, to provide a reference for SHPT management.

Case Description: A 67-year-old female HD patient had calcitriol 0.25 ug qd since 2014. On April 2015, biochemical indexes were Ca 2.02 mmol/L, P 2.1 mmol/L, iPTH 810.1 pg/mL, ALP 88 U/L, without significant abnormality in Parathyroid ultrasonography. While Corony CT showed high-density calcified plaque in the left anterior descending branch, with a calcium score of 39. Then, she discontinued calcitriol and initiated Paricalcitol (Zemplar®) treatment (Detailed treatment regimen and indexes variations in Figure 1). On Month 24, iPTH level decreased to 176 pg/ml (78%), and the left anterior descending artery calcium Agatston score was 51. During Month 24-48, iPTH were 150-500 pg/mL, with stable Ca and P levels in normal range. On Month 72, the left anterior descending calcium Agatston score was 115 and a total calcium score of 147 (CT Images in Figure 2).

Discussion: Paricalcitol can selectively activate VDR especially in parathyroid, to correct the CKD-MBD and prevent cardiovascular events. In this long-term case, we have seen its efficacy and safety in SHPT treatment, especially in controlling the risk of vascular calcification. There is still a lack of data on the clinical application of paricalcitol for long-term use in China. Further studies are needed to confirm its benefit, and to explore best dosage for preventing vascular calcification in dialysis patients.

PUB078
A Missing Key or Faulty Lock: Use of an Alternative Vitamin D Analog Opens the Door to Success
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Introduction: Secondary hyperparathyroidism is a complication of chronic kidney disease and characterized by high FGF-23 with low levels of 1,25-(OH)2-vitamin D due to low renal 1α-hydroxylase activity. Doxercalciferol requires 25-hydroxylation by the liver, a step preserved in end-stage kidney disease (ESKD), but may be subject to genetic polymorphisms that determine responsiveness. We present a case of secondary hyperparathyroidism resistant to high dose doxercalciferol but responsive to calcitriol.

Case Description: A 76-year-old man with ESKD due to diabetes on thrice-weekly hemodialysis with uncontrolled secondary hyperparathyroidism (intact parathyroid hormone (iPTH) 1348 pg/mL) was started on a calcium-based phosphate binder and doxercalciferol 1 mcg IV three times a week. Doxercalciferol was titrated to 20 mcg three times a week, an equivalent calcitriol dose of 19 mcg/week, but his secondary hyperparathyroidism remained poorly controlled (iPTH 752 pg/mL, corrected calcium (cCa) 8.0 mg/dL, phosphorus (P) 5.1 mg/dL). He had normal liver function and did not take CYP3A4 inhibitors. He was changed to calcitriol 0.5 mcg daily with dramatic improvement over three months (iPTH 247 pg/mL, cCa 9.2 mg/dL, P 3.3 mg/dL).

Discussion: We highlight the use of an unusually high dose of doxercalciferol (60 mcg per week) resulting in suboptimal iPTH and calcium response. This dose is significantly higher than the annual mean IV doxercalciferol dose of 112 mcg per patient (~2 mcg per week). Our patient had a rapid reduction in iPTH and normalization of cCa using a relatively low dose of calcitriol. Unlike calcitriol, doxercalciferol lacks a 25-OH group requiring activation by hepatic 25-hydroxylase. A deficiency, or loss of function in this key enzyme, is a rare polymorphism seen in vitamin D dependent rickets type 1B, usually treated with 25-OH-vitamin D, but needs 1α,25-(OH)2-vitamin D in ESKD. Alternatively, genetic variation of the vitamin D receptor-ligand binding domain may reduce its affinity for some vitamin D analogs. Clinicians should suspect potential polymorphisms at fault when high doses of vitamin D analog are used with inappropriate response. We recommend switching vitamin D analogs and consider genetic testing. Characterizing vitamin D receptor protein polymorphisms may influence prescribing practices of vitamin D analogs in the future.

PUB079
Persistent Severe Hyperparathyroidism After Parathyroidectomy
Tammy Yu, Jie Tang, Brown University Warren Alpert Medical School, Providence, RI.

Introduction: Parathyroidectomy is the definitive treatment for secondary hyperparathyroidism (SHPT) refractory to medical management. We report a case of persistent severe hyperparathyroidism after subtotal parathyroidectomy in a hemodialysis patient.

Case Description: A 35-year-old male with ESRD on HD due to idiopathic membranous nephropathy presented with progressive fatigue and bone pain. PTH was 3709 pg/mL, Phos 9.7 mg/dL, Ca 10 mg/dL, and ALKP 919 IU/L, in the setting of noncompliance with his medications, including cinacalcet, calcitriol, and sevelamer. He was transitioned to IV etelcalcetide given at HD, but had poor response, with PTH levels between 2000-4000. After discussion, he opted for parathyroidectomy. Preoperative
subtype of the Tio. A case description of a patient with End Stage Renal Disease (ESRD) & on hemodialysis (HD) whose FGF-23 remained elevated despite normalisation of phosphorus (Phos) levels after surgical excision of tumor, raising a question if there are other yet unidentified tumor associated factors that might be involved in Phos homeostasis. Based on the FGF-23 response in our patient, we also hypothesize that FGF-23 might not be a useful tumor marker in ESRD patients.

PUB082
Normocalcemic Hyperparathyroidism in Calcium Kidney Stone Formers
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Introduction: Primary hyperparathyroidism is a strong risk factor for calcium kidney stone (CKS) formation. However, the kidney stone effect from normocalcemic hyperparathyroidism have not been described. Here we present a case series of six recurrent CKS formers who had elevated plasma parathyrin hormone levels with normal serum calcium, concentration. All of them underwent nuclear imaging of the parathyroid gland, which did not show features consistent with parathyroid adenoma and underwent subsequent resections of the adenoma. We compared pre- and post-operative 24-hour urine calcium (UC) and phosphorus (UP) standardized by urine creatinine, as well as changes in kidney stone burden assessed 2-12 months after the surgery. All patients included in this report were instructed to maintain their diet before and after the surgery.

Case Description: Of these six stone formers, three were men, and the mean age was 60 years. All had vitamin D deficiency with normal serum 1,25-(OH)2-vitamin D. Two had hypertension. Two others had dyslipidemia. Of the three who had DEXA scans, one had all osteopenia. Mean serum calcium was 9.8 mg/dl, mean serum phosphorus was 3.0 mg/dl. Five had baseline 24-hour UC >240 mg (median 309 mg). One had normal 24-hour UC (186 mg). 24-hour UP ranged from 663 mg to 1672 mg. None of them were prescribed with thiazide diuretics, calcium containing supplements or medications that could affect phosphorus absorption during the study period. After partial parathyroidectomy, mean serum calcium reduced by 0.75 mg/dl, mean serum phosphorus increased by 0.1 mg/dl, and neither serum 25-(OH)-vitamin D nor 1,25-(OH)2-vitamin D changed significantly (mean, -0.8 ng/ml, +0.7 pg/ml, respectively). For the urine studies, two had increases in UC (mean 61 mg, 18%), four had reductions in UC (mean -23 mg, 9%). One had an increase in UP (349 mg, 53%), five had reductions in UP (mean -244 mg, -19%). Of the five patients who had kidney ultrasound performed before and 2-12 months after the surgery, four had increases in the post-operative stone burden (mean +43%), one had a 100% reduction.

Conclusion: In this small case series, normocalcemic hyperparathyroidism did not appear to have a consistent effect on the risk of calcium kidney stone formation.

PUB083
Misregulation of Interstitial Matrix Fiber Patterning in a Model of Stromal Cell Abnormalities
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Background: Murine kidney interstitial extracellular matrix (ECM) is a network of proteins and glycosaminoglycans outside cells. The ECM forms intricately patterned fibers in the developing kidney capsule, vertically aligned in the cortex, and surrounding the medullary rays. Forkhead box D1 (Fod1)1 cells synthesize interstitial matrix and are required for kidney stromal cell patterning of the nephron; however, the role of Fod1 in interstitial ECM fiber patterning has not been investigated.

Methods: Murine embryonic day (Ej)18.5 Fod1 knockout (Fod1-/-) kidneys were decellularized with sodium dodecyl sulfate, fixed and stained for ECM proteins, and rendered in 3D.

Results: Vertical fibers were abnormally, perpendicularly aligned relative to the branching nephron in Fod1-/- kidneys (open arrow), suggesting Fod1 is important for stromal cell orientation of interstitial ECM (Figure 1). However, the organization of capsule and fibers around the medullary ray sheath was maintained when compared to Fod1+/- controls.

Conclusions: Kidney interstitial ECM dramatically changes with development. Abnormalities in the vertical fibers in the Fod1-/- mouse correlate with loss of the nephrogenic zone, suggesting the fibers are involved in nephron morphology development.

Funding: Other NIH Support - 1DP2AT009833-01 to SC
Figure 1: Foxd1 knockout alters vertical fiber orientation, but capsular and medullary ray sheath fibers were maintained. (A-A') Control kidneys showed vertical fibers (closed arrow) (green = COL26A1) aligned parallel to the developing nephron (FREM2 = blue, WGA = red). (B-B') In the Foxd1\(^-\) kidney, the vertical fibers (closed arrow) were present, but some vertical fibers were abnormally perpendicular to the nephron (open arrow). (C-F) POSTN (green) capsule fibers (arrowhead, C-D) and medullary ray sheath fibers (*, E-F) appear retained in the Foxd1\(^-\) kidney. Scale bar = 100 \(\mu\)m. 25x confocal z-stacks 590 \(\times\) 590 \(\times\) 171 \(\mu\)m (A-B'), 57 \(\mu\)m (C-F).

PUB084

Adipose-Derived Regenerative Cells Treatment of Injured Kidney Organoids

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Background: Adipose derived regenerative cells are a heterogeneous cell population that include mesenchymal stem cells (ADRCs) and are derived from adipose tissue. Previous studies showed that ADRCs have beneficial effects of an anti-inflammatory activity, an anti-inflammatory activity, and an anti-apoptotic activity. Reactive oxygen species (ROS), inflammation, and apoptosis play a deleterious role in injured kidney repair. Therefore, we hypothesis that ADRCs will aid in the repair of the injured kidney.

Methods: Kidney organoids were assigned into four groups including non-injury (control), injury, ADRCs-treated in non-injury and ADRCs-treated in injury groups. Injured kidney organoids were induced by exposure to 10 \(\mu\)M hydrogen peroxide for 60 minutes.

Results: Kidney organoids in this study, ADRCs-treated injured kidney organoids had significantly larger diameter than injured kidney organoids (p=0.014).

Conclusions: ADRCs showed a positive effect by increasing or maintaining the diameter size of organoids. ADRCs show promise as a therapy of injured kidney organoids.

Funding: Government Support - Non-U.S.

Light microscope: images of control and injury rat kidney organoids after non-treating and treating with ADRCs (40x magnification).

PUB085

Urine-Derived Stem Cells Attenuate Renal Inflammation and Fibrosis After Renal Ischemia Reperfusion

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Background: After renal IRI, regeneration and recovery of the renal tubular cell occurs. However, if the renal repair process is maladaptive, it progresses to renal fibrosis. The role of stem cells in kidney regeneration or fibrosis has not been fully elucidated. We evaluated the urine driven stem cells (UDSC) for renal inflammation and fibrosis after renal ischemia reperfusion (IR).

Methods: 10 week old male male mice were used. sham, sham with adipose derived stem cells (ADRCs), IR, IR with UDSC, IR with ADSC. UDSC and ADSC were infused 1 times via tail vain 7 day After renal IR. Urine NGAL/creatinine(Cr) were checked. The kidneys were harvested at day 14 day. for. in vivo fibrosis model, HK2 cell were treated with TGF beta. co-culture of UDSC and ADSC were performed. Molecular and histologic study were performed.

Results: Urinary NGAL/Cr were significantly increased in IR mice after 14 day IR, compared to sham mice. Urinary NGAL/Cr significantly decreased in UDSC treated IR mice, compared to IR and ADSC treated IR mice. we confirmed UDSC migrate into renal tubular area after 2 weeks renal IRI. In HK2 and PAS stain, renal tubulo interstitial injury were significantly decreased in UDSC treated IR mice, compared to IR and ADSC treated IR mice. in masson trichrom stain, renal fibrosis area were significantly decreased in UDSC treated IR mice, compared to IR and ADSC treated IR mice. The expression of MCP-1, osteopontine, TGF beta, alpha SMA, collagen IV, and F4/80 positive cellswere significantly decreased in UDSC treated IR mice, compared to IR and ADSC treated IR mice. in vitro, alpha SMA, collagen IV, smad 2/3 were significantly increased in TGF beta treated HK2 cells. co-culture of UDSC decreased the alpha SMA, collagen IV, smad 2/3 in TGF beta treated HK2 cells. however, co-culture of ADRC did not decreased the alpha SMA, collagen IV, smad 2/3 in TGF beta treated HK2 cells.

Conclusions: UDSC ameliorate renal inflammation and fibrosis after renal IR.

PUB086

Effects of Açai on the Inflammatory Response of NLRP3 in Experimental Diabetes Mellitus

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Background: Inflammatory factors associated with innate immunity, such as Nod-like receptors, constituents of the NLRP3 inflammasome complex has been linked to the development and progression of diabetic nephropathy. Recent research in our Laboratory showed that açai extract (EA, Euterpe oleracea), a tropical fruit from Amazon with high antioxidant capacity, rich in polyphenols, exhibited also an anti-inflammatory activity, through the modulation of NF-kB/Nrf-2 system in a diabetes mellitus (DM) model, in cultured cells. The aim of the present study was to analyze the effects of EA on the inflammatory response of NLRP3 in experimental DM.

Methods: Human immortalized mesangial cells (HMIC) were grown in DMEM 10% FBS according to the groups: normal glucose (NG, 6.7 mmol/L), high glucose (HG, 30 mmol/L) or mannitol (osmotic control). HMIC in HG medium were treated with EA (500, 100 or 50 \(\mu\)g/mL). Cell viability and proliferation were determined by MTT after 72 hours and protein content of NLRP3 by Western Blot. In male adult Wistar rats DM was induced by streptozotocin (60mg/kg, i.v); control rats (CTR) received the drug vehicle. Both groups were treated with EA 200mg/kg BW, diluted in water, via gavage.
for 8 weeks. The rats were euthanized and the kidneys stored at -80°C. We analyzed the metabolites and measured nitrite (NO, for nitrosative stress), TBARS (an indirect measure of oxidative stress, OS) and renal function in plasma and urine. The results were described as mean ± SE, p < 0.05.

Results: Viability was 100% in all HMC groups; there was a significant increase in cell proliferation at 24 hours post-separation in HGI, which was reductolyzed with EAs. In DM rats EA reduced glycemia and normalized other metabolic parameters, in addition to improving renal function and OS analyzed after 3 days, 4 and 8 weeks of treatment, being the more prolonged treatment, more effective. The histology analysis showed that EA reduced the structural lesion of the renal cortex such as diffuse sclerosis and glycosidic degeneration, in DM animals.

Conclusions: The consumption of EA could contribute to a better control of OS associated with the reduction of inflammatory factors, suggesting the importance of these biomarkers as non-pharmacological adjuvants, to delay the complications in diabetic patients.

Funding: Government Support - Non-U.S.

PUB087

Pentoxyfylline in Diabetic Kidney Disease (VA PTXRS): Protocol for a Pragmatic Randomized Controlled Trial

David J. Leehey,1 Rajiv Agarwal,2 James S. Kaufman,3 Kimberly Carlson,4 Edward Hines Jr.,1 VA Hospital, Hines, IL; Richard L. Routebush VA Medical Center, Indianapolis, IN; VA New York Harbor Healthcare System, New York, NY; Edward Hines Jr VA Hospital Cooperative Studies Program, Hines, IL.

Background: Diabetic kidney disease (DKD) is the most frequent cause of end-stage renal disease (ESRD) in the U.S. and worldwide. Recent experimental and clinical data indicate that the use of phosphodiesterase inhibitor pentoxifylline (PTX) may decrease progression of kidney disease. However, a large-scale randomized clinical trial is needed to determine whether this agent can reduce ESRD and death in patients with DKD.

Methods: VA PTXRS is a pragmatic, randomized, placebo-controlled multicenter Veterans Affairs (VA) Cooperative Study to test the hypothesis that PTX, when added to usual care, leads to a reduction in the time to ESRD or death in type 2 diabetic patients with DKD when compared to usual care plus placebo. The study aims to enroll 2510 patients over a 4-year period with an additional up to 5-year follow-up to generate a total of 646 primary events. The primary objective of this study is to compare the time until ESRD or death (all-cause mortality) between participants randomized to PTX or placebo.

Secondary endpoints will be: (1) Health-related quality of life, (2) Time to doubling of serum creatinine, (3) Incidence of hospitalizations for congestive heart failure (CHF), (4) Incidence of a three-point major adverse cardiovascular events (MACE) composite (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke), (5) Incidence of peripheral vascular disease (PVD), (6) Change in urinary albumin-to-creatine ratio (UACR) from baseline to 6 months, (7) Rate of annual change in estimated glomerular filtration rate (eGFR) during the study period.

Ethics and Dissemination: This study was approved by the VA Central Institutional Review Board (IRB) (ID: 1382143) and will be conducted in compliance with the Declaration of Helsinki and the Guidelines for Good Clinical Practice. The Hines Cooperative Studies Program (CSP) will finalize the study results, which will be published in accordance with the CONSORT statement in a peer-reviewed scientific journal.

Funding: This study is registered with clinicaltrials.gov (Identifier: NCT03625648).

Results: Study enrollment began in November 2019. Through April 2021, 146 patients have been randomized during the ramp-up phase of the study.

Conclusions: PTX is a readily available, safe, and inexpensive medication which might be effectively repurposed to treat DKD.

Funding: Veterans Affairs Support

PUB088

Perceptions of Care Coordination During and After Hospitalization Among Patients Receiving In-Center Hemodialysis

Christian Park,1 Courtney E. Hoge,1 Ann E. Vandenbarg,1 Bernard G. Jaar,2 Janice P. Lea,1 Laura Plantinga,2 Emory University, Atlanta, GA; Johns Hopkins University, Baltimore, MD.

Background: In the United States, 34% of hospital discharges among patients receiving dialysis are followed by a 30-day unplanned readmission. As part of an ongoing pilot study (DialysisConnect), we examined the perceptions of patients receiving hemodialysis (HD) regarding care coordination between providers at the hospital and dialysis clinic.

Methods: Our study targeted all 113 patients receiving in-center HD who were being treated at one of four dialysis clinics and had been hospitalized at a single hospital in Atlanta, Georgia, in the prior 6 months. We administered a one-time survey about their care coordination during their hospitalization episode and used descriptive statistics to summarize the results.

Results: Respondents (n=24, 21% response rate) had an average age of 62 years, 100% were Black, 46% were male, and on average patients had been receiving HD for 4 years; non-respondents were similar in terms of demographics. The percentages of patients who reported that their hospital and dialysis providers knew key information or performed care coordination tasks during and after hospitalization were generally high (Figure). Most patients reported that hospital providers asked about their reason for hospital stay (79%), dialysis schedule (75%), symptoms (75%), current medications (71%), vascular access (67%), nephrologist name (67%), dialysis facility name (54%), and their weight (50%). Only half (48%) brought discharge instructions to the next outpatient HD session.

Conclusions: Most patients (62-91%) perceived that both hospital and dialysis providers were aware of the patient’s clinical situation and had exchanged necessary care coordination information, which suggests an opportunity for more active engaging in care coordination. Future efforts to improve coordination of care between dialysis clinics and hospitals should target not only providers in both settings but also patients and their healthcare surrogates.

Funding: Private Foundation Support

PUB089

Leptin Levels and Appetite Score in Patients on Hemodialysis Using High Flux or Medium-Cut-Off Membranes

Rachel G. Brennen; Lidiana Silva, Silvia A. Carvalho, Silvia R. Manfredi, Renato Watanabe, Maria Eugenia F. Canziani. Universidade Federal de Sao Paulo Escola Paulista de Medicina, Sao Paulo, Brazil.

Background: Chronic kidney disease (CKD) patients on hemodialysis may have a modified appetite due to several factors including a lack of uremic toxins elimination. The use of new dialysis membranes, such as medium cut off (MCO) has been suggested as an alternative to improve the removal of toxins, especially those of medium and high molecular weight. This study aimed to evaluate if the use of the MCO membrane would decrease toxin levels, particularly leptin and improve the appetite of CKD patients on hemodialysis program.

Methods: This is a pre-defined exploratory analysis of a randomized, open study, with a crossover design of 28 weeks of follow-up, which compared the effects of MCO and high flux membranes in 32 CKD patients on hemodialysis. Appetite assessments were performed using the Appetite and Food Satisfaction Questionnaire (AFSQ).

Results: The high-flux group had an appetite score of 3.25 ± 3.62 and 2.80 ± 3.14 at the beginning and at the end of treatment period, respectively, and the MCO group 3.62 ± 3.21 and 3.26 ± 3.28. There were no effects of treatment (p = 0.573), time (p = 0.376) and interaction (p = 0.770) between the high-flux and MCO groups. Leptin levels, at the beginning and at the end of the treatment period, were 2.47 ± 1.57 and 2712.72 ± 1.54 µg/L in the high-flux group and 2.45 ± 1.65 and 2.78 ± 1.62 µg/L in the MCO group, respectively. There was a time effect (p = 0.014), showing an increase in leptin levels in both groups, while treatment (p = 0.771) or interaction (p = 0.218) effects were not observed.

Conclusions: There is no difference between the effects of MCO or high flux membranes on leptin levels or appetite of CKD patients in hemodialysis during the study.

Funding: Private Foundation Support

PUB909

Can Restoration of Heart Rate in ESRD Lower Brain Natriuretic Peptide?

Muhammad M. Mohamed,1 Joel Raja,1 Atif Ibrahim,1 Hafiz Muhammad Ali Raza,1 Barry M. Wall,2 Mihalya B. Tapolyai.1,2 The University of Tennessee Health Science Center, Memphis, TN; VA Memphis Medical Center, Memphis, TN.

Introduction: Brain Natriuretic Peptide (BNP), is predominantly produced by the left ventricular (LV) myocytes. BNP’s production is triggered in response to stretch of the left ventricular myocardium by either increased volume or pressure within the LV cavity. Elevation of BNP is induced by bradyarrhythmia and high degree atrioventricular blocks. We describe a case of a dialysis-dependent patient presenting with complete heart block with an elevated BNP from his baseline and review whether correcting the rhythm problem resulted in correction of his BNP.

Case Description: 98 yr old male with ESRD receiving maintenance hemodialysis presented with shortness of breath and decreased heart rate. He reported shortness of breath on ambulation but denied chest pain, increased swelling, or any other symptoms. Heart rate (HR) was 40 bpm and blood pressure 138/52 mm Hg. Electrocardiogram (ECG) revealed a complete heart block, the chest x-ray did not reveal any acute cardiopulmonary abnormalities. BNP was 2667 pg/ml. Cardiac pacing pads were placed in the Intensive Care Unit while planning for permanent pacemaker placement. He remained hemodynamically stable with HR in the 30s-40s bpm and a dual-chamber pacemaker was placed 24 hr later. Symptoms of dyspnea improved after the procedure with a paced rhythm of 60 bpm. BNP repeated 90 min after the procedure remained suppressed.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

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elevated, 2506 pg/ml. The patient underwent a hemodialysis session with ultrafiltration to his usual estimated dry weight and BNP decreased to 626 pg/ml. Repeat BNP after two more dialysis sessions was 409 pg/ml.

Discussion: Our patient provided a unique opportunity to differentiate between the effects on BNP of an improved cardiac output with restored cardiac rhythm versus changes in intravascular volume. This case demonstrates that this anuric patient’s rhythm restoration was not sufficient to lower BNP values, while ultrafiltration did. Thus, we seem to be able to confirm that, it is solely the volume status that affects BNP value, not the cardiac rhythm or cardiac output.

**PUB091**

Temporal Changes in Physiology During Inpatient Hemodialysis Sessions

Katherine M. Severtz,1,2 Caroline Espersen,1,2 Katherine Curtis,1,2 Elke Platz,1,2 Finnian R. McCausland,1,2 Brigham and Women’s Hospital, Boston, MA; 3Harvard Medical School, Boston, MA.

Background: Patients receiving maintenance hemodialysis (HD) in the United States have an average of 1.6 admissions per year (~700,000 inpatient HD sessions). Little is known about the temporal changes in laboratory values, ECGs, and volume status during HD sessions in these vulnerable patients.

Methods: We performed a prospective cohort study (n=30) of hospitalized HD patients to measure serum laboratory concentrations (electrolytes, blood gases, and ionized calcium levels), ECGs, and ultrasonographic measures of volume status (8-zone lung images for the number of B-lines and internal jugular vein diameter) pre-, one hour into, and post-HD during one inpatient HD session. Ultrasound images were analyzed offline by a core imaging laboratory blinded to clinical information and imaging time point.

Results: The mean age of participants was 62 years. 53% were male and 43% were Black. Serum chemistry levels were dynamic, with the most rapid changes occurring within the first hour for all biomarkers (Figure 1). The median increase in QTc duration on ECG (post-HD QTc minus pre-HD QTc) was 7.5 [5-19] msec. Though the sum of pulmonary B-lines decreased from pre- to post-HD (median decrease: 5 [1-6.5], p=0.02), internal jugular vein diameter did not change (p=0.73).

Conclusions: Among hospitalized patients undergoing HD, there are dynamic changes in serum chemistry parameters, QTc durations, and volume status during their HD sessions. Further research is required to assess how variations in these changes during HD are associated with clinical outcomes and whether HD prescriptions can be tailored to optimize patient care.

**PUB092**

Predictors of Mortality in Hemodialysis Patients in a Large Dialysis Network in India

Suresh Sankarasubbaian1, Venkatraman Ganapathi Subraman1, Mallikarjuna Gowda B. Gowda1, Vikram A. Sonawane1, Kamal D. Shah1, Kaparaboina K. Kumar1, Satyanarayana R. Puvvada1, Mohammad S. Husain1, Nephroplus, Hyderabad, India.

Background: Mortality of HD pts is influenced by age, comorbidity, dialysis, facility and socioeconomic factors. With much unknown regarding MHD mortality in India, we aimed to study the incidence and factors predicting mortality in a large dialysis network in India.

Methods: Consecutive deaths, Jan 1 to March 31, 2021 in a HD network were reviewed for age, gender, HD freq, vascular access, Hb, comorbidity, MHD duration, payer type, educational status, and BMI. An age stratified matched control was used to compare factors using t test and Chi squared test. Binary logistic (uni & mult) was used to identify risk factors associated with death. Significance: 5%. SPSS ver 26 was used

Results: 797(4.8%) deaths occurred among 16516 patients. Table 1 shows pt characteristics. Simple logistic regression: Tier III city, < education, <6 mon HD, public Insurance, ↓ Hb, temporary access, Kt/V <1.2, Alb <3.5, DM, h/o MI and hospitalization <3 mon had significant OR (not shown). Multiple logistic regression showed OR for illiteracy: 2.7 (1.7-4.4), secondary school: 1.7 (1.1-2.5), public insurance 2.3 (1.3-3.8), <1 mon on HD: 2.3 (1.3-4.4), temporary catheter:1.7 (1.3-2.7), Alb <3.5 g%, 2 (1.3-3.8), ↓ Hb 2.9 (1.5-5.9), DKD: 1.5 (1-2), HD in PPP center: 2.1 (1.3-3.2) and hospitalizations <3 mon: 4.7 (3.3-6.6) were significant.

Conclusions: Mortality is high in MHD pts in India and is associated with temp access, ↓ Hb, recent hospitalization, DM, < education & public Insurance status.

<p>| Table 1: Characteristics of patients who died Jan 1 to March 31, 2021 (n=797) |
|----------------------------------|----------------------------------|----------------------------------|----------------------------------|</p>
<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Gender</th>
<th>Education</th>
<th>HD duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean: 62</td>
<td>53% male</td>
<td>43% female</td>
<td>1.6</td>
</tr>
</tbody>
</table>

**PUB093**

A Multicenter, Retrospective, Observational Study of Dialysis Facility-Level Hyperkalemia Burden in China: Rationale and Design of the Visualize-HD Study

Xinju Zhao, Li Zao. Peking University People’s Hospital, Beijing, China.

Background: Hyperkalemia (HK) is a deadly complication in patients (pts) undergoing hemodialysis (HD), accounting for about 1/4th of emergent dialysis treatment. Excess mortality and hospitalization have been associated with HK, especially after the long (2-day) interdialytic interval (LIDI) in thrice-weekly HD pts compared with the short (1-day) intervals. Research on disease burden, risk factors and association of HK and mortality in Chinese pts is scanty.

Methods: This multicenter (300 HD centers), observational study will involve Chinese patients with chronic HD from eastern, central and western parts of China (except Hong Kong, Macao and Taiwan) (Figure 1). HD centers having >100 chronic pts (≥3 months on HD) within 3 years before study initiation, participation willingness, having routine blood collection post LIDI and death records will be included. Pooled data (at HD facility-level) about pts characteristics, HK levels, dialysis prescriptions on facility practice patterns, and death records will be collected retrospectively.

Results: The primary and secondary endpoints will be to examine the association between suspected risk factors and HK-proportions and to describe HK burden respectively. Suspected risk factors include dialysis and sK testing frequency; patient characteristics and medication usage. The constitution ratio of different sK levels after the LIDI will be collected [(0-3.5), (3.5-5), (5-5.5), (5.5-6), (6-6.5), (6.5-7), (>7.0) mmol/L] to calculate the HK (≥5 or 5.5 mmol/L) burden. Meanwhile, we propose to explore crude mortality rates association with HK-proportions. Final results are planned to be released in 2022.

Conclusions: The results of Visualize-HD will generate contemporary evidence to fill epidemiological research gaps of HK in Chinese HD pts and explore risk factors associated with HK disease burden.
Predicted Rebalancing of Sodium in a Sorbent Dialysis System

Background: The Diality Hemodialysis Machine will provide a range of hemodialysis modalities to expand the population of patients that may benefit from hemodialysis. One modality uses a sorbent filter that will accommodate the decentralization of dialysis delivery. Specific Aims: To test sodium ion rebalancing in a 125L circulating volume over 270 minutes using a predicted alkali infusion to maintain a Na concentration of approx. 140 mEq/L.

Methods: A 125 L volume of dialysate was circulated at approx. 400 mL/min & 37 C through a sorbent filter. It is expected that with each pass through the filter the dialysate will be depleted of electrolytes and sodium [Na] and pH will lower. Dialysate is refurbished with an additional infusion of Ca, Mg and K salts. Based upon the predicted [Na] profile another pump will infuse an alkali solution at a varying rate to maintain the final [Na] at approx. 140 mEq/L. The experiment is continued until breakthrough occurs or the infusate outlet reaches 10 ppm of NH4.

Results: The [Na] over 270 mins are depicted in table 1. TP1, the [Na] of the dialysate taken prior to passing through the sorbent filter after leaving a stirring tank containing 150L of dialysate was 137.9 – 143.4 mEq/L. TP2, the [Na] in the fluid upon leaving the filter was an average of 129.5 mEq/L ranging from 119.1 – 136.0 mEq/L. TP3, the [Na] in the dialysate after refurbishing with an alkali solution prior to reentering the stirring tank was an average of 139.3 mEq/L ranging from 138.1 – 143.4 mEq/L.

Conclusions: The results validate the ability to maintain dialysate sodium balance over the dialysis period using a sorbent filter while refurbishing dialysate with a predicted alkali infusion.

Funding: Commercial Support - Diality Inc

Table 1:

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>TP1 [mEq/L]</th>
<th>TP2 [mEq/L]</th>
<th>TP3 [mEq/L]</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>141.4</td>
<td>137.8</td>
<td>139.4</td>
</tr>
<tr>
<td>30</td>
<td>141.9</td>
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</tr>
<tr>
<td>270</td>
<td>141.7</td>
<td>138.5</td>
<td>139.2</td>
</tr>
</tbody>
</table>

Effect of Hemodialysis Rounding Report Availability on Hospitalized ESRD Patient Parameters
Khalid Elharrif,1,2 Nidal Alhosainat,2 Petersen Greti,1 Rathia V. Kulasingam,1 Omar S. Al-Taweel,2 Hania Kassem.1 1Kern Medical Center, Bakersfield, CA; 2The University of Texas Medical Branch at Galveston, Galveston, TX.

Background: Each ESRD patient has a rounding outpatient HD report which is established by the outpatient dialysis unit and contains pertinent information including dry weight (EDW), dialysis prescription, and current medications. In this study, we compared pertinent dialysis-related parameters between 2 groups of patients, those for whom rounding reports were made available and those whose reports were not able to obtain.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: The outpatient hemodialysis facility list was available for all healthcare providers. The facility staff were contacted to obtain the hemodialysis report for the hospitalized patients with ESRD. The relevant parameters were obtained from these reports, which included hemoglobin, phosphorus, and EDW. The aforementioned identifiers were monitored during the course of the hospitalization on all ESRD patients. Patients with available outpatient dialysis reports were restarted on the same outpatient doses of Epogen, phosphate binders, and EDW and was adjusted to the same outpatient HD EDW. For those who do not have HD report available, their regimen was adjusted based on their clinical parameters. The dry weight was adjusted based on their volume status during the hospitalization.

Results: Sixteen ESRD patients admitted to the hospital were included. Upon discharge, those who had outpatient dialysis reports (10 out of 16) had significant improvement of phosphorus levels, better control of the volume status, and no significant changes in hemoglobin. Three out of ten patients developed intradialytic hypotension. The average length of hospitalization was 9 days. Those who didn’t have the outpatient dialysis reports available during their hospitalization (6 out of 16) had no significant changes in phosphorus levels, post-dialysis weights, or hemoglobin. Five out of six patients developed intradialytic hypotension. The average length of stay was 10 days. Table 1.

Conclusions: Patients who have dialysis rounding reports available to guide their treatment while hospitalized have better dialysis-related parameters than those who don’t.

Table 1. Composition of Naturalyte® hemodialysis. In summary, ingestion of Naturalyte® can cause severe mucous membrane effects; this was due to several factors. Acidic solutions often cause an immediate electrolyte imbalance (1) (table 1). Acetic acid ingestion can cause life-threatening toxicity and ulceration. He was treated with intravenous pantoprazole. Follow-up EGD showed no ulceration. Labs showed K 4.1 mmol/L, CO2 20 mmol/L and venous pH 7.4. The patient received calcium infusions scheduled for dialysis. While HD was being set up, he ingested 100ml of the Naturalyte® dialysate concentrate. 3.7 mmol/L and bicarbonate (CO2) of 25 mmol/L. He was admitted to intensive care and received intravenous fluids. He was agitated, but otherwise, his exam was unremarkable. Labs showed potassium (K) of 6.8 mmol/L. The patient was hemodynamically stable and was transferred to the medical floor. Gaoyuan Huang, Carly Bowser, Chibuzo C. Okoye, Elena Frolova, Winston Lee. New York City Health and Hospitals Coney Island, Brooklyn, NY.

Introduction: Naturalyte® is a liquid acetic acid solution—a common dialysate concentrate in the United States.

Case Description: A 43-year-old man with ESRD on hemodialysis (HD) and depression presented with suicidal ideation. Vital signs: BP 235/142, P 99. He was agitated, but otherwise, his exam was unremarkable. Labs showed potassium (K) of 6.8 mmol/L and bicarbonate (CO2) of 25 mmol/L. He was admitted to intensive care and scheduled for dialysis. While HD was being set up, he ingested 100ml of the Naturalyte® dialysate concentrate in attempted self-harm. He vomited immediately. After ingestion labs showed K 4.1 mmol/L, CO2 20 mmol/L, and venous pH 7.4. The patient received calcium infusions and underwent endoscopy (EGD) which revealed grade 2 esophagitis and stomach ulceration. He was treated with intravenous pantoprazole. Follow-up EGD showed healing lesions (fig 1) and the patient did well.

Discussion: To our knowledge, suicide attempt by ingesting dialysate concentrate has not been reported. Naturalyte® has a composition with a pH of 2.4-2.7 and various electrolytes (1) (table 1). Acetic acid ingestion can cause life-threatening toxicity and multiorgan failure (2). In our case ingestion of Naturalyte® did not have any systemic effects; this was due to several factors. Acetic acid solutions often cause an immediate reaction with emesis, which limits absorption (3). Our patient was also treated with early hemodialysis. In summary, ingestion of Naturalyte® can cause severe mucous membrane injury and potentially life-threatening complications.

Composition of Naturalyte®

<table>
<thead>
<tr>
<th>Component</th>
<th>% in Glue %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetic acid</td>
<td>6.4</td>
</tr>
<tr>
<td>NaCl</td>
<td>20.1</td>
</tr>
<tr>
<td>K2PO4</td>
<td>0.7</td>
</tr>
<tr>
<td>CaCl2</td>
<td>0.4</td>
</tr>
<tr>
<td>NH4Cl</td>
<td>0.2</td>
</tr>
<tr>
<td>Desmut</td>
<td>5.3</td>
</tr>
</tbody>
</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Prevalence and Severity of Pruritus in Patients on Maintenance Hemodialysis
Huei Hsun Wen, Kinsuk Chauhan, Wonsuk Oh, Steven G. Coca, Girish N. Nadkarni, Lili Chan. Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Chronic kidney disease associated pruritus (CKD-aP) is a common symptom in patients on in-center-hemodialysis (HD), reported in approximately 40% of patients. Recent clinical trials have identified novel agents for treatment of CKD-aP. Understanding the prevalence of uremic pruritus and its association with other symptoms can aid in identifying patients who would most benefit from this treatment.

Methods: We surveyed patient’s ≥18 years old who had been on HD for ≥30 days, and were receiving HD three times a week at the Mount Sinai Kidney Center. Patients completed surveys asking about the presence of absence of 21 different symptoms during the final 15 minutes of their HD treatments for 4 weeks. We performed multiple correspondence analysis (MCA) to identify associations between symptoms and group individuals with similar symptom profiles.

Results: Of the 97 HD patients who completed the study, 40 (41%) of them reported itching at least once during the study period. There were no significant differences in patient characteristics between patients who did and did not report itching (Figure 1A). Of the patients who reported itching, on average they reported itching on 30±24% of their treatments (Figure 1B). On MCA analyses, symptoms most correlated with itching was dry skin and fatigue (Figure 1C), Spearman correlation coefficient 0.63, P<0.001 for dry skin and 0.37, P<0.001 for fatigue (Figure 1D). Using symptom data only, there was no obvious patient groupings.

Conclusions: CKD-aP affects a large proportion of patients on HD, occurs repeatedly, and clusters with dry skin and fatigue.

Funding: NIDDK Support, Commercial Support - Renal Research Institute

Hyperkalaemia Prevalence, Recurrence, and Treatment in Haemodialysis: A Prospective Multicentre Cohort Study (PRECEDE-K Trial)
Zhaohui Ni,1 Haijiao Jin,1 Renhua Lu,2 Li Zu,3 Weimin Yu,4 Junsheng Wang,4 Rong Wang,5 Yuqing Ren,5 Qiongqiong Yang,5 Jie Xiao,5 Qinghong Zhang,6 Lihong Zhang,7 Xinzhou Zhang,7 Qinkai Chen,7 Chaosheng Chen,7 Guojian Shao,7 Gun Liu,8 Li Yao,9 Hongyan Shang.7 The PRECEDE-K study group 7Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China; 2Peking University People’s Hospital, Beijing, China; 3Shanxi Bethune Hospital, Taiyuan, China; 4Suqian People’s Hospital of Nanjing Drum-Tower Hospital Group, Suqian, China; 5Shandong Provincial Hospital, Jinan, China; 6Yianguan Chines Medical University (Group) General Hospital, Yianguan, China; 7Guangzhou Xinyuan Memorial Hospital, Sun Yat-sen University, Guangzhou, China; 8The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; 9Tahle Hospital of Shiyian City, Shiyian, China; 10The First Hospital of Hebei Medical University, Shijiazhuang, China; 11Shenzhen People’s Hospital, Shenzhen, China; 12The First Affiliated Hospital of Nanchang University, Nanchang, China; 13The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; 14Wenzhou, China; 15Ningbo No.2 Hospital, Ningbo, China; 16The First Hospital of China Medical University, Shenyang, China; 17Guangzhou First People’s Hospital, Guangzhou, China; 18The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; 19AstraZeneca Investment China Co Ltd, Shanghai, China.

Background: Hyperkalaemia (HK) is a potentially life-threatening electrolyte imbalance associated with several adverse clinical outcomes and is common in patients with kidney failure. However, there is no evidence on the occurrence, recurrence, and treatment of HK in patients on haemodialysis (HD) in China.

Methods: The HK Prevalence, Recurrence, and Treatment in Haemodialysis Trial (PRECEDE-K; NCT04799067) is a prospective, multicentre, observational cohort study being conducted across 18 sites in China. Approximately 600 patients with end-stage kidney disease on HD are anticipated to be enrolled and will be followed up with for ≥24 weeks. Patients will be in the long interdialytic interval (LIDI) at enrolment and will receive follow-up care every four weeks in LIDI for pre-dialysis and post-dialysis (at enrolment only) serum potassium measurements. To obtain pre-dialysis serum potassium levels in the short interdialytic interval (SIDI), a follow-up visit in SIDI in Week 1 will be performed. Concomitant medications, blood gas analysis, and biochemistry measurements will be obtained at enrolment and at each follow-up visit.

Results: The primary endpoint is the proportion of patients experiencing any HK (defined as serum potassium > 5.0 mmol/L) at the study enrolment or during a 24-week follow-up. The key secondary endpoint is the proportion of patients experiencing HK recurrence (defined as any HK event after the first HK event) within 1–6 months (if applicable) during a 24-week follow-up, including enrolment assessment.

Conclusions: PRECEDE-K will generate high-quality evidence on the occurrence, recurrence, and treatment pattern of HK in patients on HD in China, and is expected to help inform practice guidance for HK management.

Funding: Commercial Support - AstraZeneca

Dialysis in New Old Patients. Ten Years of Experience
Tatiana Tanasijevich, Daniel Kushner, Alon Antebi, Oleg Sura, Amnon Gil, Jerom Marcussen, Yasir Sanalla, Yosef Shihada, Victoria Sivustinov, Muhammad Abd Elhalim, Victor Frajewicki. Department of Nephrology and Hypertension, Carmel Medical Center, Haifa, Israel.

Background: The most fast growing dialysis population during the last decades is old-age people. Mortality on dialysis patients is still high, especially among old patients. The two year mortality rate for patients who initiate chronic dialysis over the age of 75 may exceed 50%. The risk of Acute Kidney Injury (AKI) also rises with age, while mortality risk increases dramatically in old patients with AKI. The prognosis and benefit of dialysis treatment are still unclear in very old patients. We performed a retrospective analysis of outcomes in all cases of first dialysis performed to very old patients (75 and more years old) during a 10 years period in our center.

Methods: The analysis included all ≥75 years aged patients started hemodialysis in our hospital for every indication (AKI, Acute on Chronic Renal Failure (CRF), End Stage Renal Disease (ESRD)) during the period January 1, 2009 - November 31, 2019. Patients were followed for one year from the first dialysis. The study main end point was one year all-cause mortality.

Results: In this period, 951 patients had their first hemodialysis treatment. Mean age was 82±4.5 years, 55% were male, 55.3% diabetics. Mean Charlson Comorbidity index was 8.3±2.2, Dementia was diagnosed in 11.4% of patients and 34.6% were nursing care dependent. Indications for dialysis were AKI in 16%, Acute on CRF in 64 % and ESRD in 20% of cases. One year mortality was 72.4%, 60% and 26.6% in AKI, Acute on CRF and ESRD respectively. Age, Nursing State, Dementia, AKI, Acute on CRF, and dialysis in a Intensive Care Unit (ICU) were associated with worse prognosis. Multivariate Cox regression models stratified by age, nursing state, AKI, Acute on CRF and ICU showed an OR of 1.3, 1.4, 3.2, 2.5, 2.0 respectively. Neither Charlson Score nor Diabetes mellitus (DM) were not associated with worse prognosis. DM, in opposite, was associated with a trend of better survival although the difference was not statistically significant.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: The outcome of very old patients started with elective maintenance dialysis was much better than in acute unscheduled hemodialysis. The baseline general condition and severity of acute illness seems to be the main prognostic factors for one year mortality. Charlson Score and Diabetes Mellitus did not influence the outcomes in this age group.

PUB103
Vaccination Rates Among Hemodialysis Patients in Nueva Ecija and Aurora Provinces
Rommel P. Bataclan, University of the East Ramon Magsaysay Memorial Medical Center Inc, Quezon City, Philippines.

Background: Infections is one of the most common causes of morbidity and mortality in dialysis patients. Vaccinations have been proven to give protection and reduce incidences of infection. This study investigates vaccination rates among out-patient hemodialysis patients in two provinces in the Philippines.

Methods: A cross-sectional study based on hemodialysis records among patients in 12 hemodialysis centers. Vaccination records from 2018 were checked & verified in all individuals. Descriptive statistics & chi-square analysis among selective clinical characteristics were performed.

Results: A total of 550 hemodialysis patients were included in this study. 67.5% have completed their Hepatitis B vaccination. 59.1% of patients had Tetanus Totoxid 59.1% but only 46.2% had pneumococcal vaccine. Influenza vaccinations were low (2018, 11.1%; 2019, 8.4% and 2020, 8.9%). On further analysis, there are significantly more females who received Tetanus Toxoid (66.0% vs. 50.2%, p<0.01).

Conclusions: There is still a significant percentage of patients who did not receive the recommended vaccinations. Lack of access even prior to last year, financial constraints and misconceptions on vaccines may have played important roles. These have to be addressed in order to increase vaccine confidence among hemodialysis patients.

Conclusions: The outcome of patients started with elective maintenance dialysis was much better than in acute unscheduled hemodialysis. The baseline general condition and severity of acute illness seems to be the main prognostic factors for one year mortality. Charlson Score and Diabetes Mellitus did not influence the outcomes in this age group.

Continuous variables are presented as medians and categorical variables as percentages

Table 1. Vaccination Rates of Hepatitis B, Pneumococal and Tetanus Toxoid

<table>
<thead>
<tr>
<th>Age (n=550)</th>
<th>Hepatitis B (n=371, 67.5%)</th>
<th>p-value</th>
<th>Pneumococal (n=254, 46.2%)</th>
<th>p-value</th>
<th>Tetanus Toxoid (n=325, 59.1%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-39</td>
<td>166 (72)</td>
<td>0.15</td>
<td>66 (151)</td>
<td>0.15</td>
<td>73 (124)</td>
<td>0.15</td>
</tr>
<tr>
<td>40-64</td>
<td>295 (382)</td>
<td>0.15</td>
<td>137 (386)</td>
<td>0.15</td>
<td>69 (386)</td>
<td>0.15</td>
</tr>
<tr>
<td>65 &amp; above</td>
<td>149 (302)</td>
<td>0.15</td>
<td>78 (93)</td>
<td>0.15</td>
<td>55 (93)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Conclusions: The outcome of patients started with elective maintenance dialysis was much better than in acute unscheduled hemodialysis. The baseline general condition and severity of acute illness seems to be the main prognostic factors for one year mortality. Charlson Score and Diabetes Mellitus did not influence the outcomes in this age group.

Continuous variables are presented as medians and categorical variables as percentages

Table 2. Vaccination rates of influenza among Hemodialysis from 2018-2020

| Age (n=550) | Influenza (n=201, 36.4%) | p-value | | | | |
|-------------|---------------------------|---------| | | | |
| 18-39       | 106 (72)                  | 0.15    | | | | |
| 40-64       | 309 (382)                 | 0.15    | | | | |
| 65 & above  | 149 (302)                 | 0.15    | | | | |

PUB104
Impact of Menaquinone 7 Intake on Mortality in Hemodialysis Patients
Mabel Aoum,1,2 Dania Chelala,1,2 Serge S. Finianos,1,2 Hiba Azar,1,2 'Université Saint-Joseph, Beirut, Lebanon; 'Saint-George Hospital, Ajaltoun, Lebanon; 'Hotel Dieu de France Hospital, Beirut, Lebanon.

Background: Vitamin K deficiency was shown to be associated with vascular calcifications in hemodialysis patients. Studies evaluating the impact of vitamin K2 therapy on long-term outcomes are still scarce. This study aims to assess whether treatment with Menaquinone 7 (MK7) reduces mortality in hemodialysis patients.

Methods: This is a two-center longitudinal retrospective study that included all patients on hemodialysis during August 2016 and followed until August 2020. Some patients were treated with MK7. Data collection included vascular calcification score and dp-ucMGP at baseline, mean serum calcium, phosphate, PTH and albumin of the last year of follow-up and mortality at 1, 2, 3, 4 years. Kaplan Meier analysis was used to compare survival between the MK7 group and the control.

Results: A total of 143 patients were included. Table 1 summarizes the main differences between the two groups. Mortality was not significantly different between the two groups (Figure 1), even after adjustment to risk factors such as age, phosphate and coronary artery disease.

Conclusions: This study showed no significant difference in mortality at 4 years in hemodialysis patients treated or not by Menaquinone 7.

Table 1

| Outcome of Migrant Patients Starting Maintenance Hemodialysis in Switzerland

Thomas Fernandez,1,2 Amalie Frandsen,1,3 Pierre-Yves F. Martin,1 Patrick Saudan.1,2 Hopitaux Universitaires Geneve, Geneva, Switzerland; 2Hopital de la Tour, Meyrin, Switzerland; 3Inselspital Universitatsklinik Bern, Bern, Switzerland.

Background: ESRD migrants without permanent resident status is a particularly vulnerable population in regards of chronic renal replacement therapy or kidney transplantation access. Healthcare policies greatly vary between different countries which influence their clinical outcomes. Switzerland grants medical healthcare including renal care to anyone living in the country for more than 3 months.

Methods: In this report, we retrospectively analyzed the characteristics and the outcome of migrants starting dialysis at the University Hospital of Geneva (Switzerland) between January 2000 and December 2019.

Results: 775 patients started hemodialysis during this period. 38 patients (4.9%) were non-permanent residents being either asymptomatic or undocumented. Compared to resident patients, they were significantly younger (42 and 63 years old, respectively) with less male gender (50% and 66%, respectively). The cause of ESRD was more frequently unknown with no difference for diabetes prevalence. Their modified Charlson

Figure 1. Survival of the two groups
comorbidity index was overall lower. Emergency hemodialysis initiation was more frequent and mean MPFR at dialysis start was significantly lower (5 vs 7 ml/min/1.73m²). Most of the migrant patients eventually obtained a stable resident status (24/38, 63 %). Seven were sent back to their home country (7/38, 18 %) and 3 were lost of follow-up (3/38, 8%). Among the 28 migrant patients who stayed in Switzerland, 6 patients died due to causes related to KD and 17 (61%) obtained a kidney transplantation. To account for their characteristic differences, propensity score matching was performed. Time to transplantation after dialysis initiation was significantly delayed for migrants with a median time to transplantation of 60 (43-99) and 25 (12-49) months for eligible migrants and propensity-score matched residents, respectively. Survival censoring for kidney transplantation was overall significantly much higher in migrants compared to resident patients with a 5-year survival rate of 85% and 55%, respectively. When censored for kidney transplantation, survival remained better among migrants compared to matched resident patients (85% and 65% at 5 years, respectively).

Conclusions: In conclusion, ESRD clinical outcomes are excellent when standard care is provided. Aside the ethical issue, previous data from the US suggested that it is economically sustainable.

PUB106
The Cost of the Quanta SC+ Hemodialysis System for Sustained Low-Efficiency Dialysis in the Intensive Care Unit
Thomas W. Ferguson,1 Paul Komenda,1,2 Christos Argyropoulos,1 Seven Oaks General Hospital, Winnipeg, MB, Canada; 1Quanta Dialysis Technologies Ltd, Alcester, United Kingdom; 3University of New Mexico School of Medicine, Albuquerque, NM.

Background: Over 20% of patients in the intensive care unit (ICU) experience acute kidney injury with or without requiring treatment with dialysis. There are several modalities available to provide dialysis in the ICU, including conventional hemodialysis, continuous renal replacement therapy (CRRT) and sustained low-efficiency dialysis (SLED). Recent meta-analyses have found that there is no definitive advantage of either of these modalities with respect to patient outcomes; however, they are associated with different cost and resource requirements. The SC+ Hemodialysis System is a commercially available, portable hemodialysis system that can be operated with minimal training by ICU nurses.

Methods: We described the incremental costs of CRRT, regular 4-hour conventional dialysis provided by specialized hemodialysis nurses, and SLED with the SC+ Hemodialysis System in the ICU. The analysis was performed from the perspective of the US health payer with results presented in 2020 US dollars. We considered costs with respect to the dialysis console, dialysis-related supplies (cartridges, tubing, dialyzers, dialysate, bags, and saline), and nursing-related human resources modeled from a large US based hemodialysis program.

Results: The cost of CRRT assumed that ICU nursing staff would provide the therapy, with consumables costs ranging between $320 and $380 per ICU-day. Dialysis provided with conventional 4-hour therapy in the HD unit ranged between $205 and $245 per day including both incremental nursing and renal technician expenses and consumables. Dialysis provided with the SC+ as 8-hour SLED treatments was estimated to cost between $59 and $85 for consumables and operated by the ICU nursing staff.

Conclusions: SLED treatment with the Quanta SC+ operated by ICU nurses offers significant cost advantages over CRRT and conventional HD treatments with no demonstrable disadvantage to patient funding.

Funding: Commercial Support - Quanta Dialysis Technologies

PUB107
Incident Dialysis Patients in Latin America (LA): An Unpaid Debt
Adrian M. Guinsburg,1 Maria Ines Diaz Bessone,1 Juan Carlos Berbossi,1 Alejandro Kohn Tuli,1 Ana Beatriz L. Barra,2 Eduardo A. Machuca,3 Jesus E. Munoz,4 Leonor E. Briones,5 Maria L. Quintanilla,6 Maria L. Resk,7 Gabriela R. Cannatelli,1 Beatriz P. Schiritzmeyer,4 Jorge M. Caseiro.1 Fresenius Medical Care Latin America, 1Presenius Medical Care LatinAmerica, Rio de Janeiro, Brazil; 2Fresenius Medical Care Brazil, Rio de Janeiro, Brazil; 3Fresenius Medical Care Chile SA, Santiago, Chile; 4Fresenius Medical Care Ecuador, Quito, Ecuador; 5Fresenius Medical Care Peru, Lima, Peru; 6Fresenius Medical Care Argentina SA, Buenos Aires, Argentina; 7Fresenius Medical Care Colombia, Bogota, Colombia; 8Fresenius Medical Care Caricam, Panama, Panama.

Background: Predialysis care in LA is conditioned by uneven accessibility to adequate treatment and odds healthcare systems. Timely initiation, vascular access (VA) creation and anemia and bone disease management are still barriers to overcome. The aim of this study was to compare incident (INC) and prevalent (PRV) dialysis patients outcomes from Fresenius Medical Care Latin America (FMEA) and possible correlations with survival.

Methods: Patients from FME LA (Argentina, Brazil, Chile, Colombia, Ecuador, Peru) incident and prevalent dialysis between 1 Jan and Dec 31, 2020 were included. INC were defined with <90 days since first treatment in life and PRV >90 days. INC accounted during first 90 days then they became PRV. Thus, results and time collected during first 90 days accounted to INC and after that to PRV. Values are expressed as mean ± SD. Means were compared using Student t-test. Kaplan-Meier (KM) and Cox regression models (CM) were created to evaluate survival.

Results: 43,390 patients were included (7,969 INC / 35,421 PRV). Main differences between INC and PRV are shown in table 1. KM showed mean survival time INC 322.4 vs PRV 338.7 days (LogRank p<0.0001). Cox Model showed RR for Diabetes 1.31 / Age 1.03 / Male 1.08 / Hb 0.96 / Ca 1.06 / Alb 0.44 / Creat 0.98 / Graft 1.31 / Cuffed cath 1.48 (vs fistula), all p<0.0001, but INC vs PRV showed no statistical difference after covariables were included.

Conclusions: Alb, Hb, Ca and P were lower in INC than PRV while cather prevalence was considerably higher suggesting late referral, poor clinical management and difficulties in VA creation before dialysis initiation. Survival in INC was markedly inferior than PRV, but this effect vanished when the model was adjusted, suggesting non modifiable (diabetes, age, gender) and modifiable factors (Hb, Ca, P, Alb, Creat and VA) may be driving survival. Efforts to improve the latest should be done in order to ameliorate INC survival in our region

Table 1: Incident / Prevalent patients characteristics

PUB108
Ultrafiltration Accuracy in a Modified Batch Dialysis System

Background: Ultrafiltration accuracy is an important way of improving mortality and morbidity on dialysis. The Diallyt Hemodialysis Machine will provide tight control of ultrafiltration during treatment. Specific Aims: To assess ultrafiltration accuracy during simulated dialysis utilizing a novel modified batch process. In this setup, ultrafiltration was conducted by alternating collection into two-liter reservoirs that contain both dialyseate and ultrafiltrate.

Methods: Two simulated dialysis sessions were conducted utilizing blood flowrates of 100 ml/min, dialysate flowrates of 300 ml/min and ultrafiltration flowrates of 2500 ml/hr. (Table 1) Dialysis and ultrafiltration occur off of a two-liter batch of dialysate. Once two liters of dialysate has been circulated through the dialyzer, the collected ultrafiltrate and spent dialysate are discarded and dialysis switches to a separate two-liter reservoir of dialysate while the first reservoir is drained and filled with fresh dialysate.

Results: The results are provided in Table 1. The average ultrafiltration accuracy was measured by comparing the machine-calculated ultrafiltration volume with the weight of the simulated patient. The mean error represents the average difference between machine and patient during the simulated treatments, while the total error represents the total error after the simulated run was completed.

Conclusions: The initial experiments using a modified batch system show promising ultrafiltration accuracy. Future tests will demonstrate accuracy over a larger range of flowrates, volumes and times.

Funding: Commercial Support - Diallyt Inc

Table 1
Conclusions: With most eligible patients choosing to not participate, the value of patients’ contributions to research needs to be emphasized. We encourage healthcare providers take the time to educate patients on the importance of clinical research.

Funding: Commercial Support - Fresenius Medical Care

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**Figure 1. Recruitment and enrollment flowchart**

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Anemia Status and Root Cause Analysis of Maintenance Hemodialysis

**Anemia Status and Root Cause Analysis of Maintenance Hemodialysis (MHD) Patients in Shaanxi Province**

**Hua Liu.** The First Affiliated Hospital of Xi’an Jiaotong University, Xi’an, China.

**Background:** According to the national nephrology professional medical quality control index (2020 version) and the related quality control index of renal anemia in hemodialysis patients, combined with the Chinese National Renal Data System (CNRDS) system feedback data in 2019, the anemia control rate of MHD patients in Shaanxi Province was analyzed and the root cause analysis was carried out to promote the continuous improvement of the anemia.

**Methods:** Based on CNRDS feedback data, the data of the routine timing test rate, anemia control rate, serum ferritin and transferrin saturation timing test completion rate of MHD patients in Shaanxi Province were analyzed and compared with the national situation. Meanwhile, the anemia compliance rate of different regional in Shaanxi Province was compared.

**Results:** According to the CNRDS statistics in 2019, 54.4% of the patients registered for hemoglobin at least once in 1999; no source was identified. Five cases of transfusion-related septic shock were reported between 1992 and 1999; no source was identified. Ten cases of *S. liquefaciens* blood stream infection and six pyrogenic reactions at a hemodialysis center in 2001 were found to be related to multiple punctures of single-use vials with pooling of preservative-free EpoGen®. In 2017, two cases of bacteremia were reported among nine patients who underwent myocardial perfusion scanning. Bacteria were found in the saline used to reconstitute the radiopharmaceutical. The treatment area including handwashing sinks and water boxes were in good order; no bacteria were identified. Dialysate water cultures were without significant growth. In addition to reviewing catheter care and hand hygiene, we are reviewing proper storage and handling of multidose heparin vials. Water-borne bacteria are a threat to patients receiving maintenance dialysis. Vigilance must be paid to reduce the risk of infection.

**Discussion:** *Serratia* are water dwelling bacteria which infect humans via environmental sources. Five cases of transfusion-related septic shock were reported between 1992 and 1999; no source was identified. Ten cases of *S. liquefaciens* blood stream infection and six pyrogenic reactions at a hemodialysis center in 2001 were found to be related to multiple punctures of single-use vials with pooling of preservative-free EpoGen®. In 2017, two cases of bacteremia were reported among nine patients who underwent myocardial perfusion scanning. Bacteria were found in the saline used to reconstitute the radiopharmaceutical. The treatment area including handwashing sinks and water boxes were in good order; no bacteria were identified. Dialysate water cultures were without significant growth. In addition to reviewing catheter care and hand hygiene, we are reviewing proper storage and handling of multidose heparin vials. Water-borne bacteria are a threat to patients receiving maintenance dialysis. Vigilance must be paid to reduce the risk of infection.

**Conclusion:** Hemodialysis patients who were sitting proximately receiving maintenance dialysis via central catheters developed chills and fever. Cultures grew *E. cloacae*; vancomycin and gentamicin were administered. They were hospitalized; cultures grew *S. liquefaciens*. Both recovered with antibiotics and returned without sequelae. An experienced RN with excellent catheter technique cared for both patients. The only common medication was a multi-dose heparin vial with clear solution. The patients had no relationship outside the facility and neither had evidence of catheter or exit site infection. No other patients had signs of infection.

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Vitamin D Independently Related to Right Ventricular Dysfunction in ESRD Patients on Maintenance Hemodialysis

Firoozeh Farahmand, Saint Louis University, Saint Louis, MO.

Background: Right ventricular (RV) dysfunction is a major cause of death in patients undergoing maintenance hemodialysis (HD) and a major determinant of mortality in pulmonary hypertension that is common in HD patients. There is tremendous amount of data that RV dysfunction is left ventricular function in HD patients, but data on RV dysfunction and its mechanisms in HD patients are scarce. It has been suggested that vitamin D could be involved in the development or progression of heart failure by modulating oxidative stress. We investigated changes in RV function in HD patient and its correlation with vitamin D level.

Methods: In a university affiliated dialysis center, a retrospective cohort of ESRD patients treated with HD for at least 1 month followed in a dialysis unit. Patients without vitamin D assessment, prior myocardial infarctions, heart failure, or prevalent valvular disease were excluded. Subject characteristics were recorded, including age, gender and race. Echocardiography including tissue Doppler imaging (TDI) of the RV was evaluated. PH was defined as an estimated systolic pulmonary artery pressure (PAP) higher than 25 mm Hg using echocardiograms performed by cardiologist.

Results: A total of 77 HD patients were included in the study. The mean age of the patients was 53.7±4.7 years. The mean dialysis vintage was 27±14 months. The mean ejection fraction was 45±7.7%. The prevalence of PH was 53.5%, 59% of patients with PH were female that statistically (p<0.05). 30% of patients had RV dysfunction on echo. 72% of patients with RV dysfunction had a 24hOHDLD level <370ng/ml (p<0.005). A statistical correlation was found between lower vitamin D levels and RV dysfunction. The patients with RV dysfunction were more likely to be female that was statistically (p<0.05). 30% of patients had RV dysfunction on echo. The vitamin D level was lower in patients with RV dysfunction that was statistically (p<0.05). We demonstrate a significant correlation of RV dysfunction among ESRD patients under maintenance HD and it is strong association with suboptimal vitamin D. Further investigations are required to evaluate the beneficial effects of cholecalciferol in ESRD patients with RV dysfunction.

Mortality and Associated Factors in Patients Under Hemodialysis in a Latin American Tertiary Center

Annette G. García Delgado, Jennifer P. Khoury, Nicole De Los Santos, Anthony J. Butterer, Eunice Dina-Battle, Pontificia Universidad Católica Madre y Maestra Facultad de Ciencias de la Salud, Santiago De Los Caballeros, Dominican Republic; Hospital Metropolitano de Santiago, Santiago De Los Caballeros, Dominican Republic.

Background: Risk factors are associated with the prognostic and early diagnosis of chronic renal disease. We evaluated modifiable and non-modifiable factors related to mortality in patients who receive hemodialysis therapy.

Methods: Retrospective cohort study. 124 patients were included in the study. The mean age was 56.29, 71.13% were female, and 55.6% had more than two comorbidities. Diabetes and hypertension were the most common causes of chronic renal disease. Male participants were more likely to die than females. The Charlson index was higher [6 (5 – 7)] in deceased patients than those who did not die [5 (3 – 7)]. Patients with lower hemoglobin and albumin levels were more likely to die. Also, calcium levels [9.05 (8.5 – 9.4)] were higher in deceased patients. 69.23% of patients who died used central venous catheter than those who did not die [5 (3 – 7)]. Patients with lower hemoglobin and albumin levels were more likely to die than females. The Charlson index was higher [6 (5 – 7)] in deceased patients than those who did not die [5 (3 – 7)]. Patients with lower hemoglobin and albumin levels were more likely to die than females. The Charlson index was higher [6 (5 – 7)] in deceased patients than those who did not die [5 (3 – 7)]. Patients with lower hemoglobin and albumin levels were more likely to die than females. The Charlson index was higher [6 (5 – 7)] in deceased patients than those who did not die [5 (3 – 7)]. Patients with lower hemoglobin and albumin levels were more likely to die than females. The Charlson index was higher [6 (5 – 7)] in deceased patients than those who did not die [5 (3 – 7)]. Patients with lower hemoglobin and albumin levels were more likely to die than females. The Charlson index was higher [6 (5 – 7)] in deceased patients than those who did not die [5 (3 – 7)]. Patients with lower hemoglobin and albumin levels were more likely to die than females. The Charlson index was higher [6 (5 – 7)] in deceased patients than those who did not die [5 (3 – 7)]. Patients with lower hemoglobin and albumin levels were more likely to die than females. The Charlson index was higher [6 (5 – 7)] in deceased patients than those who did not die [5 (3 – 7)]. Patients with lower hemoglobin and albumin levels were more likely to die than females. The Charlson index was higher [6 (5 – 7)] in deceased patients than those who did not die [5 (3 – 7)]. Patients with lower hemoglobin and albumin levels were more likely to die than females. The Charlson index was higher [6 (5 – 7)] in deceased patients than those who did not die [5 (3 – 7)]. Patients with lower hemoglobin and albumin levels were more likely to die than females. The Charlson index was higher [6 (5 – 7)] in deceased patients than those who did not die [5 (3 – 7)]. Patients with lower hemoglobin and albumin levels were more likely to die than females. The Charlson index was higher [6 (5 – 7)] in deceased patients than those who did not die [5 (3 – 7)]. Patients with lower hemoglobin and albumin levels were more likely to die than females. The Charlson index was higher [6 (5 – 7)] in deceased patients than those who did not die [5 (3 – 7)]. Patients with lower hemoglobin and albumin levels were more likely to die than females. The Charlson index was higher [6 (5 – 7)] in deceased patients than those who did not die [5 (3 – 7)].

Results: The most common causes of chronic renal disease were excluded. Subject characteristics were recorded, including age, gender and race. Echocardiography including tissue Doppler imaging (TDI) of the RV was evaluated. PH was defined as an estimated systolic pulmonary artery pressure (PAP) higher than 25 mm Hg using echocardiograms performed by cardiologist.

Conclusions: The use of central venous catheters is an important risk of mortality in patients who receive hemodialysis therapy. Other factors associated with mortality in these patients are an elevated Charlson index, low hemoglobin, albumin, and high calcium levels. These results show the importance of an early assessment of the patient and the factors mentioned above.

Case Report of Hemodialysis-Associated Thrombocytopenia

Samah S. Salehman, Mohamedanwar M. Ghandour, Areeca Jawed. Wayne State University, Detroit, MI.

Introduction: Thrombocytopenia associated with hemodialysis is a rare complication that can be witnessed occasionally. Studies, however, showed that dialysis membranes could result in significant thrombocytopenia due to the role they play in activating the complement system. Herein, We present to you a case of polysulfone-dialyzer-induced thrombocytopenia in a patient with a previously normal platelet count.

Case Description: Our patient is a 44-year-old male with a past medical history of uncomplicated liver cirrhosis, who presented with hematemesis. Initial blood work was remarkable for blood urea nitrogen of 24 mg/dL. Creatinine of 2.08 mg/dL. The patient was started on Ceftriaxone and Flagyl for the concern of spontaneous bacterial peritonitis in addition to pantoprazole drip, Octreotide drip, Norepinephrine, and vasopressin for hemodynamic support. Due to worsening kidney function, hemodialysis was initiated on day 18 of hospital admission using the Fresenius Optiflux 180 dialyzer with a synthetic polymer (electron-beam sterilized) membrane. The patient tolerated the first hemodialysis session, the dialyzer was switched from the F180NR to Purema-Polyethersulfone dialyzer that was gamma sterilized. This case of hemodialysis-associated thrombocytopenia in a case of thrombocytopenia demonstrates that polysulfone dialysis membranes can variably affect platelet levels, despite previous evidence indicating that polysulfone membranes do not affect platelet counts.
Case Description: A 56-year-old female with ESKD presented to the outpatient PD clinic with low flow and outflow failure. Four months after laparoscopic catheter insertion, she presented with PD catheter insertion site swelling. She underwent revision of the catheter where a pericatheter hernia at the peritoneal insertion site was found. The sac was sewn to incorporate the cuff, the old catheter was cut and tunneled to a new site. 6 months later, the patient presented with outflow failure and bulge at the catheter insertion site. Abdominal radiograph showed appropriate positioning of the catheter tip in the right lower quadrant. Laparoscopic surgery showed an incisional hernia at the previous peritoneal entrance site and no catheter in the peritoneal cavity. Incision of the bulge resulted in retracted subcutaneous tissue and the tip of the catheter. She appears to have had the hernia pulled out of the abdominal cavity, and the peritoneum had sealed behind it, causing this localized collection. The catheter was removed, the sac was resected, and the fascial defect was repaired. A new PD catheter was inserted on the opposite side.

Discussion: Pericatheter hernia can cause malposition of PD catheters. In this case, we believe the catheter suffered malposition due to the surgical technique employed in the initial surgery where the hernia sac had been sewn to the cuff. A plain posterior-anterior abdomen radiograph may be a useful tool in evaluating PD catheter position. In this case, despite the radiograph showing the tip in “appropriate position”, the PD catheter migrated into the subcutaneous tissue. Other methods of identification for catheter placement like lateral abdominal x-rays, CT scan, or surgical exploration should be considered if catheter mispositioning is suspected.

PUB120
Healthcare Perspective on Home Hemodialysis Use: Barriers and Interventions

Methods: We surveyed the Nephrology team at the University of Virginia (UVA) about their experience with HDH. UVA has approximately 950 dialysis patients among all modalities, with 12 dialysis units located in central Virginia.

Results: Of 274 individuals receiving the survey, 139 responded (50.7%) including 103 nephrologists and 36 fellows. The most common barriers included fear of the unknown (57.2%), lack of patients’ confidence to perform and worry about caring partners (53.4%, 42.1%), lack of education and training (45.2%), and lack of support, fear and lack of interest (42.9%). Inadequate electronic medical record, and insufficient patient/staff education were mentioned. The staff further added inadequate insurance coverage for in-center HDH (45.2%), lack of patients’ confidence to perform in-center HDH (45.2%), and lack of education and training (45.2%). Lack of patients’ confidence to perform and worry about caring partners (53.4%, 42.1%) was the most common barriers.

PUB121
CardioMEMS and Peritoneal Dialysis: Synchronize Data to Provide Patient-Centered Care at Home: A Road to the Future

Introduction: End stage renal disease patients are the highest risk populations for heart failure (HF), an estimated 36% with congestive heart failure at dialysis initiation. CardioMEMS is an FDA-approved wireless pulmonary artery (PA) pressure monitoring device in New York Heart Association (NYHA) class III HF patients hospitalized during the previous year. Here, we present our experience with assessing ultrafiltration (UF) needs during dialysis using CardioMEMS data. There are very few published reports of CardioMEMS in dialysis patients. We believe this is the first to report adjusting PD prescription using CardioMEMS monitoring.

Case Description: A 61 year old female with failing kidney transplant was initially referred to general nephrology clinic for impending dialysis needs. She had extensive cardiac history with ischemic cardiomyopathy, HF with ejection fraction of 25% and NYHA class III cardiac symptoms. CardioMEMS implantation a year prior and being evaluated for combined heart-kidney transplant. She also had symptomatic orthostatic hypotension at baseline. With a coordinated effort between surgery, cardiology and nephrology, she had a laparoscopic PD catheter placement and initiated on PD in hospital. Her clinical course was complicated with pulmonary edema, CMV viremia, acute uncomplicated heart failure and severe symptomatic gastroparesis raising concerns on whether she can continue PD. She was successfully discharged home on PD and home PD regimen adjusted to attain a...
goal PA diastolic pressure of 18-20 mm Hg (Figure 1). Rehospitalizations were prevented and she eventually received a combined heart-kidney transplant 3 months later.

Discussion: Assessment of UF needs in dialysis patients with HF is fraught with multiple limitations leading to frequent rehospitalizations. In our patient, PA diastolic pressure readings from CARDIOMEMS were used as a guide in assessing UF needs and adjusting PD regimen. Our case illustrates that a coordinated multidisciplinary approach can provide patient-centered care at home and improve outcomes.

FIGURE 1: SNAPSHOT OF CHANGES MADE TO PD REGIMEN BASED ON PULMONARY ARTERY DIASTOLIC PRESSURE READINGS

Switched to a 1.25% to 2.5%
Switched to a 1.25% to 2.5%
Switched to a 1.25% to 2.5%
Switched to a 0.25% to 1.25%

PUB122

Development of a Registry for Peritoneal Dialysis at Yokohama City University and Affiliated Hospitals (Yokohama Bay-Shonan PD Registry)

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Background: Patient registry has become increasingly important as a strategy to promote clinical research and to improve the patient care. Yokohama City University Hospital is one of the leading hospitals in Kanagawa Prefecture, a representative and well-known urban area in Japan.

Methods: We started to construct a registry of peritoneal dialysis (PD) at Yokohama City University Hospital and 15 affiliated hospitals (Yokohama Bay-Shonan PD Registry) from the beginning of 2020. The categories of Yokohama Bay-Shonan PD Registry include an information including the age, sex, duration of PD, method of PD (continuous ambulatory PD, intermittent PD, or continuous cycler PD), cause of end stage of kidney disease, prescription of renin-angiotensin system inhibitors (+/-), past history of heart disease (+/-), results of peritoneal function test, onset of new heart disease (+/-), onset of peritonitis (+/-), results of peritonitis function test, onset of new heart disease (+/-), onset of PD-related infection (+/-), and combination of hemodialysis (+/-).

Results: We collect data from each facility once a year. Only data of Yokohama City University Hospital were available for analysis this time, and total of 28 patients were registered at Yokohama City University Hospital. Mean age was 66.7 years old. Eleven patients were affected with PD-related infection, and 3 patients discontinued PD (1 death, 1 pancreas cancer, and 1 PD-related infection).

Conclusions: We continue to collect data from each affiliated hospital and will expand the information recorded in the Yokohama Bay-Shonan PD Registry to find the persistence rate of PD and frequency of cardiovascular events for further analysis.

PUB123

Unusual Pathogen Causing Peritonitis in a Peritoneal Dialysis (PD) Patient

Rula A. Abdulrahman. Stony Brook University, Stony Brook, NY.

Introduction: Pantoea species causes infection in humans and are pathogenic to plants. Pantoea agglomerans are mostly isolated from human and was reported to cause up to 80% polymorph neutrophils. This case describes a PD patient who had cloudy effluent noted and was complaining of abdominal pain, nausea and diarrhea. Vitals signs: temperature 38 C, BP 126/80, PR 91. on exam: tender to palpation in right lower quadrant. A blood culture was obtained. Urine analysis showed 100,000 white blood cells and 100,000 red blood cells per high power field. The urine protein was 75 mg/dL and specific gravity was 1.015. The urine output was 800 ml/day. The patient was prescribed intravenous antibiotics vancomycin and cefepime. The patient was discharged home, Cefipime was continued intraperitoneally. 2 days after discharge, effluent was noted to be cloudy again and the cell count was 2948/µl. At this time decision was made to remove PD catheter for persistent peritonitis. Effluent culture was consistent with PC & PG, susceptible to cefepime. Fungal culture remain negative. PD catheter was removed & Patient was started on hemodialysis. patient was treated with ceftazidime for 2 weeks. infection was treated. patient chose to remain on hemodialysis.

Discussion: Peritonitis is a common and serious complication of PD. It is the major cause of death in around 16% of PD patients. It is reported that Pantoea agglomerans can cause peritonitis. Our patient had peritonitis caused by PC, PG which is a very rare finding. Despite treatment with appropriate antibiotic the symptoms persist and eventually PD catheter was removed, the patient was started on hemodialysis. Pantoea species have been isolated from soil, water, plant, seeds, fruits, and human body fluids. PG, and PC were isolated from infant formula. PC was isolated from dialysate of PD patients and from urine, although pathogenicity remain unknown. In our case the patient had severe peritonitis caused by Pantoea species, the way of transmission is unclear. We recommend further research and examining the dialysate fluid in certain population, aiming that such an infection can be prevented in future.

PUB124

The Effects of Location of Peritoneal Dialysis Training, In-Home vs. In-Center, on Peritoneal Dialysis Patients

Rajeev Chauhan,1 Malliqua Chauhan,2 Renal Associates LLC., Columbus, GA; 2New York Institute of Technology, Old Westbury, NY.

Background: The objective of this study is to investigate the relationship between peritonitis rates and whether peritoneal dialysis (PD) was taught in-center (n=104) or in-home (n=16) for 120 patients in a single center located in Southern Georgia. Preceding studies have assessed the link between peritonitis rates and demographic factors among PD patients. However, there is very limited research that examines the effects of peritoneal dialysis training location on a patient’s chance of developing peritonitis.

Methods: This study is a retrospective analysis for data accumulated over a period of seven years. Subjects were categorized into two groups: one group’s dialysis administrator received peritoneal dialysis training in their homes and the other group’s dialysis administrator was trained in-center. The data collected includes gender, age, peritonitis occurrence, presence of family support to patient, and severity of comorbidities.

The initial analysis was conducted by using a Fischer’s test and Welch’s t-test. Further investigation was done through a Cox hazards model to compare the influence of in-home and in-center training on peritonitis occurrence over time during PD.

Results: A hazard ratio (HR = 0.377) was utilized to compare the home trained group to the center trained group. The HR indicates that at any time during PD, patients who were home-trained had a 62.3% lower risk of peritonitis. The confidence interval includes one. Therefore, this result is not significant, and this finding is further verified by its p-value being over 0.05. Additionally, significance between peritonitis rate and location of training (P=0.352) could not be established and all models used to analyze each variable resulted in insufficient p-values and binary squared values.

Conclusion: Considering the use of unbalanced sample sizes and limited data, the results can be deemed misrepresentative of the general peritoneal dialysis patient population, this study finds that location of training, in-home versus in-center, may not be an accurate gauge of peritonitis risk in certain populations.

PUB125

Curious Rash

Parth Worah, Jingvin Yan, Sehrish Ali. Baylor College of Medicine, Houston, TX.

Introduction: Peritoneal dialysis (PD) involves infusing a solution into the peritoneal cavity via a catheter. PD provides removal of solute/fluids by using the peritoneal membrane as an exchange surface. Primary PD solutions are glucose containing. Glucose is not an ideal osmotic agent as it’s easily absorbed; thereby attenuating the osmotic gradient driving ultrafiltration (UF). Icodextrin (ID) is an alternative to hyperosmolar glucose containing solutions. ID is an iso-osmolar solution consisting of a mixture of high molecular weight water-soluble polymers of glucose, isolated by the fractionation of hydrolyzed cornstarch. It’s added when more UF is indicated and/or when patients are at an increased risk of hyperglycemia. Icodextrin is generally well-tolerated; however, there have been reports documenting exfoliative rash from it. Our case describes biopsy proven spongiotic dermatitis on a patient who recently had ID added to her PD prescription.
Case Description: A 38-year-old female with past medical history of DM, HTN, and ESKD on PD for 1 year, presents with diffuse dry skin, pruritic rash and excoriations. This occurred 4 days after changing her PD solution to ID. It worsened despite a 3 day course of steroids. Physical exam notable for diffuse superficial desquamation and excoriations. Labs showed mild leukocytosis with a neutrophil predominance. Upon removal of ID from the PD prescription, her symptoms improved and a slow resolution of the skin rash occurred. Biopsy showed spongotic dermatitis, consistent with eczematous/contact dermatitis.

Discussion: ID provides a continuous and longer osmotic gradient because it is absorbed through the peritoneal cavity slower than standard PD solutions. Therefore, ID is used to increase UF. A few case reports and studies documented rare hypersensitivity reactions and exfoliative rashes to ID in dialysis patients. The exact pathophysiologic mechanism is not fully understood, ID is slowly absorbed via the lymphatic system from the peritoneal cavity, and is rapidly hydrolyzed by amylase in maltose, which may cause pruritis. Hypersensitivity reactions may be caused by immune complex formation on the skin. Our case shows a case of spongotic dermatitis caused by edema and exocytosis of lymphocytes. ID induced skin rashes typically resolves with discontinuation of ID, yet clinicians should remain attentive and consider these potential side effects in patients that develop skin rashes after being initiated on ID solution.

PUB126

Novel Combined Test for Osmotic Conductance to Glucose and Small Solute Diffusion Capacity in Peritoneal Dialysis


Background: Peritoneal membrane small solute diffusion capacities and osmotic conductance to glucose (OCG) are key determinants of peritoneal dialysis treatment efficiency and patient outcomes. However, current peritoneal function tests for measuring these parameters are cumbersome, inaccurate, and time-consuming. Recently we developed an easy method to determine OCG on the basis of a single 1-h 4.25% glucose dwell (Fig. 1A). Here, we retrospectively assess the ability of the single dwell method to accurately determine also the diffusion capacity (PS) for creatinine.

Methods: Using a recently developed isotopic method, creatinine PS values were firstly determined on the basis of a single 1-h 4.25% glucose dwell, and then validated against (reference) Three-pore model creatinine PS in a Bland-Altman analysis (n=28). Also, a simple equation was developed to convert between PS assessed using 1-hour dwells of 1.5% and 4.25% glucose fluid.

Results: Isotopic PS estimations based on the single 1-h 4.25% dwell correlated closely with the reference method (Fig. 1B) (r²=0.98), and had a mean difference of -0.6±1.0 (1.96 SD) mL/min (Fig. 1C). The 1.5% glucose data showed higher variation, having a mean difference of -0.6±3.9 mL/min and r=0.81 (P<0.001).

Conclusions: The combined single dwell peritoneal function test shows promising estimation accuracy for both creatinine PS and OCG. The present retrospective findings need to be confirmed in a prospective clinical study.

Figure 1. (A) X-Ray from Case 1, (B) CT from Case 2

PUB128

Hemorrhagic Pericardial Tamponade in a Peritoneal Dialysis Patient

Yihsin Chou, Chih-Ching Lin. Taipei Veterans General Hospital, Taipei, Taiwan.

Introduction: We report a case of hemorrhagic pericardial tamponade who was non-adherent to peritoneal dialysis with initial presentation of hypotension and syncope.

Case Description: A 46-year-old patient under peritoneal dialysis was hospitalized due to syncope, dyspnea on exertion and hypotension. He had high levels of BUN(~90 mg/dL) and creatinine (~20 mg/dL) in the past year. Low hemoglobin(7.9 g/dL) was found. Furthermore, chest radiograph revealed a round-head boot shape heart. Echocardiography revealed massive septated pericardial effusion with fibrinoid materials (Figure 1, A-C), which was difficult for echo-guided pericardiocentesis. He received pericardial window construction. More than 600 mL bloody effusion was drained. The pathology of pericardium showed chronic fibrinoid pericarditis. After the operation, the patient’s blood pressure increased from 90/60 mmHg to 130/100 mmHg. Follow-up transthoracic echocardiography revealed significant resolution of pericardial effusion and improvement of right ventricle compression (Figure 1D-F).

Discussion: The traditional uremic pericarditis occurs within 8 weeks of renal replacement therapy. However, it can also develop in non-adherent and under-dialyzed patients with higher level of toxic nitrogenous metabolic end products, free radicals and increased endothelial permeability. Bleeding tendency due to platelet dysfunction can be caused by uremic toxin, anemia and von Willebrand factor dysfunction. Our patient presented with acute bleeding in a chronic inflammatory pericardial space, resulting in a rapid impendence to cardiac filling and decrease in cardiac output. Uremic pericarditis used to be a sign for initiation of dialysis in patient’s with chronic kidney disease. It can also remind the clinician of reevaluating the patient’s dialysis adequacy before any catastrophic complication such as cardiac tamponade.
Abdominal Cocoon Syndrome in Peritoneal Dialysis
Julie G. van Baarlewik, Carlos Kuria, Joe N. Austin. Christ Hospital, Cincinnati, OH.

Introduction: Abdominal cocoon syndrome, also known as sclerosing encapsulating peritonitis (SEP), is a rare form of small bowel obstruction (SBO) resulting from peritoneal inflammation inducing formation of a fibrocollagenous membrane. Secondary (non-idiopathic) SEP is seen in patients on peritoneal dialysis, peritonitis, previous abdominal surgery, sarcoidosis, or tuberculosis. We present an interesting case of secondary SEP.

Case Description: A 54-year-old African American male with history of end-stage renal disease on hemodialysis (HD), sclerosing encapsulating peritonitis, recurrent SBO presented with weakness, failure to thrive and fecal drainage through his incision site. Because of his weakness, he had missed two HD sessions. Two and half weeks prior to presentation he was admitted for SBO and underwent endo-lap with lysis of adhesions, umbilicotomy, small bowel enterotomy and drain placement to left lower quadrant abscesses. He had been on peritoneal dialysis (PD) for about 20 years which was converted to HD due to interval development of intraperitoneal calcification consistent with SEP three years prior to presentation. On admission, potassium was 6.9. He was placed on empiric antibiotics and underwent emergent HD. CT scan of his abdomen demonstrated enterocutaneous fistula and extensive coarse intraperitoneal calcifications consistent with abdominal cocoon syndrome. There was also a left pelvic region abscesses with tip of JP drain within the collection. He was evaluated by surgery with recommendations to treat with antibiotics and permanent cessation of oral intake. Abdominal wound cultures grew Escherichia coli. He was discharged with intravenous antibiotics and total parenteral nutrition (TPN).

Discussion: The exact etiology of SEP is unclear due to the rarity of this condition. Abdominal cocoon syndrome is an uncommon complication of chronic ambulatory peritoneal dialysis. It has an incidence of about 2% among patients undergoing PD. The incidence increases with PD duration and can be as high as 5-8% after 3 years. Mortality rates range as high as 50%. Patients can develop SEP while on peritoneal dialysis, but incidence increases with PD duration and can be as high as 5-8% after 3 years. Mortality rates range as high as 50%. Patients can develop SEP while on peritoneal dialysis, but incidence increases with PD duration and can be as high as 5-8% after 3 years. Mortality rates range as high as 50%. Patients can develop SEP while on peritoneal dialysis, but incidence increases with PD duration and can be as high as 5-8% after 3 years. Mortality rates range as high as 50%. 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Methods: Review of the current evidenced based research including the CDC and NKF guidelines and practice. This will be discussed to answer the following specific questions: Is the relation of Hemodialysis catheters and by blood stream infection? What is the optimal practice in utilizing HD catheters? When, Where, How and Why? to use a dialysis catheter?

Results: Upon reviewing the evidence including the NKF and the CDC latest recommendation, the following answers were obtained for the above questions: There was a higher association between hemodialysis blood stream infection and catheters. The studies were retrospective with association. There were no prospective randomized controlled clinical trials still influencing the access and the type of hemodialysis blood stream infection. Tight infection control policy with full PPE for the staff and patients showed reduced risk of infection. This needed to be discussed or when using the catheter for hemodialysis. No randomized controlled trials were found. The competition between AV fistula and AV graft for access dysfunction and thrombectomy

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PUB135
The Patency of Percutaneous Intervention-Treated Vascular Access for Hemodialysis Patients and Risk Factors for Recurrent Vascular Stenosis
Wenjing Zhou, Hong Ye, Xian Wu, Junwei Yang. Second Affiliated Hospital of Nanjing Medical University, Nanjing, China.

Background: Stenosis is one of the main causes of dysfunction of vascular access for hemodialysis. Percutaneous transluminal angioplasty (PTA) has become a promising treatment. This study aimed to demonstrate the patency of percutaneous intervention-treated vascular access for hemodialysis patients in our dialysis center and to explore the risk factors for recurrent of vascular stenosis after PTA.

Methods: The general demographic information, complications, anthropometric parameters, ultrasonographic characteristics of internal fistula before operation, balloon size and stenosis opening pressure during operation, and corresponding vascular characteristics by ultrasound after operation were recorded. The patients were followed-up at 1, 3 and 6 months after operation, and follow-up every 6 months thereafter. The recurrent of stenosis and other fistula related complications were registered. Potential risk factors affecting the primary patency and postinterventional stenosis were analyzed.

Results: Among the 135 patients, 70 patients had arteriovenous fistula (AVF), the rest had arteriovenous graft (AVG). PTA was successfully operated in 90.37% of the patients. Hematoma occurs in 5 patients during the operation. The primary patency rates at 1, 3, 6 and 12 months after operation were 97.78%, 84.4%, 62.96% and 45.93%, respectively. The larger the peak systolic flow velocity ratio (PSVR) after PTA, smaller the stenosis venous diameter before PTA, and older in age are risk factors for early recurrent of stenosis after PTA. Multivariate regression analysis showed that diastolic blood pressure, patient age (every 10 years old) and balloon diameter > 8mm were risk factors for recurrent of stenosis after PTA in patients with AVG. As for patients with AVG, the risk of recurrent of stenosis in patients taking antiplatelet medicine was 2.652 times than those without taking antiplatelet medicine (95% CI 1.393-5.047, P<0.005), suggesting that patients at high thrombogenic state may have a high risk of recurrent of stenosis.

Conclusions: The safety and efficacy of PTA for treatment of stenosis of vascular access is confirmed in this study. High diastolic blood pressure, balloon with larger diameter, elderly and antiplatelet medication are risk factors for recurrent of stenosis after PTA.

PUB136
Successful Catheter Lock with Recombinant Tissue Plasminogen Activator as a Rescue Therapy in Hemodialysis Catheter Dysfunction in a Patient with Exhausted Vascular Access
Maria Guadalupe C. Núñez,1 Salvador L. Gil,1 Marcos G. Nava,2 Lilliana Pacchiano,1 Instituto Nacional de Cardiologia Ignacio Chavez, Mexico, Mexico; Instituto Nacional de Enfermedades Respiratorias, Mexico, Mexico.

Introduction: Hemodialysis (HD) catheter complications are infection and occlusion. A catheter locking solution after HD sessions try to prevent them. Heparin and citrate has been used and the efficacy is successful in general population, but in patients with thrombophilia and exhausted vascular access could not have same effectiveness. Recombinant tissue plasminogen activator (rt-PA) has been used as an option.

Case Description: A 45 year-old women with ESRD due to collapsing glomerulopathy was taken to transplantation in 2 occasions with recurrence of glomerulopathy. She was maintained in peritoneal dialysis for 15 months, migrated to HDF due to refractory bacterial peritonitis. During next years she suffered from several catheter changes because of dysfunction and infections. Also, 2 arteriovenous fistulae did not work because of thrombosis, documenting elevated factor VIII, receiving anticoagulation. Then, central venous stenosis was documented and several femoral catheters were collocated, with infrafadiay, increasing session time (240 to 270 min), using citrate locks, but blood flow pump (Qb) diminished to 80 cc/min and she was hospitalized to perform an arteriovenous axilo-atrial graft placement presenting thrombosis. Finally, we use rt-PA to lock lumen, achieving an incremented Qb from 152.21 with citrate to 251.5 cc/min with rt-PA and substitution volume from 11.2 L to 33.56 L, respectively, but without improvement in recirculation rate (Figure 1). She was discharged, but after 2 days she died due to mesenteric ischemia.

Discussion: The options to treat a dysfunctional catheter in the setting of exhausted vascular access are limited with conventional lumen locks, the utility of rt-PA to prevent them in recently placement catheters has been demonstrated, but there is no description of the utility in cases like ours, to try to rescue an access to continue the therapy. We can improve the functionality of the vascular access, but the impact in substance clearance probably will not be.
Unusual Ultrasound Graft Finding

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Mayo Clinic Minnesota, Rochester, MN.

Introduction: 42-year-old female with ESKD, dialysis dependent for 5 years, presented to ER feeling unwell and hyperkalemic to 6.8 mmol/L. Due to dialysis that morning but no missed dialysis sessions recently. Access is a right brachial artery to brachial vein loop graft created about 4 months ago. Graft had been difficult to cannulate with elevated pressures and pain requiring a decrease in blood flow rate or early treatment termination.

Case Description: Bruit, thrill and subcutaneous edema of the right arm overlying the graft noted. US revealed patent graft but unexpected findings of three adjacent fistulous communications between the distal loop graft and a superficially overlying subcutaneous branch of the right cephalic vein (figure 1). No surgical intervention recommended by Vascular Surgery. Repeat US done to mark patient’s arm with cannulation sites resulted in successful cannulation and patient discharge. 1 month later, patient readmitted with similar presentation as markings not been preserved and cannulation challenges recurred. More extensive markings were created, identifying the overlying vein as well as cannulation sites. Patient refused further use of the graft and required central venous catheter placement.

Discussion: We describe an unusual case of difficult A V graft cannulation due to overlying cephalic vein. Cannulation improved with skin marking to guide cannulation, though due to impermanence of the markings, rehospitalization occurred and central catheter placement was required due to patient refusal to allow further graft cannulation. Early assessment of cannulation challenges with diagnostic US in patent dialysis fistulas or grafts may identify unexpected causes of cannulation. US and skin marking is a potential means of improving cannulation difficulties and avoid central venous catheter placement in unusual cases, such as described.

Livestreaming in Instagram for the Kidney Health Promotion During Covid-19 Pandemic: Report of an Experience in Brazil


Background: Chronic kidney disease (CKD) awareness is an important strategy to decrease its advance. The aim of this study was to describe livestreaming in Instagram during the World Kidney Day (WKD) 2021 in Brazil.

Methods: During the WKD 2021, the Renal Health project in Brazil carried out a week of health promotion online. Due to COVID-19 pandemic, which severely affected Brazil, all the activities were conducted online. From 1st to 11th March 2021, livestreaming sessions were carried out through the Instagram (@renal.health), with healthcare specialists and patients, discussing different aspects of CKD, with focus on the patients and the general audience. The followers could ask questions during the sessions and it was recorded to be accessed later (https://www.instagram.com/renal_health/channel/).

Results: A total of 3479 views were registered. The most viewed was the session about “resignifying life after dialysis”, with 827 views, followed by “conservative treatment and lifestyle”, with 549 views, and “kidney transplant and quality of life”, with 537 views. There were 38 spontaneous feedbacks, most of them of compliments regarding the sessions. All sessions obtained a positive result from spectators, who posted compliments, such as “I loved the live, enlightening” and “congratulations on the subject, clear and highly enlightening language”. Feelings about the impact of CKD were expressed: “these conversations with the interviewees are clearing my mind, as I also have kidney problems”. Experiences that improved CKD knowledge could be shared: “I liked that the doctor said that it would be even better to have a transplant even before undergoing hemodialysis”.

Conclusions: This experience evidence the importance of connecting with patients, using simple language, and the importance of digital means, including the Instagram, as a way of reliable health education. The true impact of COVID-19 on patients with CKD is yet to be known, but the nephrology community and health professionals as a whole should already be aware that patients are getting increasingly connected, and that is possibly the direction for the future.

Funding: Government Support - Non-U.S.
Methods: The effect of an online, 30-minute, CME-certified 2-expert discussion was analyzed to determine the efficacy of online education. Three multiple-choice knowledge/competence questions and 1 self-efficacy confidence question were presented both before and immediately after each activity. A repeated pairs pre-/post-assessment study design was used and a paired samples t-test for overall and McNemar’s test at the question level (5% significance level, P < .05) assessed educational effect. The activity launched January 5, 2021 and data were collected through March 25, 2021.

Results: In total, 354 nephropaths and 334 PCPs answered all pre-/post-assessment questions and were included in the study. Overall, 54% of nephropaths and 38% of PCPs improved their knowledge (P < .01 for both groups) 37% of nephropaths and 23% of PCPs demonstrated improvements at identifying dose requirement comparisons for inflamed vs noninflamed patients (P < .01 for both groups) 17% of nephropaths and 15% of PCPs demonstrated improvements at recognizing clinical trial data related to safety for emerging HIF-PHI (P < .05 for both groups) 13% of nephropaths and 12% of PCPs demonstrated improvements at recognizing clinical trial data related to iron status for emerging HIF-PHIs (P < .05 for both groups) 54% of nephropaths and 46% of PCPs reported increased confidence in knowledge of HIF-PHIs in the treatment of anemia in patients with CKD who are iron replete or noneplete Continued gaps: 35% of nephropaths and 54% of PCPs need additional education related to identifying dose requirement comparisons for inflamed vs noninflamed patients 56% of nephropaths and 70% of PCPs need additional education related to recognizing clinical trial data for emerging HIF PHIs 23% of nephropaths and 50% of PCPs need additional education related to recognizing clinical trial data related to iron status for emerging HIF PHIs

Conclusions: This study demonstrates the success of online, video-based 2-expert discussion on improving knowledge of nephropaths and PCPs related to HIF-PHIs for the treatment of anemia associated with CKD. Continued knowledge gaps were identified for future educational targets.

Funding: Commercial Support - AstraZeneca ad Fibrogen

PUB140
Success of Online CME at Improving Nephrolgist Understanding of Strategies to Reduce Progression of CKD

Background: Clinicians need good clinical understanding of new strategies for reducing progression of CKD. We sought to determine if online continuing medical education (CME) could improve the clinical knowledge of nephrologists related to emerging treatments for HRS.

Methods: In total, 307 nephropaths and 224 PCPs answered all pre-/post-assessment questions and were included in the study Overall improvements were seen after participation in both CME activities: 16% of nephropaths and 21% of PCPs demonstrated improvements at identifying clinical trial data for SGLT2 inhibitors to reduce the progression of CKD.

Results: In total, 307 nephropaths and 224 PCPs answered all pre-/post-assessment questions and were included in the study Overall improvements were seen after participation in both CME activities: 16% of nephropaths and 21% of PCPs demonstrated improvements at identifying clinical trial data for SGLT2 inhibitors to reduce the progression of CKD (P<.01) 24% of nephropaths demonstrated improvements at recognizing clinical trial data for an emerging treatment options for HRS 27% of nephropaths improved at acute kidney injury (AKI) in a patient with cirrhosis 5% of nephropaths improved at selecting the next step in treatment for a patient with HRS Overall, 58% of nephropaths had a measurable improvement in confidence in your knowledge of emerging treatment options for patients diagnosed with HRS-AKI, for an average confidence shift of >70%. Continued educational gaps: 35% of nephropaths did not recognize clinical trial data for an emerging HRS treatment option 16% of nephropaths did not recognize AKI in a patient with cirrhosis

Conclusions: This study demonstrates the success of an online summary from a satellite symposium on improving management of HRS by nephrologists. Continued knowledge gaps were identified for future educational targets.

Funding: Commercial Support - Mallinckrodt

PUB143
Online CME Is Successful in Prompting Performance Improvements Related to Hyperkalemia Management
Amy Larkin, Donald Blatherwick, George Boutsalis. Medscape Education, New York, NY.

Background: We studied the effect of online education designed to improve the clinical performance of nephrologists, cardiologists, and NPs/PAs related to hyperkalemia management to enable/optimize RAAS inhibitor use.

Methods: The CME activity was a 30-minute online video roundtable panel discussion between 3 experts. Faculty discussion was reinforced with synchronized slides presenting supportive data. The impact of the education on performance outcomes was measured with a survey immediately post-education to assess planned changes in clinician practice as a result of participation in CME activity. Survey participants were contacted 2 weeks later to complete a self-reported actual change in practice survey, the follow-up survey (12 nephrologists, 6 cardiologists, 10 NPs/PAs) Of those, 86% reported making an average of 3.9 changes in practice as a result of this activity Changes in practice include: Consider a loop diuretic to increase potassium clearance and enhance volume management (67% nephrologists, 44% of cardiologists, and 45% of NPs/PAs) 104 patients per month taking RAAS inhibitors 63% of nephrologists, 40% of cardiologists, and 42% of NPs/PAs are in private practice 44% of nephrologists, 64% of cardiologists, and 36% of NPs/PAs reporting being in a suburban location 91% of respondents indicated an average of 3.2 planned practice changes

Results: A total of 275 clinicians completed the survey immediately post-education (91 nephrologists, 75 cardiologists, 109 NPs/PAs) 19% of nephrologists, 8% of cardiologists, and 4% of NPs/PAs tried 104 patients per month taking RAAS inhibitors 63% of nephrologists, 40% of cardiologists, and 42% of NPs/PAs are in private practice 44% of nephrologists, 64% of cardiologists, and 36% of NPs/PAs reporting being in a suburban location 91% of respondents indicated an average of 3.2 planned practice changes

Funding: Commercial Support - Bayer

PUB141
Online Video-Based CME Successful at Improving Knowledge of Nephrologists Related to Mineralocorticoid Receptor Antagonist for CKD in Type 2 Diabetes
Amy Larkin, Kelly L. Hanley, Anne L. Medscape Education, New York, NY.

Background: One goal of continuing medical education (CME) is improving knowledge related to mechanisms of action for new therapeutic options. We sought to determine if a video-based CME activity could improve the knowledge of nephrologists related to the mechanism of action of nonsteroidal mineralocorticoid receptor antagonists (MRAs) in the management of chronic kidney disease (CKD) in patients with type 2 diabetes (T2D).

Methods: The online CME activity consisted of a 30-minute, video-based presentation by 1 expert faculty using green screen technology to enhance the visual impact of the presentation Related to knowledge related to mechanisms of action for new therapeutic options. We sought to determine if online continuing medical education (CME) could improve the knowledge of nephrologists related to the mechanism of action of nonsteroidal mineralocorticoid receptor antagonists (MRAs) in the management of chronic kidney disease (CKD) in patients with type 2 diabetes (T2D).

Results: In total, 233 nephropaths answered all pre-/post-assessment questions and were included in the study. Improvements were seen after participation in the CME activity: Overall, 36% of learners improved their knowledge (P < .01) 19% of nephrologists demonstrated improvements at identifying mechanism of action of MR blockade in treating CKD in T2D (P < .01) 24% of nephrologists demonstrated improvements recognizing mechanism of action of MRAs and nonsteroidal MRAs (P < .01) 30% had a measurable increase in confidence in managing CKD in T2D (P < .01) Continued educational gaps: 22% need additional education related to mechanism of action of MR blockade in treating CKD in T2D 33% need additional education related to clinical differences in steroidal MRAs and nonsteroidal MRAs

Conclusions: This study demonstrates the success of online, video-based presentation using green screen technology on improving knowledge of nephrologists related to mechanism of action of nonsteroidal MRAs in managing CKD in T2D. Continued knowledge gaps were identified for future educational targets.

Funding: Commercial Support - Buyer

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
**Conclusions:** The outcomes in this presentation achieve a compelling evidence that participation in a 30-minute online video discussion among 3 experts prompted changes in practice to provide better hyperkalemia management to their patients.

**Funding:** Commercial Support - Vifor

**PUB144**

**Success of Virtual Patient Simulation at Improving Diagnosis and Management of Chronic Hyperkalemia**

**Amy Larkin, Donald Blatherwick. Medscape Education, New York, NY.**

**Background:** We sought to determine if virtual patient simulation (VPS)-based continuing medical education (CME) intervention could improve performance of nephrologists related to diagnosis and management of hyperkalemia.

**Methods:** The intervention comprised a patient presenting at two different time points in a VPS platform that allows learners to order lab tests, make diagnoses, and prescribe treatments in a manner matching the scope and depth of actual practice. Tailored clinical guidance (CG), based on current evidence and expert recommendation, was provided following each decision, followed by the opportunity for the learner to modify to their decisions. Decisions were collected after CG was presented with each. A pre-existing (pre-CG) decisions using a McNemar’s test to determine P values. The activity posted October 30, 2020; initial data was collected through March 10, 2021.

**Results:** To date, 86 nephrologists completed the activity (all decisions within at least 1 case) and were included. Significant improvements were observed after CG. Initial visit: Diagnose CKD stage 3b: 34% absolute improvement (8% pre-CG vs 42% post-CG; P<.01) Diagnose hyperkalemia: 29% absolute improvement (8% pre-CG vs 37% post-CG; P<.01) Initiate a potassium binder: 36% absolute improvement (22% pre-CG vs 58% post-CG; P<.01) Diagnose diuretic: 57% absolute improvement (5% pre-CG vs 62% post-CG; P<.01) Discontinue oral naproxen: 10% absolute improvement (85% pre-CG vs 95% post-CG; P<.01) Order patient education: 12% absolute improvement (50% pre-CG vs 62% post-CG; P<.01) Order nutritional counseling: 15% absolute improvement (50% pre-CG vs 65% post-CG; P<.01) Follow-up visit: Diagnose chronic hyperkalemia: 36% absolute improvement (4% pre-CG vs 40% post-CG; P<.01) Continue potassium binder: 9% absolute improvement (89% pre-CG vs 98% post-CG; P<.05) Continue loop diuretic: 11% absolute improvement (87% pre-CG vs 98% post-CG; P<.05) Order patient education: 13% absolute improvement (47% pre-CG vs 60% post-CG; P<.01) Order nutritional counseling: 17% absolute improvement (36% pre-CG vs 53% post-CG; P<.01)

**Conclusions:** VPS that immerses and engages specialists in an authentic and practical learning experience can improve evidence-based clinical decisions related to patient identification and management of hyperkalemia.

**Funding:** Commercial Support - Vifor

**PUB145**

**Online CME Improves Clinician Understanding of Quality-of-Life Issues in Patients with Metabolic Acidosis**

**Amy Larkin, Donald Blatherwick, George Boutsalis. Medscape Education, New York, NY.**

**Background:** We sought to determine if online continuing medical education (CME) could improve the clinical knowledge of nephrologists (neph) and primary care physicians (PCPs) related to quality of life issues in patients with metabolic acidosis and emerging treatments options.

**Methods:** The effect of an online, 30-minute, CME-certified 2-expert discussion was analyzed to determine efficacy of online education. Three multiple-choice knowledge/competence questions and 1 self-efficacy confidence question were presented both before and after the discussion. The outcomes gathered in this assessment provide compelling evidence that participation in a 30-minute online video discussion among 3 experts prompted changes in practice to provide better hyperkalemia management to their patients.

**Funding:** Commercial Support - Vifor

**PUB146**

**Nephrology Best Practice, Integrating Healthcare Education, and CKD: A Qualitative Perspective**

**Shahid N. Muhammad.1,2 The University of the West of England (UWE), England UK, Bristol, United Kingdom; The Renal Patient Support Group (RPSG), England UK, Bristol, United Kingdom.**

**Background:** Education and information seeking is pinnacle for patients with Long-Term Conditions (LTCs) like Chronic Kidney Disease (CKD) to take ownership of health and disease and navigate healthcare between health sectors. Patient and Public Involvement (PPI) is key to help understand gaps in health education. 1) Involving patients between two support groups to help understand which topics and subjects are pertinent to CKD patients; 2) Involving patients to understand whether, retrospectively there has been an educational neglect in healthcare; and 3) To understand how healthcare and education for CKD patients could be more integrated.

**Methods:** Two PPI workshops were implemented (May and June 2019) after reviewing NHIR INVOLVE best practice guidelines. Fourteen (14) topic tags were applied over 1-month (March and April 2020) between the Renal Patient Support Group (RPSG) (est.2009) and the Kidney Disease and Renal Support (KDArs) (est.2014) for Kids platforms. Group disclaimers encouraged informed consent. GDPR (2018) guidelines were implemented to ensure best practice surrounding confidentiality and data protection.

**Results:** Thematic Analysis was used to highlight findings, according to overarching themes having used Nvivo-12 software to code and help understand where there are healthcare educational inefficiencies. Five themes were identified through this study including: 1) Bridging Educational Gaps; 2) Using Different Modalities to Collect Qualitative Data; 3) Healthcare, Patient and Public Involvement and Maintaining Confidence through Online Methods to collect Qualitative Data; 4) Advantages, Disadvantages and Limitations to Online Data Collection and Peer Support Groups; 5) Using Qualitative Methodology to Understand Educational Needs for CKD Patients.

**Conclusions:** Wider Allied Health Professionals (AHPs) could increasingly finding themselves taking on roles, particularly where involvement is increasingly dependent bridging educational gaps and ‘alleviating misinformation’ through technology and ‘online spaces’. Conclusion: This is the first UK retrospective study that examines educational gaps between online paediatric and adult CKD patients close to two decades (16 years), and highlights where further PPI-focused research would help understand where healthcare requires investment.

**PUB147**

**What, If Any, Are the Nephrology Health Educational Needs of CKD Patients: A Qualitative Inquiry**

**Shahid N. Muhammad.1,2 The University of the West of England (UWE), England UK, Bristol, United Kingdom; The Renal Patient Support Group (RPSG), England UK, Bristol, United Kingdom.**

**Background:** An estimated 15 million patients in England have at least one Long-Term Condition with the prevalence of CKD rising. The characterization of CKD at all stages is an important part of its management and allows the initiation of appropriate treatments with the aim of slow progression of kidney disease. Providing up-to-date, accurate health education is pinnacle for patients to take ownership of healthcare. Patients require educational support as part of healthcare and help navigate understanding with different healthcare professionals. The aims and objectives of this research was to understand how CKD patients should be encouraged to take ownership of healthcare through education.

**Methods:** The theoretical framework for this research involved an Inductive Content Analysis (ICA) approach where essentially qualitative data collection and analyses will help understand what if any, are the health educational needs getting perspectives from CKD patients and Health Professionals (HPs). ICA is particularly effective to help understand analysis in linking theory, or framework, 19 participants between 4 cohorts, that included 6 General Practitioner (GPs), 4 Healthcare Scientists (HS), and 6 CKD Patients (CKDPs) were recruited and participated in telephone interviews.

**Results:** Majority of CKDPs were in between CKD4 and CKD5. Interviews allowed participants to put forward views and understanding, relating to healthcare education. Topic guides were developed for participant cohorts with several themes to collect data through one-to-one telephone interviews. NViVo-12 software provided opportunity to classify and arrange transcript context and glean insight to develop overall conclusions. Nine main themes and several sub-themes were identified when coding for healthcare professionals (HPs), and Nine (9) main themes and several sub-themes identified when coding qualitative data for patients (CKDPs).

**Conclusions:** There needs to be a coordinated effort between patients and professionals, to understand how CKD education is more integrated with healthcare, and especially wherein involvement is end-to-end. This explorative study provides evidence applying research to public health. Every effort has been made to reduce biases and diminish disparities. Point of Care Education (POCE) could be an integrated through online spaces and linked to Electronic Patient Records (EPRs).
Chronic Hyponatremia: Challenges in Diagnosis and Management
Shivangi Patel, Atlantic Health System Inc, Florham Park, NJ.

Introduction: Hyponatremia is manifestation of variety of disorders. Hyponatremia occurs as result of water intake exceeds greater than water excretion. Management becomes a challenge due to etiology and costly drugs.

Case Description: 46-year-old male computer engineer who exercises 3 times a week, takes 20 grams of protein shake daily with no past medical history, not on meds, noted to have chronic sodium of ~126 mEq/L with stable BMI 26. His only complaint was mild fatigue. His exam was normal with a negative orthostatic. Labs: Sodium 126 mEq/L, Potassium 3.6 mEq/L, uric acid 2.8 mEq/L, Creatinine 0.65 mg/dL, Serum Osmolarity 266 mOsm/kg. Urine sodium 72 mEq/L. Urine potassium 60.1 mEq/L. Specific gravity 1.018, Urine Osmolality, 626 mOsm/kg H2O and 20 mEq/L. Renal, adrenal, and thyroid function are normal. Imaging of brain, chest and abdomen is negative for pathology. He underwent colonoscopy with suprap which provided the least amount of volume load and Ure-Na prescribed to keep his serum sodium stable during the bowel prep. Max sodium achieved was 130 mEq/L after 2 g of Ure-Na. It was discovered later, his brother was noted to have sodium of 115 diagnosed at age 20 and maintained on sodium bicarb but was never tested genetically, nor achieved normal sodium levels.

Discussion: Labs were consistent with SIADH however he had undetectable cotepoin level and negative workup for malignancy. Due to family history with negative workup for any other etiology, he likely has Nephrogenic Syndrome of Inappropriate Diuresis (NSIAD). NSIAD is caused by gain-of-function mutation in AVP receptor type 2 located on long arm of X chromosome (Xq28). Genetic confirmation for NSIAD is pending and if positive will need to test other family members. Management for chronic hyponatremia was challenging as fluid restriction was not realistic to adhere to as suggested by his high urine Na+ and high urine osmolality > 500mOsm/kg. Ure-Na was useful at time of bowel prep to avoid worsening of hyponatremia, however never achieved normal sodium even after 30 g bid Ure-Na. Vaptans were not tried as are more costly than Ure-Na and unclear efficacy in NSIAD. Patient did not want to pay $80 of Urena, and he increased his protein intake to 75 g daily with fluid restriction 1.5 L/day, which maintained his sodium level at 130.

PUB149
Spontaneous Regression of Hyperammonemic Encephalopathy, Lactic Acidosis, Gastric Mucosa Injury, and Hepatic Portal Vein Gas After Infusion of 5-Fluorouracil
Yoshihiro Nakamura,1,2 Toyohashi-shi, Toyohashi, Japan; 1Chubu Rosai Byoin, Nagoya, Japan.

Introduction: 5-fluorouracil (5-FU) therapy is associated with hyperammonemic encephalopathy and lactic acidosis. 5-FU has a direct toxic effect on the gastric mucosa. Hepatic portal venous gas (HPVG) is caused by various factors including bowel necrosis and gastroduodenal ulcers.

Case Description: A 79-year-old man was referred to the nephrology department owing to lactic acidosis. He had a history of hypopharyngeal carcinoma. Two days prior to the consultation, he was started on 300 mg of carboplatin and 4000 mg/m² of 5-FU as a continuous intravenous infusion. On the consultation day (day 1), he was experiencing confusion and had a GCS score of 11/15. He was started on sodium bicarb but was never tested genetically, nor achieved normal sodium levels.

Discussion: Labs were consistent with SIADH however he had undetectable cotepoin level and negative workup for malignancy. Due to family history with negative workup for any other etiology, he likely has Nephrogenic Syndrome of Inappropriate Diuresis (NSIAD). NSIAD is caused by gain-of-function mutation in AVP receptor type 2 located on long arm of X chromosome (Xq28). Genetic confirmation for NSIAD is pending and if positive will need to test other family members. Management for chronic hyponatremia was challenging as fluid restriction was not realistic to adhere to as suggested by his high urine Na+ and high urine osmolality > 500mOsm/kg. Ure-Na was useful at time of bowel prep to avoid worsening of hyponatremia, however never achieved normal sodium even after 30 g bid Ure-Na. Vaptans were not tried as are more costly than Ure-Na and unclear efficacy in NSIAD. Patient did not want to pay $80 of Urena, and he increased his protein intake to 75 g daily with fluid restriction 1.5 L/day, which maintained his sodium level at 130.

PUB150
Methanol Poisoning Diagnosed by Brain MRI
Abhinaya Sridhar,1,2 Viviam I. Becerra rivera,1,2 Savneek S. Chugh,1,2 1Westchester Medical Center, Valhalla, NY; 2New York Medical College, Valhalla, NY.

Introduction: Methanol poisoning is deadly yet remains relatively common. Delays in diagnosis increases the risk of irreversible organ damage and death. In the absence of serum or urine levels, radiological findings may be useful in diagnosis. We report a unique case of methanol toxicity where we made the diagnosis based on characteristic brain MRI findings as timely serum or urine levels were unavailable.

Case Description: 81-year-old woman presented with altered mental status, poor appetite, lethargy and two episodes of vomiting en-route to the emergency room. On examination, her vital signs were normal but she was mildly agitated, oriented to person only. Initial blood work was significant for a low Bicarbonate level of 10mEq/L, Anion Gap 22, creatinine 0.81 mg/dL, serum Osmolality 403 mOsm/kg with calculated osmolality 290 mOsm/kg and Arterial Blood Gas (ABG) showing pH 7.29 and pCO2 24. Her CT head showed no acute changes with white matter microvascular ischemic disease. Because of high osmolar gap anion gap metabolic acidosis, patient was given intravenous Fomepizole. Overnight, her condition deteriorated requiring intubation and mechanical ventilation. Her repeat ABG showed worsening acidosis with pH 6.9 and pCO2 19. She was subsequently started on sodium bicarbonate drip. Further work up was negative for serum methanol, ethanol, salicylate, blood alcohol and 5-xo-proline levels. Her acidosis gradually improved but her mental status continued to remain poor for which she had a brain MRI which showed extensive parenchymal brain abnormality, leukoencephalopathy and basal ganglia involvement reminiscent of acute methanol toxicity and thus a diagnosis was made. Unfortunately, her mental status remained poor and after consulting with palliative care, decision was made to prioritize patient comfort and terminal extubation.

Discussion: Characteristic MRI findings in methanol toxicity are high T2 signal suggestive of necrosis of lentiform nucleus with predilection for the putamen. There may be necrosis of lobar white matter with sparing of subcortical fibers and hemorrhagic transformation. Our patient had similar findings as well. An extensive ingestion history is crucial when evaluating high osmolar gap. However, in the absence of timely blood work and ingestion history, like in our patient, brain imaging with MRI may be integral to diagnosing methanol poisoning.
PUB152
Online Dysnatremia Correction Calculators: Consistency and Practice Guideline Adherence
Christina M. Yuan,1 Maura A. Watson,1 Benjamin M. Forster,2 James D. Oliver.1
1 Walter Reed National Military Medical Center, Bethesda, MD; 2 William Beaumont Army Medical Center, El Paso, TX.

Background: Online calculators for sodium correction in dysnatremia are frequently used by non-nephrologists. We assessed 5 popular calculators which use the Androgue-Madias equation for practice guideline adherence and reproducibility in a theoretical 80-year old, 100 kg (72 inch) male.

Methods: Hypernatremia case: Na+ 150 mEq/L. Guideline-based Rx: Estimated water deficit 4.2 L. Replacement target 2.1 L. In the first 24 hours, plus 1.5 L insensible losses. Infusate: 150 mEq/L D5W. Hyponatremia case: Na+ 115 mEq/L, euvolemic with acute/severe symptoms, normal serum K+. Guideline-based Rx: Immediate treatment: 3% NaCl, 100 mL over 10 minutes up to 3 times; Na+ increase ≤ 6-8 mEq/L in first 24 hours. Alternative using the Androgue-Madias equation: 3% NaCl at 32mL/hr, with frequent Na+ determination.

Results: See Table. On-line Calculators for Hypernatremia: Water deficit calculated in 3 (range 3.6-4.3L). Insensible loss calculated in 1. Replacement target defaults: 140-145 mEq/L Na+ at 10-24 hours. On-line Calculators for Hyponatremia: One discusses volume status, acute, and symptoms. Only 2 indicate rapid correction should be used for severe symptoms. Default correction rate range: 6-12 mEq/L/day. Calculated rate of 3% NaCl: range 32-64 mL/hr. Only 1 calculator incorporated insuffate K+, and recommended Na+ and insuffate rate redetermination.

Conclusions: The 5 calculators correctly use the Androgue-Madias formula to determine insuffate rate of hypertonic or hypotonic fluids in dysnatremia. However, defaults may yield rates that exceed safe correction rate: 4/5 had no discussion of chronicity, symptom severity, or need for frequent Na+ determination/insuffate rate recalculation. These may contribute to unexpected adverse outcomes. The views expressed in this article are those of the authors and do not reflect the official policy of the Department of Army, Department of Defense, or U.S. Government.

Comparison of Online Calculator Results with Guidelines

PUB153
Mass Poisoning from Ethylene Glycol at a US Military Base
Nina Shah, Benjamin M. Forster, Sarah Petteys, Scott B. Sullivan. William Beaumont Army Medical Center, El Paso, TX.

Introduction: Ethylene glycol (EG) poisoning occurs over 5000 times annually in the US, but a poisoning outbreak (3 cases within 72 hours) has not previously been reported. We describe on an EG poisoning outbreak in January 2021, presenting at William Beaumont Army Medical Center.

Case Description: Eleven soldiers presented to the emergency room over a twelve hour period after ingestion of an unknown alcohol, later identified as radar cooling fluid containing EG. Only the first two patients were symptomatic. Serum EG levels were not immediately available, therefore treatment decisions were based on surrogate markers (arterial pH, anion [AG] and osmolar [OG] gaps, serum bicarbonate [TCO2], lactate [Lac], and creatinine [Cr]).

Discussion: Two patients received immediate hemodialysis (HD) in combination with fomepizole (FOM) due to severe acidosis plus elevated OG and AG (Table). These patients developed acute kidney injury (AKI) with renal recovery occurring within a 3-week period. Two patients with elevated Lac received bicarbonate-based intravenous fluids (IVF) and FOM. Two patients received IVF only and required prolonged observation for worsening acidosis and/or AKI. Five patients with normal lab values were treated with IVF and observation. All patients received cofactors including thiamine and pyridoxine. All patients survived. The outbreak occurred in the setting of limited dialysis resources and FOM availability and in a community with widespread COVID-19 activity. Additional guidelines are needed to determine allocation of limited resources and optimal dialysis and FOM treatment course, and identify comorbid conditions which may prolong recovery. The views expressed in this article are those of the authors and do not reflect the official policy of the Department of Army, Department of Defense, or U.S. Government.

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PUB154
Unexplained Hyperkalemia
Nityasree Srinallul, Karla G. Carias Martinez, Elizabeth Kieman, Jose M. Monroy-Trujillo. Hopkins Nephrology Johns Hopkins Medicine, Baltimore, MD.

Introduction: Hyperkalemia is a life-threatening emergency that warrants prompt evaluation and treatment. Evaluation should include ruling out falsely elevated potassium (K+) levels that would otherwise lead to unwarranted and potentially harmful therapies.

Case Description: A 69-year-old male with mantle cell lymphoma presented with multifocal pneumonia, septic shock, and acute hypoxic respiratory failure. He had an acute kidney injury (AKI) with a creatinine of 2.84mg/dL from ischaemic acute tubular necrosis. CVVHD was started for oliguria and volume overload, with a prescription of blood flow rate 250mL/min, dialysis flow rate 2L/hr (at 25mL/kg), 4mEq/L of potassium, 1.5mEq/L of calcium, and 35mEq/L of bicarbonate. On day 5 of CVVHD, he was switched to a 3mEq/L (K+) bath due to (K) 5.5-5.6mEq/L. Labs also showed worsening lymphocytic predominant leukocytosis due to underlying cancer. The initial whole blood (K+) was 6.9mEq/L. He received calcium gluconate, dextrose, and insulin, with whole blood (K+) 3 hours later of 7.7mEq/L. EKG obtained twice did not show signs of hyperkalemia. Repeat (K) obtained from an arterial blood gas analyzer was 4.9mEq/L.

Discussion: Pseudohyperkalemia is an in-vitro phenomenon in which serum (K+) exceeds plasma (K+). It can occur in patients with severe leukocytosis, erythrocytosis, or thrombocytosis. Clinical consequences of hyperkalemia are absent, and aggressive management is unnecessary as in-vivo (K+) levels are unchanged. Plasma (K+) contains both serum and clotting factors, which is why plasma is collected in tubes with anticoagulants like heparin. With extreme leukocytosis, the white blood cell membrane is fragile and prone to lysis from heparin. The release of even a minute amount of (K+) from cells can notably raise ‘measured’ extracellular (K+). Both serum and plasma (K+) samples can be affected, but the impact on plasma seems to be higher. As plasma (K+) is higher than serum (K+), it is termed “reverse pseudohyperkalemia”. If suspected, a repeat whole blood (K+) sample should be collected by a point of care (blood gas) analyzer that does not contain heparin. Early recognition of false (K+) elevations is thus crucial to prevent detrimental interventions.

PUB155
The Risks of the Administration of the Newly Introduced Potent Potassium Binders in Pseudohyperkalemia: Two Case Series
Macaulay A. Onuigbo. University of Vermont College of Medicine, Burlington, VT.

Introduction: Pseudohyperkalemia, first reported in 1955 by Hartmann and Mellinkoff, is a marked elevation of serum potassium in the absence of clinical evidence of electrolyte imbalance. Simultaneous serum potassium exceeds plasma potassium by >0.4 mEq/L. Pseudohyperkalemia has mostly been associated with moderate to severe thrombocytosis or leukocytosis. Unmistakably, true hyperkalemia is potentially lethal. Nevertheless, inappropriate treatment of pseudohyperkalemia leading to severe hyperkalemia is also life-threatening.

Case Description: Two patients with pseudohyperkalemia received inappropriate potassium binders: A 40-year-old African American male patient with sickle cell anemia with acute kidney injury, anion gap metabolic acidosis and true hyperkalemia subsequently developed pseudohyperkalemia secondary to prophylactic thrombocytosis in the same hospitalization (Figure 1). He received over one week of sodium zirconium cyclosilicate before the diagnosis of pseudohyperkalemia was considered, during the finding of a normal EKG with serum potassium of 6.7mEq/L. A 77-year-old female with previously undiagnosed erythrocytosis and thrombocytosis from polycythemia vera had received over 3 months of Patiromer, for suspected renal tubular acidosis before the PCV was diagnosed and testing confirmed pseudohyperkalemia. Both potassium binders were promptly of an unknown when pseudohyperkalemia was confirmed by simultaneous plasma versus serum potassium measurements. Subsequent potassium monitoring reverted to plasma potassium measurements only.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Symptomatic Hyponatremia and Possible Pulmonary-Renal Syndrome

Our patient was diagnosed with chronic milk-alkali syndrome. This syndrome is characterized by hypercalcemia, hyperphosphatemia, metabolic alkalosis, AKI and metastatic calcification. Hypercalcemia causes vasoconstriction, which decreases the glomerular filtration rate (GFR). It suppresses PTH secretion and leads to renal retention of phosphate. It activates the calcium-sensing receptor (CaSR) at the basolateral surface of Loop of Henle cells, inhibiting natriuresis and inducing volume depletion, which augments proximal reabsorption of calcium and bicarbonate. Alkalosis activates the pH-sensitive calcium channel, TRPV5, in the distal nephron, thereby contributing to calcium retention and hypercalcemia. Standard treatment is withdrawal of exogenous calcium and administration of intravenous normal saline. Furosemide is sometimes used in severe cases.

An Unexpected Cause of Hypokalemia

Our patient initially presented with anion gap metabolic acidosis in the setting of starvation ketosis and metabolic alkalosis.

Discussion: Physicians must always give consideration to the plausibility of pseudohyperkalemia under appropriate clinical scenarios. One recurring mantra remains that true hyperkalemia in the absence of overt kidney dysfunction must always be viewed with circumspection and doubt. Iatrogenic life-threatening hypokalemia remains a real concern and must be avoided.

Discussion: Our patient presented with abnormal labs (Table 1). She had no urinary frequency, abnormally high, nausea, vomiting, constipation, or confusion on admission. She had mild pruritus and bilateral plantar foot and elbow pain. Her EKG was unremarkable. She received 2 liters of 0.9% saline and was started on continuous 0.9% saline intravenous fluids at 150 mL/hour upon admission. She drank a half-gallon of milk per day for the last two years. She consumed a Premier protein shake each morning with breakfast, which contains 50% of the daily value (DV) of calcium and 25% of the DV of Vitamin D. She rarely took antibiotics. She had a multivitamin containing 100% of the DV of Vitamin D and an additional Vitamin D supplement. Review of systems was positive for episodes of polyuria, urinary frequency, and dry mouth, for which she compensated with large volume fluid intake.

Discussion: Hypokalemia occurs in 15-30% of hospitalized patients and is associated with increased morbidity and mortality. Here we present a case of severe symptomatic hyponatremia, acute kidney injury, and dyspnea.

Case Description: A 59-year-old female with history of chronic obstructive pulmonary disease presented to the emergency department for recurrent falls and shortness of breath. She complained of confusion, difficulty with ambulation, and increased swelling in her bilateral arms/legs with 18 pound weight gain in one week. On examination she was hypotensive, tachycardic and tachypneic. There was jugular venous distention up the mid-neck, decreased breath sounds and 2+ pitting edema of all four extremities and the anterior abdominal wall. Laboratory results are shown in Figure 1. Chest X-ray showed bilateral infiltrates. Urine microscopy showed 20 – 30 erythrocytes, but no casts. She received multiple infusions of 3% NaCl and loop diuretics. Her mentation improved, but she eventually required kidney replacement therapy. Kidney ultrasound was unremarkable. Kidney biopsy showed hypercellular glomeruli and one cellular crescent. Immunofluorescence microscopy showed 1+ mesangial staining with IgA and C3 and electron microscopy showed mesangial immune deposits. She received pulse dose methylprednisolone and cyclophosphamide for treatment of rapidly progressive glomerulonephritis due to HG. She was then treated with continuous kidney replacement therapy with post filter 5% dextrose in water (DSW) replacement to avoid over correction of hyponatremia. She had a very high A-a gradient, but with aggressive ultrafiltration her respiratory status and oxygenation significantly improved. On discharge, she had normal serum sodium concentration, but remained dialysis dependent.

Discussion: The severity of hyponatremia and a picture that suggested pulmonary renal syndrome were unusual. However, based on her response to treatment and further work up, her hyponatremia was related to severe volume overload. Her volume status stabilized with ultrafiltration and her serum sodium corrected appropriately by infusing D5W into the CRRT circuit, post-filter.
PUB159

Successful Therapy for Life-Threatening Hyperkalemia with Isotonic Sodium Bicarbonate and No Dialysis

Vijayakumar Paramasivam, Daniel G. Gomez, Spencer Hodgins, Daniel L. Landry, Gregory L. Braden. UMass/Baystate, Springfield, MA.

Introduction: Isotonic sodium bicarbonate (ISB) intravenously (iv) alone in acidotic pts was shown by K Schwarz, Circulation, 19:215, 1959 & Adler and Fraley in Kid Int, 12: 354, 1977 to cause up to a 3 mEq/L decrease in serum potassium (K) within 4 hours when 150-200 mEq iv ISB was given. We treated a pt with a serum K of 9.8 mEq/L in near sinus wave EKG pattern who refused dialysis with ISB which brought her K to normal in 14 hrs.

Case Description: A 90 yr old woman with Type 2 diabetes presented in sine wave, HR 75-80 bpm & systolic BP 80 mmHg with a K of 9.8 mEq/L. She had 1 ml/kg/d a baseline serum creatinine of 1.6 mg/dl with a K of 6.2 mEq/L & serum bicarbonate of 19 mEq/L. She was started on trimethoprin/sulfa 1 week earlier. Admission labs showed (mEq/L): Na 141, K 9.8, Cl 108, HCO3 13, serum creatinine 3.6 mg/dl, pH 7.2, UNa 43 mEq/L, UK 31 mEq/L, FE NA 1.8% & TTKG 0.5. The family & pt refused dialysis. She was given 3 amps of iv 10% calcium gluconate & her EKG converted to sinus rhythm. ISB (150 mEq of Na & bicarbonate/L) was started at 150 ml/hr along with sodium polystyrene resin 60 gm every 6 hours & 1 amp of Dextrose 50% (25 gm) followed by 10 U of regular insulin every 4 hrs. Labs in mEq/L showed: After 5 hrs: Na 145 K 7.8, bicarb 16, glucose 156 mg/dl. After 10 hrs: Na135, K 6.8, Bicarb 20 glucose 185 gm/dl. After 14 hrs: Na 135, K 5.5, Bicarb 21 glucose 248 mg/dl. After 24 hrs: Na 142, K 3.3, Bicarb 28 glucose 157mg/dl & TTKG 44.

Discussion: Our pt showed a 2 mEq/L decrease in serum K 5 h after a fast drip infusion rate of ISB giving 112 mEq of ISB a 3 mEq/L decrease after 225 mEq ISB & 4.3 mEq/L after 315 mEq ISB plus iv dextrose and regular insulin every 4 h. Sodium polystyrene resin works after 6 h and helped later lower the serum K. The low TTKG at the different times shows that increased renal excretion did not account for the dramatic decrease in serum K. We Conclude: In acidotic pts ISB by continuous iv infusion along with q 4h iv infusion can successfully reverse life threatening hyperkalemia without dialysis.

PUB160

An Interesting Case of Non-Anion Gap Metabolic Acidosis Secondary to Arginine Hydrochloride Infusion Therapy

Jwanjot K. Narula, Kiran Shivaraj, Angela Y. Kim, Nadera Rahman, Amol Mittal. Westchester Medical Center, Valhalla, NY.

Introduction: Mitochondrial disorders are relatively common inherited disorders, the syndrome of mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) is a disorder characterized by hemiparesis, cortical blindness, or hemianopia, muscle weakness, seizures. Treatment of MELAS is critical, delay may result in cortical injuries, neurologic dysfunction and ultimately dementia. The pathophysiology involves reduced vasodilation. L-Arginine is a precursor to nitric oxide, which mediates vasodilation. Despite widespread use of arginine hydrochloride, there is limited understanding of its adverse effects, particularly metabolic acidosis.

Case Description: In our case report, we present a 60 year old male with MELAS who was brought in due to a 3 week progressive weakness, falls associated with poor appetite and failure to thrive. In the hospital, he became encephalopathic with RLL Aspiration pneumonia. Head CT showed ischemic changes. He was started on 30mg IV arginine HCl in 300ml of NS over 90 minutes. Day 1 of infusion, he developed hyperchloremic non anion gap metabolic acidosis with hyperkalemia. Due to hyperkalemia refractory to medical management and development of nonoliguric AKI due to ischemic ATN, the patient was started on CVVHHD. His renal function recovered after two days with no further indications to continue dialysis, hypotension had also resolved with removal of vasopressor support.

Discussion: The pathogenesis of clinical features in MELAS has been attributed to the energy defect, causing dysfunction of the microcirculation thus poor perfusion. In our patient, who had hypoperfusion and encephalopathy, L-Arginine was the initial treatment. The recommended infusion is standardized in adults. We suspect in our patient, the renal impairment resulted in the loss of renal excretion of bicarbonate combined with the relatively high arginine dose due to low body surface area resulted in severe acidosis. To prevent metabolic acidosis with the infusion of Arginine HCl, it should be dosed as per the BSA with close monitoring of the pH. The ability of the kidney to acidify the urine is limited and hence, the goal of the newly created role of industry-sponsored patient navigators will support enriched enrollment and retention of a diverse and inclusive population in the ARENA2 trial for distal renal tubular acidosis (dRTA), a rare genetic disorder.

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potential subjects and establish rapport. Native-language welcome packets that included information on the dedicated services and mapped out home care visit sites/expectations were created. Diverse and inclusive enrollment and retention rates will be compared to prior rare disease trials upon completion of the 12-week ARENA2 study.

**Conclusions:** Industry-sponsored, culturally sensitive, bilingual patient navigators are key stakeholders in clinical trials for rare disorders, especially DC1, and can help reduce ethnic and racial disparities. The ARENA2 trial, will analyze and report on the patient navigator’s unique role impacting trial enrollment and retention of Spanish and French speaking populations by addressing complex problems in underrepresented populations.

**Funding:** Commercial Support - Advicenne

**PUB163**

*The Prevalence of Hyperkalemia and Associated Risk Factors in a General Population*

Xiaohong Pan, Wenling Ye, Jie Ma, Xuemei Li. Peking Union Medical College Hospital, Beijing, China.

**Background:** Hyperkalemia has been related to the risk of cardiovascular events associated mortality. The object was to determine the epidemiology of hyperkalemia and associated risk factors in a rural Chinese population.

**Methods:** We performed a cross-sectional study of 10,281 participants in China in 2014. All participants completed a questionnaire, physical examination, and collected venous blood to detect serum creatinine, and inorganic ions (potassium, etc.). First void morning urine was collected to detect the albumin-creatinine ratio(ACR) and urine potassium. Hyper- and hypokalemia were defined as serum potassium levels >5.0 mEq/L and <3.5 mEq/L, respectively.

**Results:** The mean age of the study population was 55.4±10.0 years; 47.1% were males. The crude prevalence of hyper- and hypokalemia was 9.3% and 0.3%, respectively. The subjects with hyperkalemia had higher urine potassium-creatinine ratio (4.4±2.6 vs. 3.7±2.5, P=0.001) and potassium excretion fraction (60.1±48.9 vs. 54.1±46.5, P=0.001). In multivariate analyses, the individuals with decreased eGFR-60ml/min/1.73m² had a 3.17-fold increase in the odds of having hyperkalemia. Hypertension, diabetes, and high low-density lipoproteinemia(LDL) were significantly associated with the increased risk of hyperkalemia. However, the female was negatively associated with hyperkalemia even after excluding those with decreased eGFR. The ACEI use was not found to be independently related to hyperkalemia.

**Conclusions:** The male and participants with hypertension, diabetes and high LDL had an increased risk of having hyperkalemia. Physicians should raise awareness of high-risk groups.

**Factors associated with hyperkalemia in the general population**

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.05 (1.04-1.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender (male vs. female)</td>
<td>1.15 (1.03-1.29)</td>
<td>0.011</td>
</tr>
<tr>
<td>BMI</td>
<td>1.10 (1.04-1.17)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.21 (1.00-1.42)</td>
<td>0.049</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.15 (1.00-1.32)</td>
<td>0.047</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>1.01 (1.00-1.01)</td>
<td>0.007</td>
</tr>
<tr>
<td>Decreased GFR-60 (ml/min/1.73m²)</td>
<td>1.17 (1.01-1.36)</td>
<td>0.039</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>1.23 (1.07-1.41)</td>
<td>0.003</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>1.20 (1.01-1.41)</td>
<td>0.038</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>0.88 (0.78-0.99)</td>
<td>0.036</td>
</tr>
<tr>
<td>Hypocholesterolemia</td>
<td>0.84 (0.73-0.98)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

BMI: body mass index; LDL: low-density lipoprotein; eGFR: estimated glomerular filtration rate; ACR: albumin-creatinine ratio; ACEI/ARBs: angiotensin-converting enzyme inhibitor/ Angiotensin receptor blockers.

**PUB164**

*A Suspected Case of Cerebral Salt Wasting (CSW) Syndrome in a Patient with Traumatic Subdural Hematoma: Revisiting a Long Debated Topic*

Karim T. Attia, Jessica M. Grecco. The Ohio State University Wexner Medical Center. Columbus, OH.

**Introduction:** It has long been debated whether CSW is a true entity causing hyponatremia in patients with central nervous system (CNS) pathology or whether the hyponatremia is actually secondary to SIADH while apparent salt wasting is due to underappreciated volume expansion. Literature agrees, for the most part, that CSW is a separate disease process and it has been mostly described in patients with aneurysmal subarachnoid hemorrhage. It has also been described in other forms of CNS pathology underappreciated volume expansion. It has long been debated whether CSW is a true entity causing hyponatremia in patients with central nervous system (CNS) pathology or whether the hyponatremia is actually secondary to SIADH while apparent salt wasting is due to underappreciated volume expansion. Literature agrees, for the most part, that CSW is a separate disease process and it has been mostly described in patients with aneurysmal subarachnoid hemorrhage. It has also been described in other forms of CNS pathology underappreciated volume expansion.

**Case Description:** A 30-year-old male with no significant past medical history was admitted to a subdural hematoma, minor cervical fractures, intraspinal ligaments strain, and lacerations. He was discharged on narcotic pain medications, gabapentin, and keppra for seizure prophylaxis. Serum sodium was 135mEq/L at the time of discharge. He returned on 5/5/21 after several days of feeling uncoordinated and having orthostatic symptoms. He was found to have evidence of volume depletion of physical examination. Computed tomography (CT) of the brain showed resolution of prior subdural hematoma. Serum sodium on admission was 115mEq/L. It later dropped to 112mEq/L post hydration with IV fluids composed of normal saline with 5% dextrose. Net sodium balance was calculated to be -60.4 mEq during that initial interval suggesting renal salt wasting. He eventually improved after several days of infusion with hypertonic saline, fluidcorrection, and prescriptions for thiazide diuretics and metformin. Death was similarly evaluated as a competing risk.

**Results:** 125,551/136,067 patients (92%) had no evidence of guilt during the pre-index period. During the period up to 11.5 years of follow-up (median 4.2 years), the following covariates were most strongly associated with incident guilt: male sex (HR 1.69, 95% CI:1.63-1.76), Black or Asian race (HR 1.52, 95% CI:1.44-1.60 and HR 1.47, CI:1.23-1.75), and hypertenrsion (HR 1.40, 95% CI:1.27-1.55). Hispanic ethnicity (HR 0.82, 95% CI:0.73-0.92), low-income status (HR 0.90, 95% CI:0.85-0.94), higher baseline eGFR (HR 0.98, 95% CI:0.979-0.983, and lower overall comorbidity burden (HR 0.98, 95% CI:0.97-0.99) were associated with a lower risk of guilt. Baseline serum bicarbonate and time-dependent change in serum bicarbonate were not associated with incident guilt.

**Conclusions:** In this longitudinal analysis of patients with CKD, serum bicarbonate was not associated with the development of guilt.

**Funding:** Commercial Support - Tricida, Inc.

**PUB166**

*Hyponatremia in a Patient with Chyle Leak*

Harish C. Nuthakki. UT, Houston, TX.

**Introduction:** Chylous ascites can cause a multitude of electrolyte abnormalities. Hyponatremia is not a very common presentation unlike hypernatremia in pts with chylous ascites. Here we present a case of hyponatremia in a patient with chylous ascites and the various management challenges we face while managing the hyponatremia.

**Case Description:** We present a case of a 75y old female with a history of papillary cancer of the thyroid status post thyroidectomy and left neck dissection, with worsening chyle leak from the surgical site with evidence of local recurrence of cancer with hypoproteinemia. She presented with hypotension, which was treated by infusing 4L of normal saline over a period of 36 hours. She was also receiving 1.5L of free water daily with her tube feeds, which were 85% free water. On hospital day 3, she developed hypo-osmolar hyponatremia which reached the nadir over the next 48 hours, and nephrology was consulted. Patient’s urine and serum studies showed a high ADH state and volume depletion. Her volume depletion is due to the chyle leak and the concomitant high ADH state due to relapsing papillary thyroid cancer. Patient’s chyle leak responded to IV octreotide and a low-fat diet with medium-chain triglyceride supplements. The hyponatremia resolved with administration of oral sodium chloride tablets once the chyle leak was controlled.

**Discussion:** Patients with chylous ascites suffer volume depletion who can be a challenge to quantify secondary to the location of the leak. Excessive fluid administration, either isotonic or hypertonic can lead to severe life-threatening hyponatremia in these patients. Physicians should pay attention to the amount free water being administered through tube feeds in these pts with active malignancies as they are prone to high ADH states.

**Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only**

*Underline represents presenting author.*

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SIADH-Related Hyponatremia due to a Non-Functioning Hemorrhagic Pituitary Adenoma

Saira Sajid, Katerina Hysi, Minesh Khatri, James Drakakis. NYU Winthrop Hospital, Mineola, NY.

Introduction: Determining the etiology of hyponatremia can be challenging. When euvolemic, one need consider a diagnosis of syndrome of inappropriate antidiuretic hormone (SIADH). This can be classified into two groups: ectopic production of ADH or release from the posterior pituitary gland related to disorders of the central nervous system, pulmonary disorders or drug administration. Mechanisms of posterior pituitary related hyponatremia are usually due to hypopituitarism or dysfunction of the pituitary adrenal axis. More rare, are reports of SIADH in patients with pituitary tumors and normal associated function. This case is presented to be related to mechanical stress.

Case Description: 39-year-old female with no past medical history presented to the emergency department complaining of numbness and tingling of the bilateral upper and lower extremities. Serum sodium was found to be 122 mEq/L. Urine osmolality was 811 mOsm/kg and urine sodium 179 mmol/L. An initial CT scan showed fullness of the sella, possibly representing an underlying lesion. Subsequent MRI of the brain revealed a sellar/suprasellar lesion most consistent with a hemorrhagic pituitary adenoma. Neurohypothalamic axis proved to be intact and the tumor appeared non-secretory. As such, the working diagnosis was SIADH caused by mechanical stress and inappropriate ADH release from the posterior pituitary. She was given a low dose (7.5 mg) of Tolvaptan with ensuing rapid correction of sodium, which required administration of DDAVP and D5W to slow down. Ultimately, salt tablets were started to help maintain an acceptable sodium range. Plan is for endoscopic transsphenoidal resection of the pituitary mass.

Discussion: The clinical and laboratory features of this case were consistent with SIADH. There was hyponatremia, in the setting of euvolemia and high urine osmolality and urine sodium. Furthermore, the function of the pituitary gland remained normal on biochemical assessment. In such a scenario of increased ADH secretion, it is important to evaluate the anatomical interaction between the pituitary tumor and the hypothalamo-neurohypophyseal system. The tumor may push the pituitary stalk upward leading to mechanical stress and the isolated gland causing inappropriate ADH release. Such a description is a very rare occurrence, but nevertheless need be considered as a cause of SIADH related hyponatremia.

Hyponatremia and Hypothyroidism: Association or Causality?

Goutham Kondapi, Eric Krutel, Joel M. Toft. Ascension St John Hospital, Detroit, MI.

Introduction: Among the various etiologies of hyponatremia, one that is frequently called into question is hypothyroidism. Literature review repeatedly indicates that only the severe state of myxedema coma has a causality with hyponatremia. Data examining the incidence of hyponatremia in less severe hypothyroidism is conflicting; there is question as to whether there is any causality at all. Here we present a case of hyponatremia that is attributable to severe hypothyroidism without myxedema coma.

Case Description: 71-year-old female with a past medical history of hypothyroidism presented to the hospital following a fall and complaint of generalized weakness. Patient had a serum sodium of 111, initially thought to be SIADH given a low serum uric acid, urine osmolality less than 20, and serum osmolality of 242. However, the patient had TSH of 65.70 mcunits/mL with T4 less than 0.1 ng/dL. An initial CT scan showed fullness of the sella, possibly representing an underlying lesion. Subsequent MRI of the brain revealed a sellar/suprasellar lesion most consistent with a hemorrhagic pituitary adenoma. Neurohypothalamic axis proved to be intact and the tumor appeared non-secretory. As such, the working diagnosis was SIADH caused by mechanical stress and inappropriate ADH release from the posterior pituitary. She was given a low dose (7.5 mg) of Tolvaptan with ensuing rapid correction of sodium, which required administration of DDAVP and D5W to slow down. Ultimately, salt tablets were started to help maintain an acceptable sodium range. Plan is for endoscopic transsphenoidal resection of the pituitary mass.

Discussion: The mechanism behind hypothyroid-induced hyponatremia is not well understood. Studies have suggested a hypothryoid state causes a decrease in cardiac output and peripheral vascular resistance, leading to decreased renal perfusion and decreased GFR. One study found that in patients with primary hypothyroidism before and after thyroid replacement, all had decreased GFR, with hyponatremia observed in greater than half the subjects. However, another study found hyponatremia to be uncommon in more short term hypothyroidism. Literature review has largely identified hypothyroidism-induced hyponatremia in myxedema coma. However, this patient presented not with symptoms suggestive of myxedema coma, but with an elevated TSH and no other attributable cause of her hyponatremia. Additionally, the low uric acid and urine sodium argue against a decrease in renal perfusion as the cause of ADH release. In summary, though some recent literature calls into question hypothryoidism causing hyponatremia, we present a case of profound hyponatremia in a patient with severe hypothyroidism without myxedema coma, which responded to treatment of her hypothyroidism as well as hypertonic saline.

A Rare Case of Low-Dose Cyclophosphamide-Induced Symptomatic Hyponatremia

Sajid Karandish,1 Tsering Dolkar,2 Dawn Maldonado,1 Ishita Bansal,1 Maritza Brown,2 Ayesha Mallick Imam.1 (Mount Sinai Health System, New York, NY); 1Mount Sinai Hospital and Medical Center, New York, New York, NY.

Introduction: We report a case of severe acute symptomatic hyponatremia with generalized tonic clonic seizures after the first cycle of adjuvant chemotherapy with cyclophosphamide.

Case Description: We present a case of 62-year-old woman who was diagnosed with breast cancer and underwent lumpectomy followed by first cycle of chemotherapy with cyclophosphamide, dexamethasone, and doxorubicin. She received low dose, 15 mg/kg or 1,030 mg IV Cyclophosphamide. On the day of chemotherapy her sodium was 144 mEq/L. The next day the patient had a seizure at home. While in the Emergency Department she had another that only high doses of physaliphosphine (>40 mg/kg) could induce hyponatremia. However, cases of low-dose cyclophosphamide (<20 mg/kg), have been reported, though uncommon. We report a rare case of low dose cyclophosphamide-induced symptomatic hyponatremia. Our patient’s rapid decline of sodium could have precipitated the seizure. Using hypertonic saline, hyponatremia resolved, and symptoms of hypothyroidism also improved. Thus, physicians should have a low threshold to suspect cyclophosphamide-induced hyponatremia which can be life threatening.

Von Hippel-Lindau Syndrome (VHL) Associated with a Breast Tumor


Introduction: We present a case of a woman who was incidentally found to have a breast tumor at the same time that she was found to have several other cysts and tumors, and was ultimately found to have Von Hippel-Lindau syndrome (VHL). The breast tumor association has not yet been described in VHL.

Case Description: A 21-year-old female presented to another facility with dysphagia and bilateral upper extremity weakness. CT and MRI of the brain demonstrated multiple cysts in the spinal cord extending to the brain stem. Her renal ultrasound findings were read as polycystic kidney disease. The patient underwent C5-C7 laminectomy and resection of the largest intramedullary tumor. Pathology report revealed grade 1 hemangioblastoma. She presented to our hospital 3 months later for dyspnea and tachycardia, so CT angiogram of the chest was performed to rule out pulmonary embolism. It incidentally revealed a right breast mass measuring 3.5x2.7 cm, a 1.9 cm liver lesion, and innumerable sub-centimeter hypodense masses in both kidneys. The dyspnea was attributed to pneumonia and atelectasis from her post-operative recovery. A repeat renal sonogram at our facility demonstrated small kidney cysts, so the diagnosis of PCOS was questioned and re-evaluated. Genetic testing ultimately returned positive for VHL-1. Her breast mass was found to be a BIRADS-4A lesion on ultrasound, and core biopsy demonstrated a fibroadenoma.

Discussion: VHL is a rare autosomal dominant disorder characterized by the presence of multiple benign and malignant tumors and a pathogenic variant of the VHL gene. VHL is a tumor suppressor gene that inhibits hypoxia-inducible transcription factor, thereby inhibiting hypoxia-induced vascular growth. Loss-of-function mutations hence lead to tumor growth in multiple organs. Tumors associated with VHL include infratentorial or cerebellar hemangioblastomas, retinal hemangioblastomas, renal cysts and pheochromocytomas. It remains unclear whether the breast fibroadenoma was associated with VHL. However, the literature on VHL remains limited, so we may not yet know all potential lesions associated with VHL. We therefore present this case to contribute to the literature on possible VHL presentations.

Perineural Cysts in Polycystic Kidney Disease

Kana R. Amari, Jennifer A. Tuazon. Northwestern University Feinberg School of Medicine, Chicago, IL.

Introduction: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common hereditary kidney disease characterized by cyst formation in the kidneys and other organs. In the neurovascular system, perineural cysts have been reported in ADPKD. Most cases are located at the nerve root canals along the spine. Only a few cases of spinal meningeal cysts/perineural cysts have been reported, though uncommon. We report a rare case of localized symptomatic meningeal hyponatremia which can be life threatening.

Case Description: We present a case of a 51 y.o. man presented to the Nephrology clinic for ADPKD. He underwent an MRI of the abdomen to calculate his total kidney volume. Incidentally found were multiple T2 hyperintense lesions in the intercostal space corresponding to the left paraspinal midline area. A dedicated MRI of the thoracic spine was subsequently performed which further characterized the lesions to reflect perineural cysts.

Discussion: Perineural cysts are benign pouches filled with cerebrospinal fluid (CSF) located at the nerve root canals along the spine. Only a few cases of spinal meningeal cysts/perineural cysts have been reported in association with ADPKD. Most cases are asymptomatic, but variable nerve root or spinal cord compression may be present. Back pain, radiculopathy, and headache due to cerebrospinal fluid leakage may also occur, thus, such symptoms in a patient with ADPKD should warrant further investigation for this condition.

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**A Male Senior with Alport Syndrome in Digenic Inheritance of COL4A3 and 4A4**

Shinichiro Koga, Section for Nephrology and Hypertension, Department of Medicine, Tokyo Metropolitan Police Hospital, Tokyo, Japan.

**Introduction:** Alport syndrome (AS) sometimes show positive in alpha 2 (α2(V)) and 5 (α5(IV)) chains of type IV collagen in the glomerular basement membrane (GBM). This could illustrate with the facts that: 1) α5(IV) in basement membranes of Bowman corpus and cortex are normally immunofluorescent in 20 % of autosomal recessive AS (ARAS) patient 1); and 2) autosomal dominant AS (ADAS) as well as normal kidney are known to be positive in α5(IV).

**Case Description:** A 21-year-old Asian male senior (“the patient”) was referred to nephrology outpatient clinic due to persistent microscopic hematuria for over fifteen years. No apparent kidney abnormality was found in echogram so was observed till fourth grade of elementary school. Not only himself but his mother and elder brother had hematuria; this brother recently had complained of low-tone hearing loss. The patient had no ocular defect nor hearing loss; no hypertension, diabetes, nor hypercholesterolemia. Serum Cr 0.95 mg/dl; urine RBC 30-100/HPF, beta2-MG 42 microg/L, and UP/Cr 47.9 mg/gcr. LM of the kidney was near normal. The routine IF examination for Iggs and complement components were negative. α2(IV) and α5(IV) were not lack in immunofluorescence staining. EM show 10% area of GBM had irregular thinning; No EDD in glomeruli. SPEED-KID version 3.0 2) next generation sequencing covered thoroughly 99.2 % genes, as well as COL4A3, 4A4, 4A5, and 4A6 genes. A known c.G469C,p.G157R 3), and a known c.T479C,p.L1598R 4) mutation was detected in COL4A3 gene. Novel c.G929A,p.R310Q was detected in COL4A4 gene. No mutation in 4A5 and 4A6 genes. The diagnosis of AS was made of persistent microscopic hematuria, type IV collagen gene mutations, and family history of nephritis. His mother also had a known D682G mutation in COL4A4 3), as well as a known G157R mutation in COL4A3 3). His elder brother has not been investigated so far.

**Discussion:** Two mutations in COL4A3 gene were located in another chromosome so indicated as having heterozygous compound mutations in COL4A3 gene of the patient. ADAS sometimes occur within a family; Its genetic manner, autosomal dominant, could differ symptoms among them. The patient had two individual gene mutations in COL4A3 and 4A4, which has severe clinical features as digenic inheritance 4). References 1) Pediatr Nephrol 2014;29:1535-44. 2) Clin Exp Nephrol 2017;21:63-75. 3) Plos One 2013;8:e71381. 4) Pediatr Nephrol 2015;30:1459-65.

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**The Importance of Family History in Evaluating Persistent Microscopic Hematuria**

Javad Najar Mojarab, Somto T. Nwaedozie, Syed M. Sajjad, Rebecca Blonsky, Marshfield Clinic Health System, Marshfield, WI.

**Introduction:** Alport syndrome (AS) is a condition caused by one or more mutations in COL4A3-5 (1,2). These result in abnormal production of alpha chains 3, 4, and 5 of type IV collagen in the basement membranes of kidneys, cochlea, and eyes (2.3). Patients exhibit progressive glomerular disease that usually occurs with hematuria, sensorineural deafness, eye abnormalities, and/or leiomyomatosis (2-5). We present a case of presumed AS in a woman with persistent microscopic hematuria and preserved renal function.

**Case Description:** A 40-year-old woman with a history of Raynaud’s syndrome and hypothyroidism was referred to nephrology for persistent microscopic hematuria. Hematuria was first noted in 2008 though renal function remained normal, and she had no significant proteinuria. Social history was non-revealing. The patient’s family history was significant for multiple family members with End Stage Renal Disease (ESRD) requiring either dialysis or transplant. The patient underwent a renal ultrasound as well as serologic evaluation which were non-revealing. However, due to the patient’s long history of hematuria in addition to her family history, a kidney biopsy was performed. Light microscopy and immunofluorescence were normal; however, electron microscopy demonstrated varying levels of basement membrane thickness. These findings are consistent with Alport syndrome. Genetic testing was performed to identify a mutation in type IV collagen but was unremarkable. Given the patient’s family history, biopsy findings, and no identified pathogenic genetic variant, the patient will undergo whole exome sequencing.

**Discussion:** AS is generally an X-linked disease though other modes of transmission are possible (1-5). Patients with autosomal recessive and X-linked forms can have similar presentations with possible sensorineural hearing loss and visual abnormalities that are rare in patients with autosomal dominant forms. One of the most commonly observed renal manifestations of AS is persistent hematuria either microscopic or gross with the latter being very rare. Females with an X-linked form usually present with microscopic hematuria (4). AS is diagnosed by genetic testing and skin or renal biopsy. Genetic testing is preferred since it is highly accurate and non-invasive though cases of AS with no detectable mutations or copy number variants of COL4A3-5 are reported (1,3).

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**A Rare Case of Gordon’s Syndrome**

Anne Marie Pop, Victoria Golas, Priya Gupta, Kelly M. Mercier, Michael S. Misuraca, Beaumont Hospital - Farmington Hills, Farmington Hills, MI.

**Introduction:** Pseudohypopaldosteronism type II (PHAI) or Gordon’s Syndrome, is a rare inherited form of hypertension. It is characterized by hyperkalemia, metabolic acidosis, normal GFR, and a low renin state³. The first case was described in 1964 with only a few hundred cases being discovered since, making each diagnosis an important and unique discovery¹. There are increasing studies investigating the alteration of genetic pathways leading to disease. In this case, a young male presents for persistent hyperkalemia and was diagnosed with Gordon’s syndrome.

**Case Description:** A 33-year-old caucasian male presented to the emergency room with the chief complaint of abdominal pain. Family history is significant for a daughter who has a history of recurrent hyperkalemia of unknown etiology. Initial vital signs were within normal limits, including blood pressure. Labs revealed potassium of 6.4, a mild non anion gap metabolic acidosis, and serum creatinine of 1.26 with no prior diagnosis of chronic kidney disease. Urine potassium was 12.3 mmol/L and considered of inappropriate renal retention of K was made. Cortisol and aldosterone levels were normal. Renin level was low at < 2.1pg/mL. He was treated with potassium binders as well as sodium citrate inpatient with improvement in hyperkalemia. Upon follow-up, hyperkalemia recurred despite an improved SCr of 0.9. Genetic testing revealed a variant in the WNK4 gene consistent with Gordon’s Syndrome. The patient was started on 12.5 mg of hydrochlorothiazide and has missed all follow-up appointments to date.

**Discussion:** The discovery of this rare, inherited disorder has lead to the understanding of potassium and sodium handling along the distal convoluted tubule (DCT)¹. The main disturbance involved is the activation of the thiazide-sensitive NaCl cotransporter (NCC) at the DCT². Mutations in WNK1 and WNK4 genes were found to further increase the activity of the NCC as well as decrease surface expression of ROMK.¹ There are also findings that a chloride shunt is present¹. It is with these studies that we have been able to identify the causation of pathogenesis and subsequent treatment. Our patient presents as a unique case as this autosomal dominant mutation was found later in life as well as being normotensive which can be present in ~20% of cases. Regardless of presentation, one must consider this rare disorder as treatment can be lifesaving.
PUB175
Market Research Studies Across Primary Hyperoxaluria (PH) Subtypes: PH1, PH2, and PH3
Claudia Dalloso,1 Donald P. Julien,1 Guy Buckland,2 Scott Hengst,2 David Eckford,3 Chris Okonis,1 1Discerna Pharmaceuticals Inc, Lexington, MA; 2Clarivate Analytics US LLC, Philadelphia, PA; 3Collective Acumen, Greenwich, CT.

Background: PH is a family of ultra-rare genetic disorders causing hepatic oxalate overproduction that can result in recurrent kidney stones, life-threatening kidney damage, and systemic oxalosis. There are 3 known subtypes of PH (PH1, PH2, and PH3). PH1 was the first subtype to be characterized and is the most studied. While PH2 and PH3 are less well understood, increasing evidence suggests that they have more severe clinical consequences than previously thought.

Methods: Several market research studies (table 1) were conducted to better understand PH disease burden across subtypes. All data are physician-reported. Copies of medical charts or genetic test reports were not provided for verification purposes.

Results: Across all studies, responders reported a large subset of PH patients with moderate to severe renal disease. Specifically, the percentage of patients in CKD Stage 3 or worse was the following: --- PH1: 87% (Study 1), 56% (Study 2), and 39% (Study 3) — PH2: 92% (Study 1), 68% (Study 2), and 55% (Study 3) — PH3: 83% (Study 1), 41% (Study 2), and 48% (Study 3). Stone burden was similar across PH subtypes: a urine concentration of 3.24 (PH1), 3.92 (PH2) and 4.95 (PH3) stones in the last year (study 1) — 62% (PH1), 71% (PH2), and 61% (PH3) of patients with no renal impairment presented with 3 or more stones in 5 years (study 3). Nephrocalcinosis was reported in 48% (PH1), 61% (PH2), and 38% (PH3) of patients (study 1). The rate of hospitalizations and emergency room visits was comparable across all subtypes: 63% (PH1), 64% (PH2), and 57% (PH3) (Study 1). Management of PH is qualitatively the same as PH1 and PH2. Hyperhydration, stone removal procedures, and vigilant monitoring of disease progression (study 3) are standard of care.

Conclusions: Results from these completed market research studies suggest that severe disease burden and progression is consistently reported across PH1, PH2, and PH3.

Funding: Commercial Support - Discerna Pharmaceuticals

Table 1: Market research studies

<table>
<thead>
<tr>
<th>Study</th>
<th>PH1</th>
<th>PH2</th>
<th>PH3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD Stage 3 or worse</td>
<td>87%</td>
<td>56%</td>
<td>39%</td>
</tr>
<tr>
<td>Stone burden (urine)</td>
<td>3.24</td>
<td>3.92</td>
<td>4.95</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>62%</td>
<td>71%</td>
<td>61%</td>
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</tbody>
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PUB176
Improvement in Metabolic Control in Patients with Distal Renal Tubular Acidosis (dRTA) After Switching from Standard of Care to ADV7103
Valerio M. Panzarino,1 Carol Ogg, MariaA. Manso-Silvan,2 Bradley P. Dixon.3,4 1University of South Florida, Tampa, FL; 2Advicenne Pharmaceuticals, Paris, France; 3University of Denver School of Medicine, Aurora, CO; 4Children’s Hospital Colorado, Aurora, CO.

Background: Patients with dRTA present with hyperchloremic metabolic acidosis leading to a high risk of renal morbidity and mortality. Current standard of care (SoC) requires a multiple dose regimen with reported poor adherence which may render metabolic control difficult. We describe three patients switched from SoC to ADV7103, a fixed bi-daily dosing (ADV7103).

Methods: Three patients with clinically confirmed dRTA (18Y-M, 22Y-F, 16Y-F) enrolled in the ARENA2 Phase 3 study (NCT03644706) prior to COVID-19 interruption. Plasma bicarbonate and potassium levels were measured >12 months post-switch from SoC to ADV7103. Adherence rates by 12 months were normal for plasma bicarbonate from 3 to 12 months after enrolment. Plasma potassium levels (3.0, 4.3, and 2.8 mmol/L respectively at baseline) were normal for patients demonstrated better adherence with ADV7103 as compared to SoC. This small cohort of patients reported improved palatability and satisfaction with ADV7103 treatment as reasons for improved medication adherence and this increased adherence is believed to have had a direct impact on the overall metabolic control achieved throughout the study.

Funding: Commercial Support - Advicenne Pharmaceuticals

PUB177
A Curious Case of Isolated Glucosuria
Umair Khan, Wala Abusalah, Heather L. Lefkowitz. Newark Beth Israel Medical Center, Newark, NJ.

Introduction: Glucosuria exceeding 25 mg/dl is pathological and is known as frank glucosuria. Glucosuria can be grouped into two categories; defective absorption of glucose and overflow glucosuria. Conditions such as hyperthyroidism, pregnancy, fever, and exercise tend to decrease the renal threshold for glucose thereby resulting in glucosuria. Here we present a case of persistent isolated glucosuria likely due to primary renal glucosuria in a healthy 52-year-old female in the absence of any secondary etiologies.

Case Description: A 52-year-old female was evaluated for incidental finding of glucosuria. She was a healthy individual with no history of diabetes mellitus or gestational diabetes, dysuria, polyuria or polydipsia, chronic kidney disease or kidney stones. Home medications included simvastatin, trazodone and a combined OCP. Hemoglobin A1c was mildly elevated at 5.9 with glucose of 121. Dipstick urinalysis showed pH of 5.5, specific gravity of 1.008 with trace glucosuria. In our workup, we were not able to identify any specific cause for our patient’s glucosuria. Her Hgb/A1c was in the prediabetes range however multiple random blood glucose readings were normal. Based on the available information, we suspect that she might have rare genetic mutation in SLCA52 gene responsible for persistent glucosuria.

Discussion: Glucosuria in a non-diabetic patient is rarely observed in the general population. Primary renal glucosuria (PRG) is an autosomal dominant condition caused by a mutation in the SLCA52 gene. A defect in this transporter disrupts the kidney normal function of maintaining glucose homeostasis. Based on a few case reports, PRG has not been associated with any renal dysfunction however polyuria, enuresis and later a mild growth and pubertal maturation on long term follow ups has been reported. In rare cases, episodic dehydration and ketosis during pregnancy and starvation have been reported. Few case reports have also linked isolated glucosuria to autoimmune diseases like Graves and undifferentiated connective tissue disease. Our case emphasizes on the importance of monitoring isolated glucosuria in the general population. Majority of the patients presenting with glucosuria also have concomitant diabetes mellitus or chronic kidney disease, however glucosuria in the absence of comorbid conditions is a rare phenomenon which warrants further evaluation and close monitoring for worsening kidney function.

PUB178
Variants of MTHFR and FGG Genes Are Associated with Levels of Leptin but Not Adiponectin in Colombian Pediatric Lupus Nephritis Gloria Garavito,1 Luis Fang,1 Nicole S. Pereira Sanandres,2 Alex Dominguez-Vargas,1 Gustavo Aroca Martínez,2 Zilac Espíltaleta,1 Ana Moreno-Woo,1 Antonio Iglesias,2 Eduardo Egaña,1 Grupo de Inmunología y Biología Molecular 1Universidad del Norte, Barranquilla, Colombia; 2Clínica de la Costa Lida, Barranquilla, Colombia; 3Universidad Simon Bolivar, Barranquilla, Colombia; 4Universidad Nacional de Colombia, Bogota, Colombia.

Background: Pediatric Systemic Lupus Erythematosus (pSLE) is a chronic autoimmune disease with unknown etiology. Pediatric Lupus nephritis (pLN) has a worse prognosis and morbidity. Leptin/adiponectin and SNPs in MTHFR and FGG genes are known to be risk factors that influence development of atheromatosis and cardiovascular disease. The aim of this study was to evaluate the association of serum leptin and adiponectin levels with SNPs of MTHFR and FGG genes in pLN Colombian Caribbean patients.

Methods: A case-control study (98/100) was carried out in Colombian children. The sample groups were selected from a pLN cohort by simple random sampling. Serum concentrations of leptin and adiponectin were determined by ELISA. SNPs in MTHFR (A1298C rs1801131) and FGG (C10034T-rs2066865) genes were genotyped by qPCR.

Results: Serum leptin and adiponectin levels were significantly increased in pLN patients (24.7%; 28.9%) compared to control group (P < 0.001; P < 0.001 respectively). There was no significant association between MTHFR rs1801131 or FGG rs2066865 SNPs and pLN neither in codominant (P=0.4; P=0.89) nor in allelic models (P=0.88; P=1), respectively. No association was observed between pLN, serum adiponolopes and MTHFR/FGG SNPs (P=0.31; P=0.32), respectively. The AG genotype of FGG gene rs2238570 SNP was significantly associated with serum leptin levels (P=0.016).

Conclusions: In our population, no association was observed between pLN with the SNP variants of the two gene systems studied nor between pLN and adiponokines. However, results in this study found an association between the FGG polymorphism and categorized concentrations of leptin.

Funding: Government Support - Non-U.S.
Proteinuria or hematuria on urinalysis. Family history was very significant and included bilaterally (8.3 cm and 7.9 cm on right and left respectively) and lack of significant serum creatinine 1.8 mg/dL presented for evaluation. Workup revealed small kidneys considered a rare and often underrecognized diagnosis and in fact, clinical features have gone undiagnosed as neonatal screening programs suggest its true prevalence is much lower than what has been reported clinically. Given its low frequency, mass screening for Fabry disease is impractical. However, a targeted screening program of high-risk individuals may uncover previously unknown cases. Our objective was to use population-level administrative health databases to identify patients at high risk of Fabry disease.

Methods: We conducted a retrospective cohort study of all residents of Manitoba, Canada between 1998 and 2018. Using databases housed at the Manitoba Centre for Health Policy, we ascertained a cohort of patients without a diagnosis of Fabry disease who had at least one of the following high-risk conditions: idiopathic hypertrophic cardiomyopathy, ischemic stroke <45 years of age, kidney failure or proteinuria of unknown cause, peripheral neuropathy. We excluded patients with known contributing factors to these high-risk conditions, including, where appropriate, diabetes, hypertension, autoimmune diseases. cancer, glomerulonephritis, and polycystic kidney disease. Those who remained and did not have evidence of GLA testing were considered to have a 0.5-4.0% probability of having Fabry disease.

Results: A total of 145,466 individuals had at least one high-risk condition. Of those, 1,386 remained after applying exclusion criteria. Only 22 of 1,386 (1.6%) had autoimmune diseases. cancer, glomerulonephritis, and polycystic kidney disease. Those who had at least one of the following high-risk conditions: idiopathic hypertrophic cardiomyopathy, ischemic stroke <45 years of age, kidney failure or proteinuria of unknown cause, peripheral neuropathy. We excluded patients with known contributing factors to these high-risk conditions, including, where appropriate, diabetes, hypertension, autoimmune diseases. cancer, glomerulonephritis, and polycystic kidney disease. Those who remained and did not have evidence of GLA testing were considered to have a 0.5-4.0% probability of having Fabry disease.

Conclusions: Administrative health databases may be a useful tool to identify patients at higher risk of Fabry disease or other rare diseases. Further directions include designing a program to screen these individuals for Fabry disease.
along this genetic continuum and where TBMN specifically fits remains an area of ongoing discussion. Our case utilized genetic testing to confirm a deletion in the COLA44 gene, after kidney biopsy findings were consistent with collagen IV nephropathy. The associated perihilar variant of FSGS and glomerulomegaly could be considered a risk factor for escalated CKD progression.

**PUB183**

**MAGED2 Mutation with Bartter’s Syndrome in Adult Patients**

**Introduction:** MAGED2 mutation is associated with a transient antenatal form of Bartter’s syndrome that can be severe enough to lead to death.

**Case Description:** 43-year-old woman with a history of pituitary adenoma on caborbline and levothryoxine, referred to nephropathy for hyperkalemia, hypocalcemia and hypomagnesemia dependent on replacement therapies, frequent lower extremity muscles cramping and weakness post exercise, with frequent ER visits for vomiting and hyperkalemia. A diagnosis of Bartter versus Gitelman’s syndrome was raised. Her Blood pressure on average is 90 systolic (80-100), asymptomatic. She noticed worsening LE edema and systolic up to 110 lately. Renin and aldo were elevated (36 and 51 respectively). FeNa was 0.03%, FeK of 6.76% and FeCa of 0.1%. The low urinary calcium (3mg/dl) was pointing towards a Gitelman’s syndrome. MRI of the abdomen showed possible liver hemangiomata, simple cyst of the left kidney and otherwise normal kidneys. As a kid, the patient had a constant craving for salt, had muscle cramping while sleeping, had lower extremity edema especially after puberty, and when she was 20 she would have a 9 lbs fluctuation in her weight in one day. Patient’s mother had a pregnancy complicated by polydrammosis and gave birth to a sister who suffered from nephrocalcinosis and died soon after birth. The patient has a daughter with an avid need to eat salt. She was started on spironolactone and enalapril which improved her edema, blood pressure and resulted in the need for potassium. She remained on magnesium, calcium and carbonate. Her recurrent vomiting improved after decreasing caborbline. A genetic panel was order and revealed c.N1188T,M1220K on exon 2. She is first mutation and was MAFED2 heterozygous mutation, normally defined as variant of uncertain significance [2P68L and c.T→C in exon 4]

**Discussion:** MAFED2 is linked to a transient form of antenatal Bartter’s syndrome including nephrocalcinosis and symptoms resolve by 1.5 years of age. The mutation present in this patient however, is not described previously and is the first mutation of MAFED2 to cause a Bartter’s syndrome that remains pathogenic at an adult age. This might be due to the fact that MAFED2 was described in relation to Bartter’s syndrome in 2016 and the focus is on a pediatric population. Learning points: MAFED2 mutation can have a variable phenotype within the same family. MAFED2 mutation can cause Bartter’s syndrome that is not limited to the perinatal period.

**PUB184**

**Renal-Limited Thrombotic Microangiopathy in the Setting of Thrombomodulin Mutation**

Kwon Soo Kim, Jean M. Francis, Andrea Havasi. Boston Medical Center, Boston, MA.

**Introduction:** Thrombotic microangiopathy is a pathological condition comprised of microvascular thrombosis involving any organ of the body leading to thrombocytopenia, Coombs-negative microangiopathic hemolytic anemia, and organ damage. Common causes of primary TMA are STEC-mediated hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and atypical hemolytic uremic syndrome. AKI secondary to TMA in severe Hypertension is not an uncommon scenario, however it is important to rule out primary TMA as a cause of Hypertension. Our case involves a very young male, who presented with elevated Creatinine and severe Hypertension, whose renal biopsy showed renal-limited TMA, with subsequent genetic panel showing Thrombomodulin mutation.

**Case Description:** This is a 29 year old African ancestry male with known history of Hypertension, diagnosed 1 year ago, not on any antihypertensive medication. Patient presented to the ED with chest pain with BP of 230/110 mm Hg. Blood work remarkable for serum Creatinine of 4.9, unknown baseline, K of 3 and serum bicarbonate of 27. Urinalysis remarkable for sterile pyuria with WBC of 100 and UPCR of 1.5 g/L. Patient was admitted under the impression of hypertensive emergency. All the work up for secondary hypertension, including PRA/serum Aldosterone and Renal Doppler were negative. Serology work up for glomerulonephritis including ANA, ANCA, Anti Cardiolipin Ab, Anti GBM Ab, HIV, Hepatitis, Anti PLA2R Ab, C3/C4 were negative. Renal function has not improved despite hypertension management, and renal biopsy was performed, which showed findings suggestive of severe TMA. Haptoglobin and LDH were not suggestive of presence of TMA. Hemoglobin level and Platelet counts were never low. Genetic panel for aHUS was sent, which showed THBD mutation, for which Ravalizumab was initiated, with the plan of 3 to 6 months treatment with close monitoring of renal function.

**Discussion:** Though most patients with TMA will present with the hematologic abnormalities of MAHA and thrombocytopenia, there are some that never demonstrate those features and only present with acute renal injury and Renal-Limited TMA. High degree of suspicion of underlying dysregulation of alternative pathway of complement is required, especially if patients do not improve with standard supportive care. Some of those mutations could present with Renal-Limited TMA without features of systemic TMA.

**PUB185**

**Endogenous Ouabain (EO) and Body Composition in Frail Subjects**

**Arianna Bologna,1 Marta De Filippo,1 Paolo Bettì,1 Marco Simonini,2 Teresa Del Mastro,1 Federico Persico,1 Lorena Citterio,2 Elisabetta Messaggio,2 Laura Zagato,3 Elena Brioni,4 Chiara Lanzi4,2 Paolo Manunta.2,1 Università Vita Salute San Raffaele, Milan, Italy; 1IRCCS San Raffaele Scientific Institute, Milan, Italy.

**Background:** The Na/K-ATPase is a highly selective receptor for cardiotonic steroids (CTS) such as ouabain and digoxin. At pharmacological concentrations used in the treatment of cardiac conditions, CTS modulate the ion-pumping function of Na/K-ATPase. At much lower concentrations, in the range of those reported for endogenous CTS in the blood, they stimulate hypertrophic growth of cultured cardiac myocytes through initiation of a Na/K-ATPase-mediated and reactive oxygen species (ROS)-dependent signaling.

**Methods:** As inflammatory mechanisms may be involved in the pathophysiology of hypertension and in endothelial dysfunction and atherosclerosis via reactive oxygen species, inflammatory and oxidative stress markers were studied in elderly frail subjects under basal condition.

**Results:** Males showed increased circulating EO (Male 189.8±22 vs Female 157.8±14, p=0.0007adjusted for BMI, age, number of drugs taken). Mental health index was not associated with circulating EO levels contrary to what is reported in an experimental model. Conversely, a direct relationship between EO and muscle mass was observed (Pearson 0.236 p = 0.042).

**Conclusions:** We conclude that EO is a novel determinant of body composition in the presence of reduced renal function in elderly.

**PUB186**

**An Atypical Case of Nodular Glomerulosclerosis**

Muhammad T. Baig,1 Asish Thakkar,2 Anjali A. Satoskar,1 Udayan Y. Bhatt,1 Salem Almaani.1 The Ohio State University Wexner Medical Center, Columbus, OH; 2Veterans Health Administration, Washington, DC.

**Introduction:** Nodular glomerulosclerosis (NG) is a pathological lesion characterized by expansion of the mesangium and increased lobularity. They are typically found in diabetic nephropathy. Other conditions associated with NG include MPGN, paraproteinemias, and chronic ischemic lesions. In rare cases, the lesion may be idiopathic, (ING).

**Case Description:** The patient is a 67yo female with a medical history of chronic kidney disease, hypertension, hyperlipidemia, and tobacco use (quit 20 years prior). She has no history of diabetes and her most recent hemoglobin A1C value was 4.5. She presented to the hospital with dyspnea and worsening kidney function and nephrotic range proteinuria (3.9g/g). Her serological evaluation, which included SLEP, ANCA, ANH, hepatitis serologies, and serum complement proteins, were all unremarkable. Because of this, she underwent a kidney biopsy. Diffuse and nodular glomerular mesangial expansion was noted on light microscopic evaluation (arrows). She had evidence of advanced disease with 40% interstitial fibrosis and tubular atrophy. On electron microscopy, the patient had features of primary TMA are STEC-mediated hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and atypical hemolytic uremic syndrome. AKI secondary to TMA in severe Hypertension is not an uncommon scenario, however it is important to rule out primary TMA as a cause of Hypertension. Our case involves a very young male, who presented with elevated Creatinine and severe Hypertension, whose renal biopsy showed renal-limited TMA, with subsequent genetic panel showing Thrombomodulin mutation.

**Discussion:** NG is most commonly associated with diabetic nephropathy. However, nondiabetic NG can also be seen secondary to a number of conditions or as a primary condition, known as ING. Clinical risk factors for ING include obesity, hypertension, and tobacco use. Heavy tobacco use is one of the strongest risk factors. In the largest series published to date, the median tobacco consumption was 52 pack-years, and 43% of patients with former smokers, which demonstrate the importance of careful history-taking in identifying risk factors for this disease.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Fibrillary Glomerulonephritis in a Patient with Long-Standing Hypertension, Proteinuria, and Advanced CKD: Not Everything Is Hypertension
Michael M. Samiratatu, Neda Shahoori, Yiqin Zuo, Jair Munoz Mendoza University of Miami School of Medicine, Miami, FL

Introduction: Fibrillary glomerulonephritis (FGN) is a rare glomerular disease that mostly affects patients in their fifth or sixth decade of life. Clinical manifestations include elevated creatinine, hypertension (HTN), hematuria, and proteinuria. FGN has been associated with monoclonal gammopathy, autoimmune diseases and viral infections. However, many of the cases ultimately have no precipitating factor identified.

Case Description: We present a case of a 65-year-old man with a history of diabetes mellitus for 6 years without retinopathy, HTN and chronic kidney disease (CKD) who presented to our hospital with acute kidney injury after increasing dose of lisinopril for uncontrolled hypertension. Physical exam was unremarkable except for high BP 154/85 mmHg, and mild lower extremity edema. Laboratory studies revealed a serum creatinine of 4.13mg/dL (baseline 2.9 mg/dL, eGFR 22 ml/min/m²), UPCR of 7.1 g/d, UA showed 10 RBCs and 3+ protein. No RBC on repeat UA. He was negative for Hepatitis B, C, and ANA, anti-GBM, ANA, and anti-dsDNA Ab. C3,C4 were normal, SPEP showed no M spike, and elevated kappa/lambda ratio of 1.81 (89.7 / 49.6 mg/L). Renal biopsy revealed 20-30% interstitial fibrosis, diffuse, moderate to severe mesangial expansion by eosinophilic deposits with segmental mild increase in mesangial cellularity, polyclonal IgG-dominant smudge mesangial staining with capillary loop extension with kappa/lambda light chain shift, and mesangial and subendothelial deposits with non-branching randomly arranged fibrils (7-21 nm). A Congo red stain was negative for amyloidosis. Immunohistochemical staining for DNAJB9 was positive, supporting the diagnosis of FGN.

Discussion: This case highlights the importance of pursuing a kidney biopsy in patients with worsening proteinuria and kidney function even without active sediment and negative work up for GN. In patients with long standing history of HTN, it is not uncommon to blame HTN as the cause of the CKD. However, diseases such as FGN although rare should always be considered as part of our differential diagnosis. Whether we should treat with immunosuppresion or continue conservative management in this patient with advanced chronic kidney disease is debatable but knowing the diagnosis of FGN will certainly help to establish a better prognosis.

Is This Primary or Secondary Membranous Nephropathy? Rajan Rengan, Bianca Madrid. Medical College of Wisconsin, Milwaukee, WI

Introduction: The definition and management of membranous nephropathy (MN) has rapidly evolved over the past decade, following the identification of PLA2R-Ab. A host of other target antigens have been discovered including thrombospondin type 1 domain-containing 7A, neural epidermal growth factor-like 1, and sephamorphin-3B. Primary membranous nephropathy is considered to involve a humoral autoimmune response to a normal podocyte antigen, in the absence of known secondary etiologies including autoimmune diseases, infections, malignancies and certain drugs.

Case Description: We present a 72 Y male with medical conditions including HTN, pre-diabetes, grade 1 obesity, CAD, and remote history of laryngeal cancer, who presents to nephrology clinic for evaluation of lower extremity edema and proteinuria of 11 gms. Labs are consistent with nephrotic syndrome, and he is subsequently started on Furosemide and Lisinopril. His GFR is preserved with serum creatinine of 0.9 mg/dL. Additional work up includes HEP B/C, HIV, SPEP/UEP/TLc, and ANA, which are negative but PLA2R-Ab is markedly elevated (PLA2R IFA positive with titer of 1:500 and PLA2R ELISA positive at 250.00 RU/mL). The patient referral also noted that he had a heart failure exacerbation a few days prior to presentation. In the absence of a biopsy, a mutual decision is made to treat the patient with rituximab. However, after two doses of rituximab 1g spaced two weeks apart, the patient fails to achieve clinical or biochemical remission within 6 months. The need for a biopsy is again discussed to further determine treatment options, and is eventually done. Biopsy features suggest features of secondary MN, including mesangial expansion, intracapillary leucocytes on light microscopy (LM), IgG (1 and 3) and IgM, C3 and C1q deposits, absent PLA2R stain on immunofluorescence (IF), and subepithelial, intramembranous as well as subendothelial electron dense deposits on electron microscopy (EM). Through assessment for secondary causes of MN remains unremarkable. A CT head/chest, abdomen, and pelvis is also obtained which does not reveal any malignancy.

Discussion: Although the biopsy findings are suggestive of a secondary MN, the significantly high titer of PLA2R-Ab have persisted. The patient is offered an alkylation agent based therapy, but has opted to enroll in an ongoing clinical trial on anti-CD 38 therapy. He remains under surveillance for possible secondary etiologies due to his biopsy findings, while awaiting his response to anti-CD38 therapy.

Two Clinical Scenarios Leading to the Diagnosis of Staphylococcus Infection-Associated Glomerulonephritis
Varun Chalasani, Parmjyot Singh, Swati Arora. Allegheny Health Network, Pittsburgh, PA; Lake Erie College of Osteopathic Medicine, Erie, PA

Introduction: Historically, infection-associated glomerulonephritis (IAGN) has been associated with group A streptococcus infections. At this time, staphylococcus infection-associated glomerulonephritis (SAGN) has become more prevalent in developed countries. We describe two different patients and clinical scenarios, who merge at the diagnosis of SAGN.

Case Description: The first patient is a female in her 60s who had recently been treated for methicillin sensitive staphylococcus aureus (MSSA) bacteremia. Three weeks later she was admitted with heart failure exacerbation and started on diuresis. Labs showed creatinine of 2.22, from baseline of 0.9, and proBNP was 30,583. Her respiratory status improved, however her creatinine increased day by day, peaking at 6.9, and she became oliguric. Renal biopsy showed IgA dominant immune complex mediated diffuse segmental proliferative glomerulonephritis consistent with post-staphylococcal glomerulonephritis. Immunofluorescence showed granular mesangial staining for IgA and C3. She was started on hemodialysis and was discharged to inpatient rehab. The second patient is a 19 year-old female who was transferred for treatment of tricuspid valve endocarditis and methicillin resistant staphylococcus aureus (MRSA) bacteremia. After transfer her renal function worsened, with peak creatinine of 3.5 from a baseline of 0.6. She became oliguric and hypertensive, and hemodialysis was started. A few days later, she developed a necrotizing small vessel vasculitis and was treated with prednisone for presumed leukoerythroblastic vasculitis. This resulted in improvement in her renal failure. After steroids were stopped her renal function again worsened. Renal biopsy showed diffuse segmental proliferative and necrotizing glomerulonephritis with crescent formation; immunofluorescence revealed granular mesangial and capillary staining for IgA and C3. Steroids were restarted with plans for a lengthy taper, and she was discharged a few days later.

Discussion: SAGN has become a prevalent cause of infection-associated glomerulonephritis. Clinicians should recognize the broad risk factors associated with SAGN in patients with staphylococcus infections are exceedingly common. Including infections and diverse clinical presentations; defining the best therapeutic strategies for different cases, including cases with SAGN, as well as cases associated with known secondary causes of MN requires additional research. Antimicrobials and possibly dialysis support can be used in appropriate and timely manner.

Nothing Out of Nothing: A Rare Case of Pulmonary Renal Syndrome with Paucci-Immune Glomerulonephritis and Diffuse Alveolar Hemorrhage with Negative Serologies
Lucas Wang, Roberto L. Collazo-Maldonado. Methodist Dallas Medical Center, Dallas, TX

Introduction: Paucci-immune (PAN) crescentic glomerulonephritis (CrGN) is one of the most common etiologies of rapidly progressive glomerulonephritis. PAN CrGN presents and progresses with little to no immunoglobulin staining and negative serology for the most part. However, in a few cases, a few days later, a positive antineutrophil cytoplasmatic autoantibody (ANCA). Patients with PAN CrGN usually have underlying systemic small vessel vasculitis, but in rare cases, it is not associated with vasculitis or ANCA. ANCA-negative PAN CrGN is often isolated to kidney tissues, but here we present a case in association with severe diffuse alveolar hemorrhage (DAH).

Case Description: A 66-year-old Hispanic woman with no significant medical history presented with four days of fatigue and dysphagia. On admission she was hypotonic on room air, and her physical exam was remarkable for crackles bilaterally. Initial laboratory results revealed anemia (5.2 g/dL), hyperkalemia (6.3 mmol/L), and AKI with serum creatinine of 4.5 mg/dL. Urinalysis showed dysmorphic RBCs and proteinuria. A computed tomography scan of the chest/abdomen/pelvis was obtained and revealed multifocal pulmonary consolidations. The patient developed hypoventilation, and a bronchoscopy showed DAH. The ICU team proceeded to intubate her as the hemorrhage continued to worsen. Further workup revealed a positive ANA titer of 1:40, but otherwise negative serologies, including MPO-ANCA, anti-GBM, and anti-dsDNA. Kidney biopsy showed necrotizing GN with negative immunofluorescence. She was diagnosed with PAN ANCA-negative vasculitis with associated DAH and nephritis and was started on
A Case Report of ANCA-Negative Vasculitis Presenting with Pauci-Imune Glomerulonephritis
Khalid Elharri,1,2 Mica Alex,2 Petersen Greeti,1 Rathaa V. Kulasingam,1 Hania Kassem,2 1Kern Medical Center, Bakersfield, CA; 2The University of Texas Medical Branch at Galveston, Galveston, TX.

Introduction: Crescentic glomerulonephritis (GN) is a severe form of GN characterized by a rapid decline in kidney function. Pauci-immune GN is one of the most common causes of rapidly progressive GN and is usually associated with positive anti-neutrophil cytoplasmic antibody (ANCA). We present a rare case of ANCA-negative pauci-immune GN that was successfully treated with immunosuppression.

Case Description: A 17-year-old girl without significant PMH was admitted to the hospital with abdominal pain and diarrhea. She initially had dark colored urine but became anuric shortly thereafter. On admission, she had a blood pressure of 139/83 mmHg (98 percentile), Pulse of 87 bpm and Temp of 98.3 °F. Physical exam was unremarkable. Initial laboratory investigation revealed creatinine of 11.9 mg/dl. Urinalysis was positive for proteinuria and hematuria. Protein to creatinine ratio was 28 g/g. Urine microscopy showed RBCs with dysmorphic features. ANA, ANCA and anti GBM antibodies were negative. C3 and C4 were normal. Viral serology was negative. Kidney biopsy was consistent with small vessel vasculitis with pauci-immune necrotizing GN. She has initially required dialysis for several sessions but her kidney function improved after we started her on steroids and cyclophosphamide with subsequent improvement of her condition.

Discussion: Pauci-immune crescentic glomerulonephritis is one of the most common causes of rapidly progressive glomerulonephritis. The majority of patients with pauci-immune had circulating ANCA. Some patients with pauci-immune crescentic glomerulonephritis lack ANCA. There are recent studies about the association between anti LAMP 2 antibody and ANCA negative pauci-immune GN.

A Case Report of ANCA-Negative Vasculitis Presenting with Pauci-Imune Glomerulonephritis
Khalid Elharri, Mica Alex, Petersen Greeti, Rathaa V. Kulasingam, Hania Kassem

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noted methicillin sensitive staph aureus(MSSA). Patient was given rituximab, and was transferred to a tertiary center for consideration of pleuropneumothorax. Preoperative data revealed significant correlation with deterioration of renal function. Bone marrow biopsy was negative for evidence of clonal plasma cell disorder.

Discussion: Pulmonary disease in MC is characterized by dyspnea, dyspnea, and rarely hemoptysis. Hemoptysis from diffuse alveolar hemorrhage (DAH) is considered as a clinical feature of cryoglobulinemia with an estimated incidence of 0.4–4.6%. We report a case of a mixed cryoglobulinemia with persistent hemoptysis despite antibiotics. No sequential BAL done to investigate DAH. M SSA pneumonia noted on BAL is likely a complication of immunosuppression with intravenous steroids. Our case is a valuable addition to the few cases of hemoptysis in MC described in the literature.

**PUB195**

**Management of Infective Endocarditis-Related Glomerulonephritis**

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**Introduction:** Antibiotics can be effective and curative if infective endocarditis (IE) infection is mild. However, in severe cases of IE, surgical intervention is necessary to restore integrity of heart value and to halt or cure IE related glomerulonephritis (GN).

**Case Description:** 28-year-old male with Crenin’s disease, hepatitis C ( viral load >10,000,000 IU/ml), admitted at an outside hospital (8/10-9/15) with creatinine (Cr) of 1.28 mg/dL. (baseline Cr 0.83 mg/dL) after intravenous (IV) drug use resulting in Cr after his surgical intervention.

**Discussion:** Despite ~6 weeks of antibiotics and negative bacteremia, the persistent hypocomplementemia suggests failure to control the infection as seen by worsening renal function, hypertensive urgency, nephrotic proteinuria, and anasarca. By undergoing a repair rather than replacement of TV not only resulted in lower operative mortality but also achieved a higher long-term survival, both from cardiac and renal standpoint. MPGN was related to his IE and not hepatitis C as he had resolution of his proteinuria and stable repair rather than replacement of TV not only resulted in lower operative mortality but also achieved a higher long-term survival, both from cardiac and renal standpoint.

**PUB196**

**Proliferative Glomerulonephritis with Monoclonal IgG Deposits (PGNMID) with Fibrillary Deposits Progressing to Macrophage-Driven Systemic Vasculitis: An Autopsy Case**

Kazumori Karasawa, Kenichi Akiyama, Yoei Moriya, Takahito Moriyama, Kosaku Nitta. Tokyo Women's Medical University, Tokyo, Japan.

**Introduction:** Proliferative glomerulonephritis with monoclonal immunoglobulin (Ig) deposits (PGNMID) is a renal-limited glomerular disease characterized by disordered glomerular parenchyma.

**Case Description:** Here, we report the case of a 62-year-old Japanese woman undergoing hemodialysis 3 years after PGNMID onset. After kidney failure, prednisolone treatment for managing PGNMID was discontinued. Thereafter, fever of unknown origin (FUO), multiple vascular occlusions in the brain, fingers, and retina were observed. Finally, the patient died of hemorrhagic cerebral infarction 8 months after kidney failure.

**Discussion:** Autopsy revealed the presence of subendothelial fibrillary deposits in differently sized vessels. Furthermore, electron microscopy revealed that macrophages phagocytosed fibrillary and underlying autophagy. Liquid chromatography-mass spectrometry (LC/MS) analysis was performed to diagnose IgG1 type PGNMID. Furthermore, MS revealed that the deposits contained an amyloidogenic protein, which was responsible for the systemic deposition and macrophage-driven systemic vasculitis, eventually resulting in FUO and vasocclusive disease. Furthermore, macrophage-driven vasculitis was confirmed to be a contributory factor in a pro-inflammatory cell death peculiar to phagocytes. Systemic PGNMID reported in the present case is a rare subtype of PGNMID.

**PUB197**

**Urinary GADD45G Protein Excretion Predicts IgA Nephropathy Progression**

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**Background:** Growth arrest and DNA damage 45G (GADD45G) is a family of proteins involved in DNA damage response and cell growth arrest. We have previously shown that GADD45G promotes apoptosis leading to acute and chronic kidney injuries (KI 2008; Am J Nephrol 2009; PLoS One 2019). In this study, we show evidence that urinary GADD45G protein can predict progression of IgA nephropathy (IgAN).

**Methods:** IgAN patients were included in the study if they did not have acute kidney injury on the day of sample collection and had at least one follow up serum creatinine (Scr) measurement after renal biopsy. A 50% or greater increase of serum creatinine levels was used as an endpoint of deterioration of renal function. RELISA assay was performed using a Human GADD45G ELISA kit. Renal biopsy tissue was stained with a monoclonal mouse anti-GADD45G antibody.

**Results:** Forty-five patients were enrolled in this study whose renal biopsy revealed IgAN. Urinary GADD45G and urinary protein concentrations were 1.89±0.12 µg/g and 1.47±0.98 g/day, respectively. Urinary GADD45G showed a significant positive correlation with SCR-slopes and with urine protein. The SCR-slope of the highest tertile group (above 1.95 µg/g) of urinary GADD45G was significantly higher than that of the lowest tertile group (below 0.90 µg/g). Urinary protein was significantly higher in the highest tertile group compared to the other tertile groups. Univariate Cox regression analysis showed that urinary GADD45G was significantly associated with deterioration of renal function. Kaplan-Meier test showed a significant difference in event-free survival for deterioration of renal function between patients with the highest urinary GADD45G tertile vs. the other tertile groups. The area under the receiver operating characteristics (ROC) curve indicated urinary GADD45G had a good performance in predicting renal outcome. The cut-off point of 1.67 µg/g was determined from the ROC curve. This cut-off point yielded a positive predictive value of 36.8% and a negative predictive value of 100%. Immunohistochemistry showed that GADD45G was expressed in all biopsy samples of IgAN whereas no staining was noted in normal control tissue. Staining was mainly detected in the cytoplasm of renal tubules.

**Conclusions:** In the present study, we showed that urinary GADD45G excretion is significantly associated with kidney disease progression in patients with IgAN.

**PUB198**

**Expanding the Differential: Goodpasture’s Disease in the Setting of the COVID-19 Pandemic**

Abdullah Jalal, Overlook Medical Center, Summit, NJ.

**Introduction:** The 2020 COVID-19 pandemic was a challenging time in healthcare. Physicians struggled with limited resources, overwhelming patient volume and limited knowledge of COVID-19. During this period many hypoxemic patients with pulmonary infiltrates were empirically managed as COVID-19 patients. However, anchoring to COVID-19 diagnosis narrows differentials and potentially lead to missed diagnosis. Herein we highlight a case of delayed Goodpasture’s disease diagnosis in the setting of COVID-19 pandemic.

**Case Description:** A 51 year old male was admitted for several days of malaise, diarrhea and decreased oral intake. On arrival the patient was hypotensive 88.6 °F, BP 122/67 mm Hg, SpO2 91% on room air. On exam he was encephalopathic, diffusely edematous with sonorous wheezes. Initial labs notable for (mEq/L): Na 135, K 7, Cl 107, low CO2 38, significantly elevated Bun 184 and Cr 279. CT chest showed bilateral airspace opacities, renal ultrasound was unremarkable. Initial diagnosis was sepsis secondary to presumed COVID-19 infection despite several negative COVID tests. Emergent hemodialysis was complicated by hypertension and hypoxemia requiring intubation. The patient rapidly deteriorated requiring 3 vasopressors. Autoimmune serologies resulted several days later were negative (ANA, ANCA, C3, Anti-dsDNA Ab, Hepatitis B/C, HIV, SLEP with immunofixation) with the exception of positive anti-GBM IgG Ab (8+). Renal biopsy was unattainable given his tenuous clinical status; however, bronchoscopy performed revealed bloody alveoli consistent with alveolar hemorrhage. The patient was subsequently started on cyclophosphamide, pulse dose steroids and plasmapheresis. Respiratory status steadily improved allowing ventilator liberation. The patient underwent several more cycles of immunosuppression, plasmapheresis during hospitalization and was discharged after 80 days. 1 year later the patient remains dialysis-dependent.

**Discussion:** This case illustrates the unique challenges of diagnosing Goodpasture’s Disease (GD), a rare immune complex-mediated small vessel vasculitis characterized by alveolar hemorrhage and renal insufficiency. During the COVID-19 pandemic. Similarities in their presentation (pulmonary infiltrates, hypoxemia, renal failure) led to our patient being initially treated for COVID-19. However, maintaining a broad differential is essential as the treatment for GD and COVID-19 are vastly different.
The Alteration of Neutrophil Nuclear Morphology: A Potential Predictor for Corticosteroid Response in IgA Nephropathy
Reiko Muto, Sawako Kato, Shoichi Maruyama. Nagoya University Graduate School of Medicine, Nagoya, Japan.

Background: In patients with active IgA nephropathy (IgAN), immunosuppressive treatment using corticosteroid is widely used. It should be useful to detect a poor corticosteroid responder in advance. Neutrophils are the most abundant white blood cells (WBC) in circulation, representing a first line of defense from daily environmental insults. Recently, there have been reported associations between an alteration of neutrophil nuclear morphology and treatment responses in patients with infection, cancer, and autoimmune diseases. In these states, the neutrophil nuclear breaks down, then the nucleosome components extrude. The aim of study is whether an alteration of neutrophil nuclear morphology associates with poor corticosteroid response in IgAN.

Methods: We investigated IgAN patients starting corticosteroid therapy between July 2020 to March 2021. We excluded patients with apparent infection or cancer. We defined the alteration of neutrophil nuclear morphology as neutrophil blebs (NB) with Giemsa stain (Figure 1). The participants with NB greater than the median NB were grouped in the high-NB group and the rest were in the low-NB group.

Results: We enrolled five biopsy-proven IgAN patients; number of female, 4; median age, 51 [interquartile range (IQR): 41-57] years old; median WBC count, 7700 [IQR: 6100-9550] /μL; median eGFR, 58.5 [IQR: 56-69] mL/min/1.73m²; median CRP, 0.06 [IQR: 0.01-0.64] mg/dL; median UP, 0.7 [IQR: 0.2-1.4] g/gCr; median NB, 53.2 [IQR: 37.6-69.2] % at baseline. The high-NB group showed the significantly decrease in UP than that low-NB group after 4 weeks from the initiation of corticosteroid therapy (p=0.0516). There was no differences in eGFR.

Conclusions: The alteration of neutrophil nuclear morphology could predict the response to corticosteroid therapy in IgAN patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

Reiko Muto, Sawako Kato, Shoichi Maruyama. Nagoya University Graduate School of Medicine, Nagoya, Japan.
**PUB203**

Unexpected Severe Thrombocytopenia Linked to Mixed C- and P-ANCA-Positive Vasculitis

**Jesus D. Vega Colón, Hospital Episcopal San Lucas, Ponce, PR.**

**Introduction:** The Anti-Neutrophil Cytoplasmatic Autoantibody (ANCA)-associated vasculitis are a rare group of disorders that affect multiple organ systems with a peak age of 65-74 years. It encompasses several diseases including Granulomatosis with polyangiitis, Microscopic polyangiitis, and Eosinophilic granulomatosis with polyangiitis. Few cases have been able to demonstrate the existence of mixed ANCA vasculitis related to severe refractory thrombocytopenia.

**Case Description:** We report a 74-year-old male with Past Medical History of Hypertension, Chronic Kidney Disease (CKD) Stage IV that came to our hospital complaining of fatigue and decrease urinary output since 5 days. Physical exam was remarkable for bilateral crakcles and lower extremity edema. Initial labs showed evidence of anemia and thrombocytopenia of 5.8 g/dl and 66 10^9/L respectively. Multiple electron microscopic examination found inclusion body injury over 80%, with creatinine 7.23 mg/dl (baseline: 3.85), marked azotemia BUN=101 mg/dL and metabolic acidosis: 13 mEq/L. Patient was admitted with diagnosis of volume overload to start emergent renal replacement therapy along with PRBC transfusion. Follow up labs revealed evidence of hemoglobin optimization (10.2 g/dl), improved azotemia (65 mg/dL) and metabolic acidosis (19.3 mEq/L). Further work-up sent by nephrology service showed evidence of high levels of Proteinase 3 ANCA antibodies: 4.9 U/ml and Myeloperoxidase ANCA antibodies: 96.4 U/ml. Decision was made to start induction therapy with Rituximab and high dose pulse IV steroids. Despite aggressive treatment, clinical course continued to worsen with thrombocytopenia reaching critical values of 19×10^9/L. Other causes in the differential diagnosis were ruled out such as Thrombocytopenia Purpura, Chronic lymphocytic leukemia, HIV, Hepatitis C, Thrombotic thrombocytopenia purpura, among others, which indicated an association between mixed ANCA vasculitis and severe thrombocytopenia.

**Discussion:** This case illustrates a routinely found inpatient lab abnormality not generally seen in this rare vasculitis type. It is important to keep a wide-ranging differential diagnosis in patients presenting with refractory thrombocytopenia concomitant to advance renal failure. Prompt identification and suspicion of ANCA vasculitis can lead to early start of induction therapy which can delay the progression to end stage kidney disease.

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**PUB204**

Atypical Haemolytic Uremic Syndrome in Lung Transplantation and Treatment with Eculizumab: Our Experience

**Raquel B. Rico, Hospital Universitario 12 de Octubre, Madrid, Spain.**

**Background:** Atypical haemolytic uremic syndrome (aHUS) is a clinical entity characterized by acute kidney injury, thrombocytopenia and microangiopathic hemolytic anemia. There are several cases of aHUS in non-renal solid organ transplants described in the literature, included lung transplant. Kidney and patient survival are compromised by this complication because of the lack of an effective treatment. Eculizumab C5 complement factor specific blocker already administered in another kind of secondary aHUS with encouraging results.

**Methods:** We analyze six lung transplants in a retrospective single-center study between 2008-2020 who developed an aHUS and were treated with eculizumab. Clinical and analytical data were collected along the follow-up. Principal outcome was to explore haematological and renal response after treatment with eculizumab.

**Results:** We included a total of six patients (83% female) with a median age of 57 years at aHUS onset, median platelet count 2.9×10^9/L (0.9-2.2). Two patients developed an aHUS in the immediate post-transplant, one of them died because of surgical complications. Another four patients developed an aHUS 59 months (33-95) after transplantation. Previously of thrombotic microangiopathy, three patients were on treatment with everolimus instead of mycophenolate and two patients have cytomegalovirus reactivation. At the aHUS onset, median serum creatinine was 4mg/dl (2.4-5.7) and acute dialysis was performed in 50% of patients. Median hemoglobin was 7.2g/dl (6.9-7.7), platelet count was 32×10^9/L (17-58), and DHL was 1343 U/L (581-1597) at the start of eculizumab despite having treated the trigger. After a median of 6 doses of eculizumab, the five surviving patients had haematoaglomerular and renal response. No patients underwent chronic dialysis. Serum creatinine was 2.2mg/dl (1.7-2.3), hemoglobin 9.8g/dl and platelet count 159×10^9/L at the end of follow-up.

**Conclusions:** aHUS is a critical complication in lung transplantation, shortly related with immunosuppressive therapy. Patients are at risk of end stage renal disease. Eculizumab treatment appears promising.

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**PUB205**

Proliferative Glomerulonephritis with Monoclonal Immune Deposits: A Continued Treatment Conundrum

**Ibrahim Khambati, Michael A. Mao. Mayo Clinic’s Campus in Florida, Jacksonville, FL.**

**Introduction:** Proliferative Glomerulonephritis with Monoclonal Immune Deposits (PGNMD) is a rare entity characterized by abnormal light chain, heavy chain, or intact immunoglobulin deposition in the kidneys. Cases generally are Caucasian, female, >50 years, and present with renal dysfunction and nephrotic-range proteinuria. Pathogenesis involves clonal plasma or B-cells depositing abnormal monoclonal proteins into the kidneys. The clone however is rarely found, and this contributes to the lack of a standard treatment regimen.

**Case Description:** A 32-year-old Caucasian male with PMH of uncontrolled HTN, chronic microscopic hematuria, and anemia presented with hypertensive emergency (111/94 mmHg) and acute kidney injury (BUN 58 mg/dL & SCR 4.41 mg/dL). UA showed microscopic hematuria and proteinuria. 24-hr urine protein was 8.5 g/24hr. Renal US was unrevealing. Other studies were negative including autoimmune panel, SPEP, UPEP, C3/C4, serum FLC, anti-PLA2R, anti-THSD7A, illicit drug screen, and anti-VHL antibodies. Serum anti-Neutrophil cytoplasmic antibodies (ANCA) were negative and ANA 1:40. Study for parvovirus was negative. He is a non-smoker and non-drug user. Stool was negative for stool ova and parasite. CT of chest revealed a left upper lobe nodule. A biopsy of his left upper lobe nodule showed a 5.8 cm solid mass involving the pleura and diaphragm. A PET scan revealed numerous hypermetabolic lesions in the left pleural effusion, left upper lobe nodule, and liver consistent with metastatic disease. A biopsy of his liver revealed a metastatic right lobe adenocarcinoma from a primary distal ileal adenocarcinoma as confirmed by the pathology of the ileal adenocarcinoma. The pathological findings were consistent with a primary distal ileal adenocarcinoma and metastatic right lobe adenocarcinoma. The patient was found to have stage IV adenocarcinoma of the bowel. A repeat CT scan revealed disease progression with new left upper lobe nodule and multiple new hypermetabolic lesions in the left pleural effusion.

**Discussion:** The patient was referred to the medical oncology department. Further work-up after genetic testing was negative for familial adenomatous polyposis (FAP), Lynch syndrome (MSH2, MLH1, MSH6, PMS2, and/or MSP3) and a variety of other rare genetic syndromes. The patient was diagnosed with metastatic right lobe adenocarcinoma from a primary distal ileal adenocarcinoma. The pathological findings of the liver biopsy were consistent with a primary distal ileal adenocarcinoma and metastatic right lobe adenocarcinoma. The patient was found to have stage IV adenocarcinoma of the bowel. A repeat CT scan revealed disease progression with new left upper lobe nodule and multiple new hypermetabolic lesions in the left pleural effusion.

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**PUB207**

IgA Nephropathy (IgAN) and Focal Segmental Glomerulosclerosis (FSGS) in a Patient with Crohn’s Disease (IBD) on Infliximab

**Aulo E. Bustos, Michael D. Klein, Viviam I. Becerra rivera. Westchester Medical Center Westchester Medical Center Health Network, Valhalla, NY.**

**Introduction:** IgA nephropathy and FSGS are common conditions which can coexist in the same patient either due to the nature of the underlying nephropathy, or to the use of anti-inflammatory agents. We present a case of IgAN and FSGS in a patient treated with anti-tumor necrosis factor-α therapy (aTNF-α) for IBD.

**Case Description:** A 21-year-old male with diffuse IBD on semi-monthly Infliximab, presented with nephropathy manifesting as 4.2 grams proteinuria, hypoalbuminemia to 2.8 g/dl, and high dose pulse IV steroids. Despite having treated the trigger, four patients developed an aHUS 59 months (33-95) after transplantation. Previously of thrombotic microangiopathy, three patients were on treatment with everolimus instead of mycophenolate and two patients have cytomegalovirus reactivation. At the aHUS onset, median serum creatinine was 4mg/dl (2.4-5.7) and acute dialysis was performed in 50% of patients. Median hemoglobin was 7.2g/dl (6.9-7.7), platelet count was 32×10^9/L (17-58), and DHL was 1343 U/L (581-1597) at the start of eculizumab despite having treated the trigger. After a median of 6 doses of eculizumab, the five surviving patients had haematoaglomerular and renal response. No patients underwent chronic dialysis. Serum creatinine was 2.2mg/dl (1.7-2.3), hemoglobin 9.8g/dl and platelet count 159×10^9/L at the end of follow-up.

**Conclusions:** AHUS is a critical complication in lung transplantation, shortly related with immunosuppressive therapy. Patients are at risk of end stage renal disease. Eculizumab treatment appears promising.
Double Positive Glomerulonephritis: A Disease Associated with Unfavourable Outcome Requiring Aggressive Treatment: A Case Report and Review of Literature

Mariana Napoli, Maria Mattiotti, Anita Campus, Carlo Stefanini, Olga Baraldi, Gisella Vischini, Benedetta Fabbrizio, Gaetano La Manna, Università di Bologna, Bologna, Italy.

Introduction: Co-presentation with both ANCA and anti-GBM Ab is not unusual and associated with worst outcome (Tab.1); the prevalence of double-positivity in Good-Pasture Syndrome (GPS) is higher (30-38%) than in ANCA-associated vasculitis (AAV) (5-14%).

Case Description: A 70-year-old woman was admitted with a severe respiratory distress and AKI (stage 3) requiring urgent dialysis. Laboratory tests revealed high titer of ANCA (MPO >134 IU/ml, PR3 20 IU/ml) and anti-GBM Ab (54 IU/ml). Histopathological renal analysis showed chronic lesions (Fig.1). Steroids, plasma-exchange and Rituximab were therefore administered. A sensible improvement of respiratory insufficiency, but no recovery of renal function was observed.

Discussion: Double-positive patients show hybrid features: the acute phase, similarly to GPS, is characterized by frequent lung hemorrhage, warranting plasma-exchange sessions; the subacute phase, like AA V, by high rate of recurrence, requiring a more intense and prolonged maintenance immunosuppressive regimen. Renal biopsy represents a useful diagnostic tool to establish chronicity degree and to speculate about pathogenetic contribution of each component. The worst renal outcome and higher risk of relapse require a careful follow-up.

A Rare Case of Severe AKI from Fibrillary Glomerulonephritis

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Introduction: Fibrillary glomerulonephritis (GN) is an uncommon disorder found on less than 1 percent of native kidney biopsies done worldwide. Due to its rare prevalence, the association of this disorder with other diseases is not fully understood. Here we present a case of a 60 year-old woman with a history of hypertension and untreated Hepatitis C who presented with acute oliguric kidney injury and was subsequently found to have biopsy proven fibrillary GN.

Case Description: 60 year-old woman with history of hypertension and Hepatitis C presented with shortness breath and back pains. Labs on admission showed an elevation in BUN and Cr to 121 mg/dL and 7.69 mg/dL respectively. Other findings included an elevated globulin gap of 4.6 g/dL and a urine dipstick with minimal proteinuria. Renal ultrasound was negative for obstruction and showed normal sized kidneys. Serum and urine protein electrophoresis with immunofixation revealed the presence of free monoclonal lambda light chains. Beta-2 microglobulin level was elevated to 12.4 mg/L. These clinical and laboratory findings raised suspicion for light chain cast nephropathy secondary to multiple myeloma and so renal and bone marrow biopsies were performed. Bone marrow biopsy showed no abnormal plasma cell clones, suggesting against a diagnosis of multiple myeloma. Furthermore, no lytic lesions were noted on skeletal survey. Renal biopsy showed findings consistent with fibrillary GN as well as acute pyelonephritis even though patient experienced no symptoms of urinary tract infection during the entirety of the hospitalization. She was started on intravenous antibiotics, and her renal function returned to near normal on day 14 of hospital stay. She was discharged home with appropriate Nephrology and Oncology follow up.

Discussion: Fibrillary GN is a poorly understood cause of renal failure. Treatment of the disorder is based on the underlying cause if one can be found. Approximately 30-50% of cases are associated with a hematological malignancy, autoimmune disease, monoclonal gammopathy, or Hepatitis C infection. For our patient, the renal biopsy failed to show monoclonal immunoglobulin deposits, suggesting that the most likely presentation was the underlying Hepatitis C. Also, the finding of acute pyelonephritis on the biopsy likely indicates an entirely separate (though still possibly related) disease process which probably also contributed to the renal injury.

A Case of TAFRO Syndrome with Two Consecutive Renal Biopsies Following the Pathological Course of the Kidney

Noritsuko Kato,1 Tomonori Hasegawa,2 Reiko Muto,1 Akihito Tanaka,1 Yuko Sato,3 Kayaho Maeda,1 Kazuhiro Furuhashi,2 Shoji Saito,1 Tomoki Kousui,1 Shosuke Maruyama,1 Nagoya University Graduate School of Medicine, Nagoya, Japan; 2Handa City Hospital, Nagoya, Japan.

Introduction: Renal involvement of TAFRO syndrome consist of diffuse glomerular endothelial injury. But due to thrombocytopenia and deterioration of general condition, there are few reports on kidney biopsy results. We report a rale case of TAFRO syndrome with two consecutive renal biopsy which shows pathological time course of endothelial injury from acute to chronic phase.

Case Description: A 20-year-old female who presented with high fever, pleural effusion, ascites, thrombocytopenia, lymph node enlargement, and proteinuria around 1.0g/day. First, she was diagnosed as systemic lupus erythematosus and treated with prednisolone. But she showed poor response to the therapy. Then she was transferred to our hospital and received renal biopsy for definite diagnosis. The renal specimen showed no evidence of immune complex nephritis, but showed diffuse global swelling of endothelium and expansion of subendothelial space. TAFRO syndrome was diagnosed based on 3 major and 2 minor criteria. She was treated with oral prednisolone and tocilizumab, and once CRP titer became negative. But 3 weeks after first tocilizumab treatment, her CT images revealed worsening of ascites, lymph node swelling. CRP titer again became positive, and massive proteinuria appeared. We considered the situation as relapse of the disease and reduced the interval of tocilizumab doses. A second renal biopsy was performed two months after the first one to investigate the cause of the large amount of proteinuria. Interstitial fibrosis was observed in 15% of renal cortex. Gomori stained showed global collapse or focal segmental double contour. One glomerulus showed mesangiolysis and endocapillary hypercellularity. No thrombosis was observed on PAS staining, and partial loss of CD31 staining was confirmed in a damaged glomerulus. Owing to the enhanced treatment, she achieved remission for one year.

10 glomeruli (8 global and 2 segmental sclerosed), 60-70% of tubulointerstitial fibrosis and moderate arteriolar intimal fibrosis (PAS stain 100X)
Discussion: The pathological course of renal damage associated with TAFRO syndrome is unique among ANCA-associated vasculitis. The clinical course of the disease was characterized by high-grade proteinuria, hematuria, and decreased ADAMTS-13 activity. The patient's renal biopsy showed focal segmental glomerulosclerosis with a full-house staining pattern. The patient's high CRP level and decreased ADAMTS-13 activity may indicate an ongoing inflammatory process.

PUB211
Complement Inhibition with a Short Course of Eculizumab for Refractory Vasculitis
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Background: Systemic vasculitis (SV) is a life-threatening disease and, in some cases, refractory to intensive multi-immunosuppressants drugs. Complement hyperactivation has gained interest in the pathogenesis of the SV. We report the efficacy of the early use of C5-inhibitor (eculizumab) in refractory cases of lupus nephritis (r-LN) and refractory ANCA-associated glomerulonephritis (r-AGN).

Methods: In this retrospective study, nine consecutive patients were included (r-LN:n=3 and r-AGN:n=6). All patients were previously treated with three or more drugs: corticosteroids(n=9), mycophenolate(n=9), rituximab(n=5), immunoglobulin(n=5), therapeutic plasma exchange (n=4), cyclophosphamide(n=1), and belimumab(n=1). Eculizumab was considered for use in off-label indication in patients with progressive renal deterioration (worsening creatinine, protein-to-creatinine ratio) or developing a high-risk lethal complication after the induction immunosuppressive therapy. The histologic lesson observed were: a) r-LN: Type VI (n=1), Type V (n=1), and type IV (n=1), and b) r-AGN: sclerotic (n=3), and malignant hypertension (+/-thrombotic microangiopathy (n=1), in two patients who developed pulmonary haemorrhage, no renal biopsy was performed.

Results: Mean age (SD): 54(7) years. Median (min-max) of follow-up: 23(24/8) months. Overall, 22(22%) patients are in chronic renal replacement program (one r-AGN patient who was dialysis dependent at presentation, and presented a complement H mutation, and one r-LN within 12 months after the onset eculizumab). 8 patients showed hypocomplementemia. As a whole the mean (95%CI) eGFR (EPI-CKD), increased: 8.0 (-3.0 to 19.1) ml/min/1.73m2 (P = 0.13). In r-LN, the mean (95%CI) eGFR increased: 13(-1.8 to 28.25), P= 0.07; while in r-LN, a slight change was observed: -2.1(-24.8 to 20.59), P = 0.72. The median(25-75p) protein-to-creatinine ratio decreased from 2.6 (1.6-3.5) to 0.660(4.1-12) mg/mg (P= 0.01). The eculizumab doses [median(25-75p)] required in r-LN and RAGN patients were: 8400 (7800-10200) mg and 3150 (2475-5700) mg, respectively. No major side effects were recorded.

Conclusions: The add-on complement inhibition with eculizumab stabilized or improved renal function and decrement in refractory vasculitis. The short course of eculizumab seems to be highly effective in r-AGN, and also was associated with lower doses needed.

PUB212
Lupus Nephritis Presenting with Positive PR3-ANCA and Decreased ADAMTS13
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Introduction: Lupus nephritis is a well-described entity. The simultaneous presence of ANCA abs is rare and is related to poor prognosis. Positive patients usually have MPO-ANCA. We present a case of biopsy-proven Class IV/V Lupus nephritis with PR3-ANCA and decreased ADAMTS-13 activity in an AA man.

Case Description: This 46-year-old AA man with no known past medical history presented to the ED for two weeks of SOB, leg, and scrotal swelling. He denies any associated symptoms. He denies using any other OTC medications and illegal drugs. On exam, vital signs were stable. He had 2+ pitting edema in LE bilaterally, scrotal and penile edema. Other systems were unremarkable. Labs were significant for Hg 5.1, Platelets 106, K 6.9, CO2 9, BUN 78, Cr 10.2, and Albumin 2.4. UA showed dysmorphic RBCs with amyloid deposition and nephrotic syndrome respectively. An echocardiography, skeletal survey and PET scan obtained to exclude any other organ involvement, were insignificant. Patient was referred to hematology-oncology and he underwent a bone marrow biopsy which showed 10-20% involvement by a plasma cell neoplasm. With the information gathered, the diagnosis of AL amyloidosis with multiple myeloma was made. The patient later underwent therapy with CyBorD whereafter his swelling improved.

Discussion: Monoclonal gammopathy is defined by presence of a monoclonal immunoglobulin in plasma, urine or both produced by clonal plasma cells. It could be associated with hematologic malignancy, smoldering, MGUS or a relatively new term monoclonal gammopathy of renal significance. We present a case of monoclonal gammopathy associated with renal damage leading to the diagnosis of multiple myeloma.

Case Description: A 69 year old male with history significant for hypertension, CAD, PVD presented to the office with bilateral lower extremity swelling extending up to his trunk and significant weight gain over the past month. Laboratory investigations revealed serum albumin of 2.6g/dl, cholesterol 300mg/dl, LDL 187mg/dl. Urine analysis revealed macroalbuminuria with a urinary protein-to-creatinine ratio of 14,314g/g in the setting of a normal serum Cr of 0.89. SPEP followed by serum immunofixation showed an M-spike which was difficult to quantitate. Kappa to lambda ratio was low at 0.06. Extensive work up to determine the etiology for nephrotic syndrome was performed which was followed by a kidney biopsy, showing lambda light chain deposition on immunofluorescence and positive birefringence of Congo red stained material under polarized light. Electron microscopy showed haphazardly arranged fibrils and foot process effacement, consistent with amyloid deposition and nephrotic syndrome respectively. An echocardiography, skeletal survey and PET scan obtained to exclude any other organ involvement, were insignificant. Patient was referred to hematology-oncology and he underwent a bone marrow biopsy which showed 10-20% involvement by a plasma cell neoplasia. With the information gathered, the diagnosis of AL amyloidosis with multiple myeloma was made. The patient later underwent therapy with CyBorD whereafter his swelling improved.

Discussion: An unimpressive SPEP should not be ignored. In the setting of high clinical suspicion, work up should always be followed by kidney and bone marrow biopsy. About 12-15% of patients with renal AL amyloidosis have associated multiple myeloma which require treatment with chemotherapeutic agents. Even though our patient fits into the monoclonal gammopathy associated with hematologic malignancy, MGUS is an evolving topic which deserves considerable attention because many of these entities benefit from clonal based therapies.
Hematuria and Proteinuria in a Patient of Cypriot Descent
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Introduction: C3 glomerulonephritis (C3GN) caused by a mutation in complement Factor H-related protein 5 (CFHR5) is enigmatic in patients of Cypriot descent. CFHR5 nephropathy bears a striking resemblance to IgA nephropathy (IgAN). We present a case of CFHR5 nephropathy in a Cypriot patient who was initially diagnosed with IgAN and highlight the importance of family history, labs, renal biopsy, and genetic testing in diagnosis of CFHR5 nephropathy.

Case Description: A 22-year-old male of Cypriot and Greek descent presented in June 2019 with recurrent microscopic hematuria and proteinuria in the setting of upper respiratory tract and gastrointestinal illness. Blood pressure was 132/78 and he had no edema. Serum creatinine (SCr) was 1.6 mg/dL (SCr was 0.7 in 2012, 1.0 in 2018, and 1.3 in 2019). Urinalysis revealed microscopic hematuria and proteinuria. Spot urine protein/Cr ratio (UPCR) was 580 mg/g Cr. Serologic workup was unremarkable. He was diagnosed initially with IgA nephropathy. Due to slowly progressive renal dysfunction, a renal biopsy was performed in January 2020, which showed mild mesangial hypercellularity, segmental duplication of basement membranes, and glomerular C3 deposits. Immunofluorescence was negative for IgG, IgM, C1q, light chains, or fibrin. Electron microscopy revealed segmental mesangial, subepithelial, and subendothelial immune-type electron dense deposits with segmental duplication of glomerular basement membranes. He was diagnosed with C3GN. Genetic testing confirmed the CFHR5-CFHR5 fusion gene that has been causally linked to C3GN by a gain-of-function effect leading to overactivation of the alternative complement pathway. He was treated conservatively with Lisinopril 10 mg daily. Home blood pressures remain stable. SCr remains 1.5 to 1.9 mg/dL and UPCR remains 610 to 810 mg/g Cr.

Discussion: CFHR5 nephropathy is endemic in patients of Cypriot descent. Therefore, a high index of suspicion for CFHR5 nephropathy should be maintained in Cypriot patients presenting with nephritic syndrome. The presentation of CFHR5 nephropathy bears a striking similarity to IgAN. The main distinguishing features of CFHR5 nephropathy vs. IgAN are its familial nature and absence of IgA deposition. Therefore, family history, renal biopsy, and genetic testing for CFHR5 mutation are critical in establishing a diagnosis of CFHR5 nephropathy.

Benralizumab Monotherapy Substitution Therapy in Symptomatic Asthma Exacerbations of Eosinophilic Granulomatosis with Polyangiitis
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Introduction: There is increasing interest in the use of the biologicals including anti-interleukin 5 and anti-interleukin 5 receptor antibodies in the management of steroid-resistant or steroid-dependent eosinophilic granulomatosis with polyangiitis (EGPA). Benralizumab, an anti-IL 5 receptor antibody is steroid sparing. We describe successful substitution Benralizumab monotherapy in EGPA.

Case Description: In late 2005, a 38-year old male was diagnosed with multisystemic illness that included asthma, polyarthritis and nephrotic syndrome. He was treated with cyclophosphamide and was later continued on combination prednisone and mycophenolate mofetil and prednisone, 14 and 16 months, respectively, after starting treatment. In April 2019, he was started on Benralizumab, 30 mg IV cyclophosphamide and was later continued on combination prednisone and MMF. Symptomatic and associated eosinophilia (Figure 1). In April 2019, he was started on Benralizumab, 30 mg subcutaneously every 4 weeks for 3 doses and thereafter every 8 weeks. His asthma symptoms resolved, eosinophil count promptly dropped to zero and he was weaned off mycophenolate mofetil and prednisone, 14 and 16 months, respectively, after starting Benralizumab (Figure 2). FEV-1 trajectory has been most impressive with Benralizumab monotherapy (Figure 1).

Discussion: We describe the successful Benralizumab substitution monotherapy in EGPA with eosinophilic asthma. We support calls for larger trials of the biologics in EGPA.

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Composite showing impact of Benralizumab monotherapy on FEV-1 (Figure 1) and Eosinophil count (Figure 2) after its introduction in April 2019.

Infection-Related Glomerulonephritis: Is It Only Related to Infection?
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Background: Infection-related glomerulonephritis (IRGN) encompasses a wide relationship between active bacterial infection and associated glomerular lesion. The treatment relies on eradication of infection. The role of immunosuppression (IS) is still in debate. We aimed to assess factors that could be related to kidney and patient outcomes in a series of IRGN patients.

Methods: Clinical and outcome data from patients >18y, with histologic and laboratory diagnosis of IRGN, were collected retrospectively. Pathologic patterns were reviewed and evidence of simultaneous infection was confirmed.

Results: Fifteen patients (12 male; mean age 70±10y) were included; 33% were diabetic and 33% had alcoholic habits. Median baseline eGFR was 78.7mL/min. All presented haematuria and proteinuria, 53% in nonglomerular range. Median SCr at admission was 3.7mg/dL. C3 was decreased in 60% and IgA levels were elevated in 40%. The commonest infection site was skin (47%) and Staphylococcus aureus infection was the most prevalent. The most common pathologic patterns were mesangial (86.7%) and endocapillary proliferative GN (93.3%), 60% with crescentic proliferations. IF showed mesangial and capillary C3 deposits (93%), 60% of cases were IgA-dominant. All patients were treated with antibiotics and 73.3% underwent IS. All developed kidney dysfunction (median SCr 6.1mg/dL), 60% needing RRT. In hospital mortality was 20%. At discharge 26.7% remained RRT-dependent and 46.7% had AKD; only one patient presented total recovery. At 3mo of follow-up (n=12), one new patient had total recovery, 33.3% remained RRT-dependent and 66.7% had median eGFR 40.0mL/min. At 12mo (n=11) one patient died (unrelated cause); 36.3% remained with CKD, 36.3% maintained RRT and 27.3% maintained recovery. Data related outcomes regarding IS and IgA dominance showed that neither influence recovery. During follow-up a new episode of infection was detected in 50% of cases, most of them with AKI associated.

Conclusions: Overall IRGN had poor kidney outcome and it seems that treatment with IS did not improve that, although it is important to highlight that all patients IS-treated had more severe disease. Patients with IgA-dominant IRGN had better eGFR. Our results correspond to a small series of a single centre; therefore, future research is needed to better understand risk factors for outcomes.

Benralizumab: A Descriptive Study of the Demographic, Clinical, and Biopsy Findings at the Time of IgA Nephropathy (IgAN) Diagnosis
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Background: In patients with IgAN, higher proteinuria, glomerulosclerosis, and tubular atrophy are associated with poor outcomes. We summarize the demographic, laboratory, and biopsy findings of an IgA nephropathy cohort from the US southwest.

Methods: We identified patients diagnosed with IgAN between 2002 to 2016 on whom data was available within 30 days of the biopsy. We summarized the data by calculating n (%), mean (SD), or median (IQR) as appropriate. We compared the clinical data at biopsy stratified on Oxford IgA nephropathy (MEST-C) classification.

Results: We identified 67 patients with IgAN (Figure 1). Approximately half of the cohort was female and most of the patients identified as Hispanic (40.3%) or Native American (22.5%). The mean biopsy age was 37.8 years with a median serum creatinine (SCr) of 3.7mg/dL. C3 was decreased in 60% and IgA levels were elevated in 40%. On the Oxford classification, patients’ with M1, E1, and S1 lesions had a lower creatinine level and higher urinary RBCs and serum creatine compared to those with M0, E0, and S0 lesions, respectively (Figure 2a). T lesions were positively correlated with creatinine and higher urinary RBCs and serum creatine compared to those with M0, E0, and S0 lesions, respectively (Figure 2a). T lesions were positively correlated with creatinine and proteinuria. The majority of the biopsies showed negative for C4q and positive for C3 on immunofluorescence (IF) microscopy (Figure 2b).

Conclusions: This IgA cohort was predominantly Hispanic or Native American. Most of the patients had established CKD, proteinuria, segmental sclerosis, and tubular atrophy at the time of the diagnosis. At the time of biopsy, higher T lesions were associated with an increased crescentic lesion level and a trend towards increased proteinuria. On IF, C3 was...
Diabetic Nephropathy: A Great Mimicker or Mistaken Identity

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Introduction: Monoclonal gamopathy of renal significance (MGRS) is often a challenging diagnosis due to wide spectrum of disease and difficulty in establishing a pathogenic link between monoclonal proteins and kidney disease. Here, we describe a biopsy ‘proven’ diabetic kidney disease in a non-diabetic patient, diagnosed as membranoproliferative glomerulonephritis (MPGN) years later with robust clinical response to treatment.

Case Description: A 68-year-old male with stage 3A-B CKD, hypertension and monoclonal gamopathy of uncertain significance (MUGS) was referred to renal clinic for second opinion on biopsy ‘proven’ diabetic kidney disease in 2013 despite never being a diabetic. A repeat kidney biopsy in 2020 for persistent proteinuria revealed MPGN with segmental subendothelial electron dense deposits (Figure 1). Unfortunately, IF was inconclusive due to inadequate sample. After ruling out other etiologies, he was treated as MGRS with velcade and dexamethasone with excellent clinical response with improvement in renal function and resolution of proteinuria (Figure 2).

Discussion: This case brings up an interesting clinical question: could the original diagnosis of diabetic nephropathy be early changes related to MGRS and was it a mistaken identity? Serial kidney biopsies are rarely done in MGRS but could provide guidance as illustrated by our experience.

Figure 1: Electron microscopy with sub-endothelial deposits

Figure 2: Response to treatment with Velcade and dexamethasone

AKI Associated with Anticoagulant-Related Nephropathy in a Newly Diagnosed IgA Nephropathy

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Introduction: Anticoagulant-related nephropathy (ARN) is a type of acute kidney injury (AKI) that may be caused by anticoagulation with warfarin and other anticoagulants. It is an underestimated cause of AKI with poor renal prognosis. AKI is probably resulting from glomerular hemorrhage and the characteristic pathologic findings consist of obstruction of renal tubules by red blood cell casts, which do not contain Tamm-Horsfall protein.

Case Description: A 58-year-old Caucasian man presented with AKI stage 3 (serum creatinine 5.9mg/dL) complaining of macroscopic hematuria. Two months ago, he underwent aortic valve replacement with a mechanical valve and he began taking anticoagulants as an anticoagulant agent (serum creatinine 0.9mg/dL). He also presented INR 2.2, several dysmorphic erythrocytes in urinary sediment and 24-h urinary protein excretion 5g/day. The renal biopsy revealed mild mesangial hypercellularity, acute tubular necrosis with extensive red blood cell casts and interstitial inflammation. The immunofluorescence presented mild mesangial deposits of IgA (2+) and C3 (1+).

We consider that the cause of AKI was anticoagulant-related nephropathy rather than IgA nephropathy because there was no history of prior infection and the presence of numerous RBC tubular casts could not be explained just by these glomerular findings and only mild mesangial proliferation, as well as mild deposits of IgA by immunofluorescence. Due to the severe interstitial nephritis, pos prednisolone 1mg/Kg/daily was added to his treatment, with a gradual reduction in 4 months and acenocoumarol was replaced by tinzaparin. After 1year renal function remains stable at creatinine level 2.5mg/dL, proteinuria <1gr/24h, without microscopic hematuria.

Discussion: This case highlights an unusual severe cause of AKI “anticoagulant-related nephropathy”, in which the majority of patients remains hemodialysis dependent. Patients with underlying glomerulopathies, associated with hematuria are predisposed to be risk factors. Considering the poor renal prognosis, it highlights the necessity for close vigilance of renal function, as well as, urine sediment in patients, who begin on anticoagulation, especially with pre-existing renal diseases, including glomerulopathies and those with glomerular hyperfiltration.

Eculizumab for Treatment of Recurrent Pregnancy-Triggered Atypical Hemolytic-Uremic Syndrome with a Mutation in Complement 3: A Case Report

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Introduction: In atypical hemolytic-uremic syndrome (aHUS), thrombotic microangiopathy (TMA) often develops due to mutations in complement-related genes or autoantibodies to complement regulators. Anti-C5 monoclonal antibodies (eculizumab and ravulizumab) are expected to improve prognosis. However, the significance of genetic testing is unknown. We report a case of pregnancy-triggered aHUS that was successful with plasmapheresis and eculizumab administration.

Case Description: A 37-year-old Japanese female who had a twin pregnancy underwent a scheduled cesarean section at 37 weeks gestation. On the second day after her delivery, she developed thrombocytopenia, hemolytic anemia, and renal dysfunction. TMA was suspected, and plasma exchange (PE) was started on the 3rd day after her delivery, and steroid pulse was started on the 4th day, and then prednisolone 60 mg/day was administered. Since Shiga toxin-producing Escherichia coli in her stool was negative and both ADAMTS13 activity and inhibitor were normal, the patient was clinically positive with a negative C1q pointing towards alternate and/or mannose-binding lectin complement pathway activity.

Figure 1: Electron microscopy with sub-endothelial deposits

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Underline represents presenting author.
diagnosed with aHUS. Her clinical findings tended to improve, so PE was interrupted after 28 days. She was relapsed due to infection 15 days after her delivery. We decided that eculizumab was necessary because of the relapse of aHUS due to the infection even under high doses of steroids. Eculizumab was administered 22 days after her delivery, and her clinical findings improved. After that, the pathogenic variant p.Leu157Thr was identified by genetic testing. Since aHUS due to C3 gene mutation has been reported to have a high recurrence rate, eculizumab administration was continued every two weeks.

Discussion: When thrombotic thrombocytopenic purpura (TTP) and aHUS are suspected, patients with aHUS should be started as soon as possible, and eculizumab administration should be considered when aHUS is diagnosed by ADAMTS13 testing. In the case of aHUS, genetic testing is essential because it enables the definitive diagnosis and the prediction of prognosis.

PUB222

Severe AKI: A Case of Histiciolytic Gerulonephropathy

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Introduction: Histiciolytic gerulonephropathy (HGP) is a rare and potentially life-threatening cause of acute kidney injury (AKI) which can occur coincident with macrophage activation syndrome (MAS) or hemophagocytic lymphohistiocytosis (HLH). HGP has also been recognized secondary to viral infections and autoimmune diseases (AD). Early identification with renal biopsy (RB) to exclude other forms of rapidly progressive glomerulonephritis (GN) and to initiate prompt treatment is of utmost importance to improve outcomes. We present a case of AKI secondary to HGP in the setting of acute viral illness.

Case Description: 52-year-old male with DM, HTN presented (Pre-Pandemic) with 4 days of fever, chills, myalgia with severe joint stiffness and pain. On exam, he had hand swelling and tenderness. Labs noted hemoglobin 11.9, platelet (p) 69000, bicarbonate 23, BUN 47, creatinin (Cr) 3.4 mg/dL, urinalysis (UA) with > 100000 red cells, 11 red cells and 10 white cells. UA and Cr (0.8) was normal one year prior. Other tests noted a 24-hour urine protein of 4gm, TSt 12%, ferritin 295, ANA (1:320), anti ds-DNA 1:80, elevated EBV and Parvovirus IgM and IgG, positive EBV nuclear antigen, low Cr (0.8-1.4), C4 12-18.65, LSR 46, low cryoglobulins, hepatitis B, C, anti-GM, RF, ANCA, urine immunofixation and serum protein electrophoresis. By day 2 of admission, he became oliguric with urine output (UO) <500cc/day, CO2 decline to 19 a hyperuricemia. RB demonstrated endocapillary histiocytes, endothelial cell swelling with mild glomerular deposits and 80% foot process effacement. With supportive therapy (IV fluids, holding ACE, analgesics) his arthritis resolved. By day 4, UO increased, Scr improved to 1.5 and pH normalized. Anemia persisted and was treated with IV iron

Discussion: HGP has been reported secondary to acute viral illnesses and may be associated with MAS in the setting of ADs and malignancies. When associated with MAS or HLH, multiorgan failure may be life threatening prompting early immunosuppressive treatment. Though rare, HGP should be considered in the differentials of acute AD prompting early renal biopsy. If clinical picture is severe, treatment with steroids and calcineurin inhibitors may be renal and life saving. In our patient, with a more benign course of HGP likely due to EBV, clinical improvement was rapid with supportive care alone. Without RB, appropriate treatment for other forms of GN, microangiopathic injury might have been delayed

PUB223

A Case of ANCA-Associated Vasculitis (AAV) in Patients with Systemic Sclerosis (SSc)

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Introduction: AAV in patients with SSc has been reported rarely. As both diseases can present with renal involvement, diagnosis is challenging. We report the case of a 56 year-old female who was admitted for proteinuria AKI found to have biopsy-proven P-ANCA-associated crescentic glomerulonephritis.

Case Description: 56 YOM with PMH of SSc in the setting of filiagnathic malignancies. When associated with MAS or HLH, multiorgan failure may be life threatening prompting early immunosuppressive treatment. Though rare, HGP should be considered in the differentials of acute AD prompting early renal biopsy. If clinical picture is severe, treatment with steroids and calcineurin inhibitors may be renal and life saving. In our patient, with a more benign course of HGP likely due to EBV, clinical improvement was rapid with supportive care alone. Without RB, appropriate treatment for other forms of GN, microangiopathic injury might have been delayed

Discussion: When thrombotic thrombocytopenic purpura (TTP) and aHUS are suspected, patients with aHUS should be started as soon as possible, and eculizumab administration should be considered when aHUS is diagnosed by ADAMTS13 testing. In the case of aHUS, genetic testing is essential because it enables the definitive diagnosis and the prediction of prognosis.

PUB224

ANCA Negative, Yet Pulmonary Embolism Positive

Latoya N. Gayle, Deborah A. Fein. Englewood Health, Englewood, NJ.

Introduction: Pauic immune glomerulonephritis (GN) with negative ANCA serology occurs in ~1/3 of pauci immune GN patients. ANCA negative patients are thought to have a lower incidence of extra-renal involvement but poorer renal prognosis than those who are ANCA positive. We present a case of ANCA-negative Pauic-immune Rapidly Progressive GN (RPGN), returning 4 weeks after discharge with pulmonary embolism (PE).

Case Description: A 39-year-old male presented (pre-pandemic) with 2 weeks of fever and chills. For ~3 years, he has had intermittent arthralgia, dyspnea, facial and ankle swelling with gross hematuria and a 12lb weight gain 2 months prior to admission. Baseline creatinine (Cr) was 1.3(0.7-1.3 mg/dl) a month prior. On admission Cr was 2.6, Alb 3mg/dl and Urine protein noted 100mg/dl, RBC 20-30 and WBC 10-20. A 24-hour urine protein measured 8g/day. Serologies were positive for dsDNA 1:10 and Antistreptolysin O, with negative ANA, ANCA, anti-GM, SPEP, Hepatitis B, C, HIV and normal C3/C4. Renal sonogram noted normal sized kidneys with increased echogenicity. A renal biopsy was done and Methylprednisolone pulse therapy commenced. His renal biopsy showed focal necrotizing and crescentic GN with negative IF, consistent with pauci-immune GN. Cr peaked at 3.6 and IV Cyclophosphamide was given. He was discharged on Prednisone with Rituximab given 2 weeks later. 4 weeks after discharge, Cr improved to 1.3, however he then discharged on Enoxaparin for anticoagulation.

Discussion: Renal disease manifests as a pauci-immune GN in ANCA-Associated Vasculitis (AAV)~ 1/3 of patients with pauci immune vasculitis are ANCA negative. Whether these patients should be included in the spectrum of AAV or are a separate pathophysiologic mechanism is unknown. Our patient presented with RPGN and a PE after initial treatment despite negative ANCA panel and current evidence suggesting a lower incidence of other organ involvement. The presence of an underlying pulmonary vasculitis could not be excluded. We postulate that all patients with ANCA negative RPGN should be followed for additional organ involvement and further study of this patient population is warranted.

PUB225

Autologous Mesenchymal Stromal Cell Therapy for Idiopathic Nephrotic Syndrome: The MESNEPH Study

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Background: Corticosteroids represent first-line treatment of idiopathic nephrotic syndrome (INS). However, 60-80% of patients present multiple relapses and require steroid-sparing immunosuppression with significant toxicity. New therapeutic approaches with a better safety profile are needed. Mesenchymal stromal cells (MSC) exert immunomodulatory functions, regulating cells of both adaptive and innate immune system.

Methods: Approximately 20 patients (age-range 5-40 years) with multi-relapsing INS (a2 relapses despite prednisone and/or a1 other immunosuppressive steroid-sparing agent) in remission will be recruited. After screening and informed consent, a bone marrow aspirate will be performed, followed by a 6-12 week MSC-expansion period during which oral immunosuppression will be maintained. Each patient will receive 2 intravenous infusions of 1-10x10^6 autologous MSCs 7 days apart. One month after the first infusion, all concomitant immunosuppressive therapy will be tapered and withdrawn. The observational phase will last 12 months after the first MSC infusion (Table I). This is a prospective, phase 1 open-label non-randomized multicentric study evaluating the safety and efficacy of autologous bone-marrow derived MSC treatment in patients with severe frequently-relapsing or steroid-dependent INS.

Results: The study is ongoing, last patient visit is expected in July 2021.

Conclusions: The study will primarily assess the feasibility and safety of this approach for the treatment of severe INS. Secondly, it will evaluate treatment effect on INS relapses, immunosuppressive therapy dose and toxicity, kidney function at baseline and 12 months after MSC infusion.

Funding: Government Support - Non-U.S.
Safety and Efficacy of Avacopan (CCX168) in a Pediatric Patient with C3 Glomerulopathy

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Introduction: C3 glomerulonephritis (C3GN) is a subtype of C3 glomerulopathy, characterized by alternative pathway complement activation and intense C3 immunofluorescence on renal biopsy. C5a is a potent pro-inflammatory mediator of the complement system, whose chemotactic effects are mainly mediated by the interaction with complement C5a receptor (C5aR) expressed on the cell surface. Avacopan is an orally administered selective inhibitor of C5aR.

Case Description: An 11-year-old female with biopsy-proven C3GN was initially treated with three intravenous (IV) boluses of methylprednisolone then tapered to oral prednisone (PND) given with mycophenolate mofetil (MMF) and an angiotensin-converting enzyme inhibitor (ACE-i). Complete remission was achieved, PND was stopped, and MMF and ACE-i were maintained. Twelve months following remission, due to relapse of proteinuria (urinary protein/creatinine ratio (UPCR) 1.19 mg/mg), a second course of PND therapy was started and cyclosporin (CyA) was added to the therapy. A high level of C5b9 was found. Since the patient never achieved complete remission, she was enrolled in the ChemoCentryx ACCOLADE study, which was a randomized, double blind, placebo controlled study. Patients received avacopan or matching placebo for the first 26 weeks, followed by open-label avacopan in all patients for the following 26 weeks. At the end of the open-label phase, her UPCR was 2.09 mg/mg. Following avacopan, a progressive reduction of proteinuria of approximately 0.5 mg/mg was observed. In the last 4 weeks of the study, avacopan was discontinued, and an increase in proteinuria (UPCR 0.7 mg/mg) was observed, which continued to >1 mg/mg in the subsequent weeks. The patient also reported increased fatigue. After about 3 months, authorization for compassionate use of avacopan was obtained and the patient experienced improvement in her physical well-being and a reduction of proteinuria of approximately 0.5 mg/mg. CyA was discontinued, but it was rapidly reintroduced due to a transient increase of proteinuria. In the following months, proteinuria remained low despite the interruption of MMF. At the last follow up (+16 months from open-label start) UPCR was 0.29 mg/mg and the drug was well tolerated.

Discussion: To the best of our knowledge, this is the first report on the use of avacopan in a pediatric case of C3GN.
Kidney Function in Patients with Lupus Nephritis Followed Up for a Very Long Time

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Background: Most investigations of long-term outcome in patients with lupus nephritis (LN) focus on end-stage kidney disease (ESKD), but seldom on the progression of patients left with chronic kidney disease (CKD). Both CKD and lupus are non-traditional risk factors for cardiovascular morbidity. We therefore looked at the development of CKD in a subset of LN followed for a very long time in an LN clinic.

Methods: A retrospective chart review was conducted in biopsy-proven LN patients followed for >10 years in a single-center, multidisciplinary LN clinic. Patients with CKD were defined as having an eGFR <60 ml/min/m², and those with ESKD as having an eGFR <15 ml/min/m² or requiring permanent kidney replacement therapy. eGFR was determined by the clinical laboratories the patients used and was race adjusted. Results are analyzed with descriptive statistics.

Results: 72 patients were followed for a median of 17.1 years (range 10 to 38.7) after LN was confirmed by kidney biopsy. The mean ± standard deviation, SD) age at diagnostic biopsy was 31.8±14.1 years. 21 patients were of African ancestry, 4 were Asian, and 47 were White. ESKD developed in 12 patients (16.7%) after a median of 14.6 years. At the time of last follow-up, 27 patients (37.5%) had CKD with a mean (±SD) eGFR of 40.4±13.0 ml/min/1.73m². Of the 27 patients who developed CKD, 21 experienced at least one episode of eGFR <50 ml/min/1.73m² that lasted for at least 6 months. Of the other 6 CKD patients, 4 (67%) had at least one 6 month (or longer) episode of proteinuria >3.5 g/d.

Conclusions: These data suggest that over 50% of LN patients may be at risk for developing ESKD or CKD if followed for 10 or more years. Almost all of these patients had sustained periods of kidney injury resulting in a median eGFR decline of 12.9 ml/min/1.73 m² per year. This observation highlights the need for early intervention to slow progression of LN.

Staphylococcus aureus Infection-Related IgA Vasculitis with Kidney Involvement

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Introduction: IgA Vasculitis (IgAV), a systemic small vessel vasculitis with IgA dominant/co-dominant immune deposits, is characterized by purpura, arthralgias, and kidney involvement. IgA Vasculitis (IgAV) with nephritis: IgAV-N. Staphylococcus, including methicillin-resistant Staphylococcus aureus (MRSA), infection with glomerular IgA deposits known as IgA-dominant infection related glomerulonephritis (IgA-IRGN), is a variant of IRGN whose management remains controversial.

Case Description: A 46-year-old male with diabetes, lumber discitis with recurrent MRSA bacteremia, and normal kidney function [baseline Scr 0.7 mg/dl] presented with bilateral lower extremity palpable purpura and petechiae, polyarthralgia, diarrhea; without urinary complaints. Comorbid MRSA bacteremia without an adequate source (lumbar hardware and repeat lumbar hardware) or evidence of endocarditis was found. Skin biopsy revealed leukocytoclastic vasculitis with direct IF (++) for IgA, C3, and fibrin confirming IgAV. Urinalysis revealed nephritic sediment. Sr albumin was 2.3 g/dl; random UPCR was 3 g/24h. Workup including lupus serologies, cryoglobulins, ANCAs, Anti-GBM, RF, ASO, Hepatitis B/C, HIV, paraproteinemia testing were negative. Complements were normal. Scr on admission was 0.8 mg/dl; peaked to 1.4 mg/dl on the 3rd hospitalization day likely in setting of contrast-related AKI, multifactorial ATN, and potential IgAV-N secondary to MRSA infection. He was started on IV vancomycin, IV methylprednisolone, IVIG, and dapsone. Scr returned to baseline on 5th day. Prednisone 60 mg/d with a rapid taper was started. Rash, kidney function, and proteinuria improved; hence a kidney biopsy wasn’t pursued. Blood cultures turned negative; he was discharged on IV daptomycin/cefaroline and prednisone TID X 6 weeks.

Discussion: Kidney histopathological features of IgA-IRGN are similar to those of IgAN/IgA-N. Correct diagnosis is imperative as IgAN and IgA-N likely necessitate immunosuppressive (IS) treatment, while initial IS can exacerbate infection in IgA- IRGN. In our patient, skin biopsy clinched diagnosis of IgAV, and was treated with IS given widespread systemic disease, and antibiotics, with rapid improvement of kidney function allaying need for kidney biopsy. Individualized approach for the management of IgA-IRGN is therefore warranted.
Publication-Only
Davide
An Unexpected Case of Rapidly Progressive Renal Failure (RPRF)
Sometimes an Ultrasound Scan Before the Kidney Biopsy Is Enough:
Changes in outcomes between responder group and non-responder group.

PUB235
Vitamin D status and Its Association with PTH in 73645 Caucasian Outpatients
Xin Chen,1,2 Chang Chu,1,2 Cornelia Doebis,1 Bernhard K. Krömer,1 Volker V. Baehr,1 Berthold Hocher.1,2
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Background: 25-hydroxyvitamin D (25(OH)D) inhibits the synthesis of PTH. However, the limited size of clinical studies to date has only allowed a relatively crude analysis of the relationship between 25(OH)D and PTH.

Methods: We investigated this relationship in 73645 patients (Figure 1).

Results: The relationship between 25(OH)D and iPTH has three phases: an initial drop in iPTH (25(OH)D: 6–20 ng/ml), a horizontal phase (25(OH)D: 20–66 ng/ml); a final drop in iPTH (25(OH)D: ≥60 ng/ml). A Cox regression analysis of these three phases considering age, sex, 25(OH)D, calcium, phosphate, and creatinine showed that in the initial phase age (RR: 0.20; CI: 0.09–0.31, p<0.0001), sex (RR: 15.84; CI: 11.40–20.28, p<0.0001), 25(OH)D (RR: -1.75; CI: -2.22–1.25; p<0.0001), and creatinine (RR: 45.52; CI: 42.58–48.16; p<0.0001) are independently correlated with iPTH, whereas in the second horizontal phase age (RR: 0.14; CI: 0.09–0.20, p<0.0001), sex (RR: 14.84; CI: 13.01–16.66, p<0.0001), calcium (RR: -10.73; CI: -17.81–3.64, p=0.003), phosphate (RR: -19.19; CI: -23.46–14.92, p<0.0001), and creatinine (RR: 46.36; CI: 45.30–47.41, p<0.0001) are relevant. In the third phase, only sex (RR: 17.94; CI: 5.38–30.50, p=0.005) and creatinine (RR: 42.07; CI: 35.39–48.74, p<0.0001) play a significant role. Analyzing the relation between iPTH and 1,25-dihydroxyvitamin D (1,25(OH)2D) in a subset of the study (N=2441) revealed that serum 1,25(OH)2D concentrations have no effect on iPTH concentrations in subjects with normal kidney function.

Conclusions: In conclusion, circulating 1,25(OH)2D does not contribute substantially to the regulation of iPTH in healthy subjects. Presumably, serum 25(OH)D that is converted to 1,25(OH)2D after megavitamin-mediated uptake in the parathyroid chief cells plays the critical role. The relationship between 25(OH)D and iPTH has three phases. Factors correlating independently with PTH in the different phases differ substantially. 25(OH)D is only relevant in the first initial phase.

PUB233
Sometimes an Ultrasound Scan Before the Kidney Biopsy Is Enough: An Unexpected Case of Rapidly Progressive Renal Failure (RPRF)
Davide Raimondo,1 Chiara Lanzani,1 Alessandro Barruscotti,2 Marta Vespa,1 Paolo Mannuta,1,2 Giuseppe Vezzoli,1,2 IRCCS Ospedale San Raffaele, Milano, Italy; 1Università Vita Salute San Raffaele, Milano, Italy.

Introduction: RPRF is a clinical diagnosis in patients with progressive renal impairment of short duration. The underlying etiology may be a primary renal disease or a systemic disorder. Early definitive diagnosis of RPRF is essential to reverse progression to end-stage kidney disease.

Case Description: Male patient, 64 yo, referred to us after hospitalization elsewhere for RPRF with nephritic-like syndrome. PMH: DM2 history. At age 58 (2015) aortic surgery substitution with a mechanical prosthesis. Discharged on 05/26 with creatinine 3.14 mg/dl. Ampicillin, after 2 weeks renal function improved (3.8 mg/dl). On 05/04 he underwent valve replacement surgery. Diagnosed a systemic disorder. Early definitive diagnosis of RPRF is essential to reverse progression to end-stage kidney disease.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

PUB234
A Case of Malignancy in NELL-1 Membranous Nephropathy
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Introduction: The predominant target antigen for primary membranous nephropathy (MN) has been Phospholipase A2 receptor (PLA2R), which is present in approximately 70% of cases. Neural epidermal growth factor like 1 protein (NELL-1) was recently identified as one of four new antigens in a distinct type of primary MN. NELL-1 is a rare emerging subtype of MN that has been identified in both primary MN and malignancy associated nephropathy. A thorough malignancy workup is warranted in all non-diagnostic for a malignancy. Her biopsies showed reactive nephropathy with concern for evolving B-cell lymphoproliferative disorder with plasmacytic differentiation. Given her biopsy findings and high clinical suspicion for NELL-1 MN, the patient was treated with rituximab.

Background: NELL-1 is a rare emerging subtype of MN that has been identified in both primary MN and malignancy associated nephropathy. A thorough malignancy workup is warranted in all non-diagnostic for a malignancy. Her biopsies showed reactive nephropathy with concern for evolving B-cell lymphoproliferative disorder with plasmacytic differentiation. Given her biopsy findings and high clinical suspicion for NELL-1 MN, the patient was treated with rituximab.

Discussion: NELL-1 is a rare emerging subtype of MN that has been identified in both primary MN and malignancy associated nephropathy. A thorough malignancy workup is warranted in all patients diagnosed with NELL-1 MN. More research is needed in the association between NELL-1 and specific cancers, in hopes of guiding future treatments for this disease.

Changes in outcomes between responder group and non-responder group.

PUB245
Vitamin D Status and Its Association with PTH in 73645 Caucasian Outpatients
Xin Chen,1,2 Chang Chu,1,2 Cornelia Doebis,1 Bernhard K. Krömer,1 Volker V. Baehr,1 Berthold Hocher.1,2
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Background: 25-hydroxyvitamin D (25(OH)D) inhibits the synthesis of PTH. However, the limited size of clinical studies to date has only allowed a relatively crude analysis of the relationship between 25(OH)D and PTH.

Methods: We investigated this relationship in 73645 patients (Figure 1).

Results: The relationship between 25(OH)D and iPTH has three phases: an initial drop in iPTH (25(OH)D: 6–20 ng/ml), a horizontal phase (25(OH)D: 20–66 ng/ml); a final drop in iPTH (25(OH)D: ≥60 ng/ml). A Cox regression analysis of these three phases considering age, sex, 25(OH)D, calcium, phosphate, and creatinine showed that in the initial phase age (RR: 0.20; CI: 0.09–0.31, p<0.0001), sex (RR: 15.84; CI: 11.40–20.28, p<0.0001), 25(OH)D (RR: -1.75; CI: -2.22–1.25; p<0.0001), and creatinine (RR: 45.52; CI: 42.58–48.16; p<0.0001) are independently correlated with iPTH, whereas in the second horizontal phase age (RR: 0.14; CI: 0.09–0.20, p<0.0001), sex (RR: 14.84; CI: 13.01–16.66, p<0.0001), calcium (RR: -10.73; CI: -17.81–3.64, p=0.003), phosphate (RR: -19.19; CI: -23.46–14.92, p<0.0001), and creatinine (RR: 46.36; CI: 45.30–47.41, p<0.0001) are relevant. In the third phase, only sex (RR: 17.94; CI: 5.38–30.50, p=0.005) and creatinine (RR: 42.07; CI: 35.39–48.74, p<0.0001) play a significant role. Analyzing the relation between iPTH and 1,25-dihydroxyvitamin D (1,25(OH)2D) in a subset of the study (N=2441) revealed that serum 1,25(OH)2D concentrations have no effect on iPTH concentrations in subjects with normal kidney function.

Conclusions: In conclusion, circulating 1,25(OH)2D does not contribute substantially to the regulation of iPTH in healthy subjects. Presumably, serum 25(OH)D that is converted to 1,25(OH)2D after megavitamin-mediated uptake in the parathyroid chief cells plays the critical role. The relationship between 25(OH)D and iPTH has three phases. Factors correlating independently with PTH in the different phases differ substantially. 25(OH)D is only relevant in the first initial phase.

Changes in outcomes between responder group and non-responder group.

PUB236
Metabolic Features of Patients Older than 80 Years Receiving Total Parenteral Nutrition (TPN)

Background: Advances in surgical and interventional techniques has extended the use of TPN in patients unable to receive enteral support. Metabolic abnormalities in “elderly” individuals receiving TPN has been reported > 65 yo but few focusing on > 80.

Changes in outcomes between responder group and non-responder group.
Reduced GFR, low muscle mass, and multiple comorbidities create unique management challenges. Use of a multidisciplinary approach as described may mitigate TPN associated electrolyte derangements and mortality. For this retrospective study we report some of the clinical parameters associated with “extreme” elderly patients receiving TPN.

**Methods:** A TPN team consisting of a nephrologist/intensivist, abdominal/critical care surgeons, anesthesiologist, a dietician, and a surgical PA met daily at 1030 to consider all referrals and create orders by 1230 for a TPN specialty pharmacist review followed by administration at 1730. 38 patients between 1/1/2019-12/15/2020 receiving CENTRAL parenteral nutrition (no PPN) were included. Metabolic complications of 1 or more times were reported.

**Results:** Baseline demographics of the study population was male, 55% for Mean Age (range): 86 (80-98 years) BMI: 19.8 kg/m2; BMI 30-39 kg/m2: 24%; Severe Malnutrition: 66%; Hba1c >6.5%; 5% GFR <60 mL/min/1.73m2: 34% TPN Characteristics Mean days on CPN (range): 14 days (4-39 days) Mean energy dose: 26.7 kcal/kg/day; Mean Albumin: 4.1 g/dL; Mean Cardiac Caloric distribution: 26% protein, 50% CHO, 24% lipid Metabolic Complication(n= 38) Hyperglycemia (blood glucose >200 mg/dL) 50%(19) Hypoglycemia (blood glucose <60mg/dL)(3)% (1) Hypertension (systolic blood pressure >140mmHg)(40%)(5)% Hypoalimenta (-3 mL/kg/h)(3)% Hypophosphatemia (<2 mg/dL) (18%) Hypomagnesia (<1.5 mg/dL)(2)% Hypocalcemia (<4 mg/dL)(2)% Low potassium (<3.5 mg/dL) in 1st 3% on TPN 12%(12) Low phosphorus (<2.5 mg/dL) in 1st 3% on TPN 34%(13)

**Conclusions:** Expected “refeeding” hypo K and PO4 were observed but critical levels <2 and 1.5 respectively and early fatalities were not encountered daily monitoring and aggressive supplementation. Very frequent hyperkalemia largely of the “SIADH Type” was mitigated by fluid restriction and high osmolar load. Na levels < 125 or >150 were not seen after initiation of TPN. We believe that a concerted multidisciplinary team approach is extremely useful in provision of the high risk “TPN medication”.

**PUB237**

Comparison of the Triglyceride and glucose index in predicting CKD among hypertensive population: Six Southern China community cohorts

**Hequn Zou, Pinghu Hospital of Shenzhen University, Shenzhen, China.**

**Background:** Hypertension (HTN), as a major disease concern around the world that impacts middle-age and elderly population. We intend to explore the relationship between HTN and CKD through a new insulin-related index: Triglyceride and glucose index (TyG).

**Methods:** A cross-sectional cohort study of six populations in the southern coastal town of Wanzhai (Zhuhai, China) was carried out over four months. Group assignment criteria: Systolic Blood Pressure (SP) ≥140mmHg with or without a Diastolic Blood Pressure (DP) ≥90mmHg or self-reported currently under treatment with anti-hypertensive medications for the hypertensive group; while the control group population had normal blood pressure and no previous history of HTN. CKD was defined with the following criteria for diagnosis: urinary albumin/creatinine ratio (ACR)≥30mg/g with or without an estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73m2.

**Results:** Lipid and glucose metabolic index TyG showed a correlation with the occurrence of CKD in the hypertensive population. In binomial logistic regression analysis, the risk of occurrence of CKD was 1.503 (odds ratio) with the 95% confidence interval (CI) of each standard deviation of TyG lying between 1.127-2.03 (p=0.05). Area under the curve (AUC) of a receiver operating characteristic (ROC) was 0.5807 (p=0.001; 95%CI: 0.5337-0.6278), showing the utility of TyG as a prognosticator of CKD in people with HTN.

**Conclusions:** TyG may predict the prevalence of CKD occurrence among hypertensive population of Southern China.

**PUB238**

Renal Artery Stenosis: Ticking Bomb

Shivangi Patel, Morristown Medical Center, Morristown, NJ.

**Introduction:** Untreated renal artery stenosis leads to poorly controlled and difficult to manage hypertension, congestive heart failure, and progression of renal disease. A high index of suspicion is essential for clinical diagnosis and to potentially reverse a condition with narrow time window.

**Case Description:** 82-year-old female with poorly controlled blood pressure, 27 pack year smoking history, quit 2007 was evaluated for worsening creatinine of 2.64 mg/dL, eGFR 16, 8/24/2020 (cr 1.29 mg/dL, eGFR 37.11/2019). Each time a RAAS antagonist was given, this would result in decreased renal function and would improve on discontinuing the drug. Blood pressure 180/60 BM 28, <2 edema. Labs: proBNP 9.317 ng/mL, D-Dimer 137 mg/dL. Protein creatinine ratio 1.588 mg/g, 3+ dipstick. Serology for proteinuria was negative. Renal ultrasound: right kidney 8.7cm with cortical tissues are echogenic and markedly thin consistent with areas of atrophy and left kidney 10.5 cm with normal cortical tissue and medulla. Renal duplex: arterial velocity 95.4cm/s peak systolic, right renal artery 134.5cm/s peak systolic and left renal artery 386.8cm/s peak systolic. Resistive index right kidney average 0.55 and left kidney 0.72. Renal artery to aortic velocity ratio 1.4 on right and 4.1 on left. Echo: moderate to severe concentric LVH, abnormal diastolic relaxation. After left renal artery stent placement, her creatinine was 1.31 mg/dL from 2.11 mg/dL. A month later after addition of losartan to carvedilol and Lipitor her creatinine was 1.2 mg/dl eGFR 42, protein creatinine ratio 745 mg/g with no edema, “more energy” and blood pressure 110/60.

**Discussion:** She has solitary left functioning kidney due to right renal atrophy. When RAAS antagonist was introduced her kidney function deteriorated demonstrating reduced GFR, low muscle mass, and multiple comorbidities create unique management challenges. Use of a multidisciplinary approach as described may mitigate TPN associated electrolyte derangements and mortality. For this retrospective study we report some of the clinical parameters associated with “extreme” elderly patients receiving TPN. Combination of ultrasound and duplex showed a window of opportunity to intervene on viable kidney tissue with an atherooclerotic lesion. She was safely placed onARB to further reduce her risk of progression of renal and heart disease.

**Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.**

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**PUB239**

Epithelial Overexpression of Human ACE2 in Mice as a Model for Studying Renal Disease

Jacqueline M. Emamhinger, Joshua A. Robertson, Jonathan W. Nelson, Susan B. Gurlay. Oregon Health & Science University, Portland, OR.

**Background:** ACE2 is an integral part of the renin angiotensin system (RAS) and is highly expressed at the brush border of epithelial cells of the renal proximal tubule. Within the lumen, ACE2 is poised to metabolize angiotensin II and extinguish its effects as part of the counter-regulatory arm of the RAS. Use of transgenic mouse models has been essential in exploring the cardiovascular and renal functions of ACE2. Limitations in using mouse models for SARS was overcome by generation of mice expressing human ACE2 (hACE2) downstream of the keratin 18 promoter (K18-hACE2) by McCray et al. 2007. K18-hACE2 mice express hACE2 in epithelial cells throughout the body and have proved valuable for the study of SARS-CoV and CoV2 viral infectivity and pathogenesis. Here, we investigate whether K18-hACE2 mice might serve as a unique tool with which to study the role of ACE2 in the intra-renal RAS.

**Methods:** We assessed ACE2 activity in urine collected from K18-hACE2 mice (obtained from Jax and bred in our own colony) and their wildtype littermates. Urine was collected over 24 hours in individual metabolic cages, and enzymatic activity was determined using an ACE2 activity assay. Duplicate samples tested for each animal.

**Results:** Our lab has a longstanding interest in the role of ACE2 in the kidney and our preliminary experiments demonstrate that K18-hACE2 mice have significantly increased ACE2 enzymatic activity in the urine compared to wildtype littermates (1597.0±379.74 vs 396.0±43.92, p=0.013).

**Conclusions:** The increased urinary ACE2 activity suggests that there are elevated levels of ACE2 receiving the kidney. While this seems most likely due to increased expression of renal epithelial ACE2, soluble ACE2 derived elsewhere and able to reach the lumen of the nephron must also be considered. Thus, K18-hACE2 mice with increased urinary ACE2 activity can serve as a model to examine the effect of ACE2 and the RAS on kidneys such as those with hypertension and acute renal injury.

**Funding:** Other NIH Support - NIH TL1 TR002371, ST32GM108935-03

**PUB240**

Nephrotic Syndrome Secondary to Paraneoplastic Syndrome of Leukemia

Jan P. Rosaly, Elizabeth Pabon-Vazquez, Mayaguez Medical Center, Mayaguez, Puerto Rico.

**Introduction:** Paraneoplastic glomerulopathies are rare manifestations of neoplastic disease that must be differentiated from iatrogenic renal injury. Nephrotic Syndrome is one of the most frequent presentations of paraneoplastic glomerulopathies. Such findings might serve to identify prognosis of disease course. It has been reported that solid tumors are associated with membranous nephropathy while lymphomas are associated with minimal change disease. While the incidence of paraneoplastic glomerulonephropathies in Chronic lymphocytic leukemia (CLL) is unknown and rare. CLL is one of the most common type of leukemia in Western countries. It is commonly observed in elderly patients but it has wasn’t associated with renal glomerulopathies. Recent studies suspected that leukemic cells might have certain properties that lead to the development of nephrotic syndrome.

**Case Description:** This is the case of a 82 y/o male patient with past medical history of hypertension, lymphoproliferation, and prostate cancer that presented to the hospital with complaints of edema. Associated symptoms were malaise, poor urinary output and nausea. Physical examination was remarkable for generalized edema with pitting edema +2 on lower extremities. Initial laboratory work up was remarkable for findings of acute renal injury accompanied by oliguria and proteinuria + 3. Despite foley placement and diuresis no major improvements on renal function was observed. Due to constant deterioration he was started on hemodialysis with adequate response but further work up for nephrotic syndrome was requested. ANCA and ANA was negative with low cryoglobulin. Complement such as C3 and C4 were within normal limits. Fat Biopsy was performed. Report was remarkable for changes suggestive of membranous
glomerulonephritis. In addition, due to sudden decrease in hemoglobin levels and elevated light kappa chains bone marrow biopsy was performed. Report was remarkable for changes suggestive of CLL.

Discussion: This case exhibits a patient that did not presented with symptoms or findings suggestive of CLL at the time of renal injury. Therefore, this case strongly underlines the importance of performing a bone marrow biopsy to patients that present with abnormal electrophoresis and immunofixation in order to detect lymphoproliferative disorder. Early detection can help to treat such disease at early stages and avoid further complications that might affect patient’s prognosis.

PUB241
A Case of Immune-Complex-Mediated Glomerulonephritis Associated with Pembrolizumab
Marco A. Bonilla, Vanesa Bijol, Antonio Corona, Kenar D. Jhaveri. Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY.

Introduction: Immune checkpoint inhibitors (ICI) are changing the way we treat cancer. However, these agents have various systemic adverse events that may preclude their use and cause poor patient outcomes. ICI-associated acute kidney injury is an emerging complication of this treatment.

Case Description: An 80-year-old man diagnosed with metastatic adenocarcinoma of the lung with high PD-L1 expression was evaluated for new-onset proteinuria and elevation of serum creatinine. The patient had completed four cycles of carboplatin, pemetrexed, and pembrolizumab at the initial evaluation. His only complaint was foamy urine. Vital signs were remarkable for elevated blood pressure. The physical exam was unremarkable. Laboratory data showed serum creatinine of 1.8mg/dl (baseline of 1.1mg/dl), two months prior, blood urea nitrogen of 24mg/dl, and serum albumin of 3.3g/dl. Urinalysis showed proteinuria, and moderate blood with 9 RBC/HPF. A spot urine protein/creatinine ratio of 10.8 g/g. A kidney biopsy was performed, which showed immune complex-mediated glomerulonephritis, with a membranoproliferative and diffuse segmental endocapillary proliferative pattern of glomerular injury.

Discussion: Kidney immune-related adverse events occur in about 2.5% of patients receiving ICI therapy. Recently there has been increasing recognition of its association with glomerular diseases. Several differential diagnoses were considered that could have instigated these pathological findings. Ultimately, our team had a high clinical suspicion that they were associated with ICI therapy. After a multidisciplinary discussion, the decision was to hold pembrolizumab and start prednisone at a 1mg/kg dose. The patient responded well to therapy, was discharged home with prednisone taper; subsequent protein/creatinine ratio had a striking improvement to 1.6g/g. The serum creatinine was back to baseline. To our knowledge, this is the first case reported of pembrolizumab-associated immune-complex glomerulonephritis. Patients undergoing ICI therapy require close monitoring for potential kidney adverse events. Physicians must remain vigilant and should be able to recognize a potential glomerular injury from ICI therapy.

PUB242
Renal Cell Carcinoma Incidentally Discovered in Native Kidney During Imaging for Superior Vena Cava Obstruction
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Introduction: Papillary RCC accounts for approximately 15% of all kidney cancers, and these can be divided into type 1 and type 2 subtypes based on histopathologic features. As with clear cell cancers, papillary RCC originates from the proximal tubule, but these tumours are morphologically and genetically distinct malignancies. The initial information on their molecular pathogenesis was derived from cases arising in patients with hereditary forms of RCC.

Case Description: A 37-year-old male patient with recurrent FSOS post renal transplantation currently on dialysis. He had aneurysmal AV dialysis fistula and he had CT Scan to evaluate superior and inferior vena cava obstruction which picked up a large complex heterogeneous well-defined mass arising from the lower pole of the atrophic right kidney highly suspicious for renal cell carcinoma (image 1). CT venogram showed chronic obstruction of SVC. This has resulted in extensive varicoed collateral veins in the anterior lateral chest wall and abdominal walls (image 2). The dilated collaterals drain into the femoral veins bilaterally. The patient undergone SVC angioplasty followed by elective right Nephrectomy. The renal mass histology showed Type II papillary renal cell carcinoma, G3, ISCN 2, NCI 1. No extension or renal sinus invasion identified. It was graded as pT1b pNx (AJCC 8th edition). As per EUA Guidelines for CT scan control at 6 months, 1 year, 2 years, 3 years then every 2 years for 10 years.

Discussion: Treatment approach For localized disease, the general approach to treatment is total removal in clear and non-clear cell renal cell carcinomas. Surgical resection offers the best chance of cure.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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PUB243
Immune Checkpoint Inhibitor (ICI)-Associated Hypopituitarism Presenting as Severe Hyponatremia
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Introduction: ICI has improved the prognosis for patients with advanced malignant disease. However, as their use increases, it is important to be aware of their potential side effects that require prompt attention. Here, we report a case that presents with life-threatening severe hyponatremia from secondary adrenal insufficiency as the first sign of hypopituitarism secondary to ICI therapy.

Case Description: A 67-year-old man with a past medical history significant for metastatic clear cell type renal cell carcinoma, status post radical right nephrectomy, and adrenalectomy. He was found to have a metastatic lesion to his lungs and was initially treated with Pembrolizumab along with Axitinib for almost one year. 5 months later, He was found to have a metastatic necrotic mass in the right renal fossa and was started ipilimumab/nivolumab x 4 cycles followed by maintenance monthly nivolumab. Almost 4 months after being initiated on ICI therapy and almost 3 weeks after the last dose, labs showed severe hyponatremia with serum sodium of 115 mmol/L with serum osmolality of 249 mmol/L. Clinical examination was suggestive of euvolemic. Urine osmolality of 1510 with urine sodium of 59 was consistent with the diagnosis of the syndrome of inappropriate antidiuretic hormone release (SIADH). Further workup included 8.00 AM cortisol of 0.5 mcg/dl increasing up to 9.3 mcg/dl in two hours after Cosyntropin 250 mcg IV stimulation along with inappropriately normal levels of ACTH of 18.4 pg/ml suggestive of secondary adrenal insufficiency. Additionally, relatively low TSH (with low free T4) along with low LH were suggestive of pituitary insufficiency. FSH and prolactin were within normal range. MRI brain was without any evidence for pituitarytomas. No laboratory or clinical evidence for hypoadosteronism. The patient was treated with the addition of hydrocortisone and levotyroxine. Follow-up labs at one month showed serum sodium of 132 mcg/L.

Discussion: This case is an excellent illustration that hyponatremia in the patients receiving checkpoint inhibitors could be from hypotrichotellamia. Extensive work up to detect pituitary insufficiency should be considered in such cases as hypotrichotellamia could present as the initial sign of pituitary insufficiency.

PUB244
TMA Associated with Hypereosinophilic Syndrome

Introduction: Thrombotic microangiopathy (TMA) is a rare but serious form of renal injury that can be a manifestation of an array of conditions, including malignancies. Here we illustrate a case of renal TMA due to hypereosinophilic syndrome associated with PDGFRA gene rearrangement.

Case Description: A 29-year-old male presented with endocarditis-like features and findings of myocarditis on cardiac MRI. He was found to have AKI with creatinine up to 2.0 mg/dL, six months prior his creatinine was 0.96 mg/dL. Laboratory data was notable for peripheral eosinophilia, sub-nephrotic range proteinuria, and urine sediment showed many dysmorphic red blood cells. FISH testing showed FIP1L1-PDGFRα fusion rearrangement. A kidney biopsy was performed which revealed an acute TMA with...
focal glomerular capillary thrombosis, multifocal arteriolar thrombosis, and arteriolar fibrinoid necrosis (Figures 1, 2). The patient was started on imatinib with improvement of creatinine to 1.75 mg/dL.

Discussion: Hypereosinophilic syndrome with PDGFRA mutation has been associated with renal TMA in only a few reported cases. It has been hypothesized that eosinophil granule proteins lead to the endothelial injury and platelet activation that precipitates this form of renal injury. This case highlights the importance of early diagnosis of AKI in these patients and the need for prompt treatment.

Results: Between January 1, 2000 and December 31, 2019, 184,056 creatinine levels were enriched for 1,099 patients for the period from day -42 before to day +118 after ASCT. The overall incidence of AKI was 87% (n=956). 782 (71%) Patients have shown an AKIN 1, 145 (13%) an AKIN 2 and 29 (3%) an AKIN 3. During the observation period 122 (11%) patients died. For 32% (204/644) the transition to CKD has been observed.

Conclusions: AKI after ASCT is the rule and not the exception. As the vast majority of patients show AKIN 1 it might be often clinically overlooked. However early intervention might mitigate the development of long term renal impairment. Automated detection (AKI alert systems) as well identification and avoidance of factors contributing or aggravating injury (e.g., conditioning, immunosuppression, perfusion, inappropriate dosing of drugs) might minimize long-term renal complications in ASCT.

PUB246

Gemcitabine-Induced TMA: A Rare Side Effect Associated with High Mortality: A Case Report of Partial Response to Eculizumab

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Introduction: Thrombotic Microangiopathy (TMA) is a well-known complication in cancer, and it could be secondary to neoplasms itself or to its treatment. Gemcitabine-induced TMA is rare, but associated with high mortality rate and negative renal prognosis.

Case Description: A 71-year-old woman treated with Gemcitabine for recurrence of endometroid carcinoma developed a rapid progressive kidney injury, hypertension and pulmonary edema. Laboratory tests revealed signs of TMA. Histological analysis showed both acute and chronic TMA signs (Fig. 1). Upon suspicion of GiTMA, antiblastic therapy was discontinued and, in order to prevent complement activation, Eculizumab was administered. According to literature, a sudden improvement of blood count was observed. Because of worsening of renal function, dialytical treatment was started. Histologically chronic lesions were documented (Fig.2).

Discussion: GiTMA is mostly misdiagnosed, because blood count instability and renal impairment could recognised multiple triggers in neoplastic patients. An early diagnosis enables drug withdrawal and complement system inhibition: the only measures that seem to be associated with increased survival and a better renal outcome.
Electrolyte Disorders Associated with the Use of Immune Checkpoint Inhibitors: A Single-Center Cohort

Swetha Rani Kanduri, Nicholas J. Carbajal, Karthik Kovvuru, Aldo E. Torres Ortiz, Luis A. Matute Trochez, Juan Carlos Q. Veliez.

Background: Electrolyte imbalances have been reported in association with exposure to immune check point inhibitors (ICI). However, the incidence of these disorders has not been widely established. Herein, we report a single center experience on the incidence of electrolyte abnormalities associated with ICI therapy as well as risk factors associated with their development.

Methods: We conducted a retrospective review of medical records searching for patients who received ICI over a 10-y period at Ochsner Health. Demographic and clinical characteristics were extracted up to 1 year post ICI treatment. Common Terminology for Cancer Adverse Events version 5.0 criteria were used to grade the severity of electrolyte abnormalities. Risk factors were examined by logistic regression.

Results: A total of 102 patients were identified. The mean age was 64 ± 11 years, 43% women, 82% of white race. Pembrolizumab was the most commonly used ICI (46%), followed by nivolumab (26%) and atezolizumab (15%). The mean baseline glomerular filtration rate is 58 ml/min. ICI was more frequently administered to patients with lung cancer (47%). The incidence of hyponatremia (<134 mEq/L) and severe hyponatremia (<124 mEq/L) were 17% and 2%, respectively. Hypocalcemia (<8.4 mg/dL) was observed in 7%, whereas 11% experienced hypomagnesemia (<1.5 mg/dL) and 3% hypokalemia (<3.4 mEq/L). Melanoma was found to be numerically associated with hyponatremia, but not statistically significant (OR 3.1, 95% CI 0.7-14.8%). White race was associated with 3 times greater risk of hyponatremia with ICI therapy (OR 3.5, 95% CI 1.2-9.9). Although co-administration of cisplatin, underlying chronic kidney disease and use of SSRI are known risk factors associated with hyponatremia, those variables were not associated with hyponatremia in our cohort, suggesting that hyponatremia secondary to use of ICI could be mediated by a mechanism independent of those variables.

Conclusions: Exposure to ICI is associated with the development of electrolyte imbalances. In our study, white race was identified as factor having 3 times higher odds of hyponatremia. Further studies are needed to examine race and other factors and the risk of electrolyte abnormalities. Risk factors were examined by logistic regression.

Spontaneous Tumor Lysis with Normal Electrolytes


Introduction: Tumor lysis syndrome (TLS) leading to renal failure can occasionally occur prior to treatment in highly proliferative hematological malignancies. We present a case of AKI due to spontaneous TLS without the typical antecedent electrolyte derangements normally expected with TLS.

Case Description: A 76-year-old male with no prior medical history presented to the emergency room with abdominal pain and weight loss. CT scan revealed a gastric mass, ascites and abnormal liver consistent with cirrhosis. Gastric biopsy revealed diffuse large B cell lymphoma. He initially had a bland UA and a slight increase in baseline creatinine. The primary team treated him for hepatorenal syndrome with no response. His renal function rapidly deteriorated and he became anuric. A follow up UA showed protein and blood. Although the uric acid (UA) was 13.7 mg/dL, the phosphorous and potassium remained in their normal ranges leading us away from a diagnosis of TLS and toward the possibility of a rapid progressive glomerulonephritis. On biopsy the renal tubules contained calcium oxalate and calcium phosphate crystals with vacuolization of the tubular epithelial cells and tubular changes consistent with prior uric acid crystal deposition. The glomeruli were normal. At this point the uric acid level had risen to 25 mg/dl. Rasburicase was initiated and the patient eventually recovered renal function.

Discussion: In TLS, tumor cells lyse and release their intercellular electrolytes and purines (which are metabolized to uric acid) leading to elevated potassium, phosphorus and uric acid. Rarely the potassium and phosphorus can be normal. Our patient had renal failure further limiting the excretion of potassium and phosphate, making the normal levels of these electrolytes especially notable. Identifying the mechanism of normokalemia and normophosphatemia in spontaneous TLS may give us insight on how to diagnose it earlier, thus leading to earlier treatment.

H&E with calcium oxalate crystals (arrow), tubular lumen that likely contained uric acid crystals (asterisks)
PUB250

Pattern of Renal Diseases Detected on Renal Biopsy at Pakistan Institute of Medical Sciences (PIMS) Islamabad
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Background: Renal biopsy is an important tool for evaluation and diagnosis of glomerular, vascular, tubulointerstitial and genetic kidney diseases. It helps in determining the stage of disease, making treatment protocol and predicting prognosis as well. Purpose of the study is to find out pattern of renal diseases diagnosed on renal biopsies.

Methods: This is retrospective analysis done from February 2012 to April 2018. This data was taken from pathology department of Pakistan Institute of Medical sciences Islamabad Pakistan. These were adult patients above 18 years who underwent percutaneous renal biopsy due to some clinical indications. Their data was analyzed for spectrum of kidney disease on renal biopsy

Results: Total biopsies were 254. Most common lesions were glomerular lesions. Among them primary forms were found. Most common GN found was Membranous Nephropathy (14%), second most common lesion was Focal segmental glomerulosclerosis (FSGS) (12.5%) followed IgA Nephropathy (10.6%) Membranoproliferative glomerulonephritis MPGN (9.1%). Most common secondary glomerular lesion was found was Lupus Nephritis (7.8%). Other lesions were chronic kidney disease (12.5%), Interstitial fibrosis with tubular atrophy (IFTA) (5.9%), Rapidly progressive GN (5.9%), Renal cortical necrosis (4.3%), Acute tubular necrosis (ATN) (4.3%), IgM Nephropathy 2%, chronic tubulointerstitial disease (TID) (2.4%), Diabetic Kidney disease (DKD) (2%) Minimal Change Disease (2%), Amyloidosis AA (1.2%), HTN (0.8%), post-streptococcal GN (0.8%), Postinfectious GN (0.4%), diffuse proliferative GN (0.4%). In young patients’ glomerular lesions were common whereas in middle age and elderly Chronic tubulointerstitial diseases and DKD were the common lesions.

Conclusions: In review of renal biopsies most common histological lesion found was membranous nephropathy (12.5%) followed by focal segmental glomerulosclerosis (FSGS) (12.5%) and IgA Nephropathy (10.6%).

PUB251

Can Antinuclear Antibody (ANA) Be Monoclonal? A Case Report of Unusual Immunofluorescence Findings in a Patient with Monoclonal Gammopathy of Uncertain Significance (MGUS)
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Introduction: Nuclear staining by immunofluorescence in a kidney biopsy is often seen in patients with positive ANA in the serum. These ANA are usually polyclonal, but herein we report an unusual finding by immunofluorescence of IgG2 lambda monoclonal nuclear staining in a patient with MGUS.

Case Description: The patient is a 72-year-old Caucasian male with a history of diabetes mellitus type 2 (hemoglobin A1c is 6.1%) who was recently treated with hydralazine, and he was found to have positive ANA (homogenous pattern, > 320), but after discontinuation of hydralazine the ANA decreased to 21. He had positive P-ANCA (positive MPO, A and negative C-ANCA (negative P3). Also he has positive anti-double-stranded DNA. His serum creatinine was 1.7 mg/dl (1 mg/dl baseline), proteinuria 0.34 gm/24h. He did not have monoclonal protein in the urine, but in the serum by immunofluorescence there was IgG2 lambda monoclonal protein (two monoclonal bands were noted). He has elevated serum both kappa and lambda light chains with normal kappa-to-lambda light chain ratio. Kidney biopsy showed acute tubular necrosis (ATN), moderate chronic kidney injury and there was no evidence of immune complex deposition, monoclonal immunoglobulin deposition or amyloid. Immunofluorescence showed positive nuclear staining for IgG2-IgG2 subclass only and lambda but not kappa light chain (Fig 1). These findings raise the possibility that his ANA are of monoclonal origin.

Discussion: Our case demonstrates the unique pattern of IgG2 lambda monoclonal nuclear staining by immunofluorescence in the patient with MGUS. The prevalence of this type of findings is not well studied.

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Renal Tuberculosis: An Uncommon Presentation of a Common Disease: Case Report

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Introduction: Renal tuberculosis is an endemic country for tuberculosis (TB) with 3 500 cases per year, 85% correspond to pulmonary presentation. Genitourinary tuberculosis is uncommon, it is considered a severe form of extrapulmonary TB; it is secondary to infection with Mycobacterium tuberculosis complex with a long-standing dysuria, sterile pyuria, fever and consumptive symptoms. We present the case of an atypical renal TB having hematuria and fever as the only clinical features.

Case Description: A 54-year-old Guatemalan male came to the emergency room with a history of intermittent fever during the last year that worsens in the last 2 weeks. He lived in a rural area at the southern-coast of Guatemala. No previous medical history, no pets at home. The fever was between 38.3-40°C. Urinalysis showed pyuria, fever and consumptive symptoms. We present the case of an atypical renal TB having hematuria and fever as the only clinical features.

Discussion: Renal TB has a prevalence of 10% worldwide and 20% in Latin-America mainly from pulmonary origin. The reported cases have higher prevalence in developing countries, male gender, immunosuppressed state as in HIV infection and post-transplanted. It is an under-diagnosed disease that can lead to CKD. The diagnosis of renal TB must be considered in patients with dysuria, hematuria, pyuria with negative urinary cultures.

Real-Time Percutaneous Kidney Biopsy Experience: Is There a Change in the Trend of Complication?

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Background: Percutaneous kidney biopsy (PRB) is essential in establishing diagnosis and guides the treatment of renal diseases. The procedure of kidney biopsy has evolved through technique and procedural refinements. Bleeding and its consequences are the most concerning complications of kidney biopsy. This is a UK renal centre experience to report the post-kidney biopsy bleeding complications.

Methods: We included all patients (inpatient and day case) who underwent PRB between January 2014 and Dec 2016. Biopsy was performed using a 16-gauge biopsy needle with a spring-loaded trigger device. Pre-biopsy parameters such as Blood pressure, haemoglobin, platelet counts and coagulation studies of patients were recorded. Data on kidney biopsy outcome were collected retrospectively. Bleeding complications were macroscopic hematuria, drop in haemoglobin requiring blood transfusion or requiring intervention radiology. Statistical analysis was performed.

Results: A total of 458 kidney biopsies were carried out with 58.9% male and 53.1% as day case. There was a 2.4% technical failure and 96.9% histological adequacy. Indications for kidney biopsy were acute kidney injury (37.1%), nephrotic syndrome (24.5%), proteinuria (17.7%) and hematuria (8.2%). Histopathology diagnoses were IgAN (12.2%), pauci-immune glomerulonephritis (10.4%), tubulointerstitial nephritis (9.3%), FSGS (7.6%), diabetic nephropathy (7.1%) and membranous glomerulonephritis (6.4%). Bleeding episodes were seen in 19.4% (with 30.6% having haematoma and 10.2% patient had embolisation. Day case (2.1%) compared to in-patient (6.8%) kidney biopsy and platelet count (>100 x 109) had less bleeding complication (p < 0.05). Mean creatinine was higher among in-patient kidney biopsy (361.93 ± 216.41 vs. 151.21 ± 94.26, p = 0.005). In-patient kidney biopsy were older, had higher hemoglobin and higher INR (p = 0.05). Lower mean hemoglobin (104.42 ± 15.39 vs. 115.35 ± 21.03, p = 0.025) and higher mean creatinine (413 ± 288.41 vs. 242.16 ± 185.72, p = 0.005) were noted in those who had hematuria. We reported no nephrectomy or death.

Conclusions: We report a low post kidney biopsy bleeding complication. Day-case procedure has a lower rate of kidney biopsy bleeding complication when compared to in-patient kidney biopsy.

Variation in Interpretation of 24-Hour Ambulatory Blood Pressure Monitoring (ABPM) in Children with Confirmed or Suspected Hypertension (HTN) by Canadian Pediatric Nephrologists and Cardiologists

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Background: ABPM is more accurate compared to a single office-blood pressure (BP) measurement. However, it is unclear how physicians interpret ABPM and make management choices, especially where evidence supporting recommendations is limited. This study’s goal is to evaluate ABPM interpretation variation by HTN category and disease among pediatric nephrologists and cardiologists.

Methods: Survey content included physician demographics, ABPM indications, interpretation, and management. The same questions were asked of all respondents, except kidney-related conditions which were only shown to nephrologists.

Results: The survey was sent to 196 physicians, with 69 (35.2%) responses. Most respondents were age 45+, in practice for 11+ years and university-based. Table shows significant differences in ABPM interpretation for BP load, isolated systolic and diastolic HTN, and between nephrologists and cardiologists for different conditions (not all data included in abstract table). Rates of HTN treatment are lower than guidelines recommendations.

Conclusions: There is significant practice variation among physicians in ABPM interpretation and management. Gaps in guidelines create ambiguity regarding management decisions for different ABPM parameters. A more protocolized approach may help to standardize practice.

Initiation or alteration of antihypertensive treatment with respective ABPM parameters in various conditions.

An Electronic Health Record (EHR) Algorithm to Identify Patients with Autosomal Recessive Polycystic Kidney Disease (ARPKD)

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Background: ARPKD is an important cause of pediatric chronic kidney disease, hepatic fibrosis, and portal hypertension. Its rarity makes it difficult to collect larger-scale natural history data and to identify patients for clinical trials.

EHR-based algorithms can identify ARPKD patients at a single site in PEDSnet (v3.9, 1/2009-7/2020), a national pediatric learning health system. A training/testing cohort consisted of 50 clinician-confirmed ARPKD patients and 150 non-ARPKD controls (enriched for patients with cystic/dysplastic diagnoses). A random forest algorithm was implemented to classify patients as cases and non-cases, with variable importance permutation-based, with high performance (precision 98%, recall 94%). The random forest was implemented to classify patients as cases and non-cases, with variable importance permutation-based, with high performance (precision 98%, recall 94%). The algorithm was applied to a denominator of 45,186 patients with either a nephrology visit, a GI visit + a liver diagnosis, or a NICU visit to classify patients as cases or non-cases.

Two clinicians blinded to model case classification used a standardized form to review 97 patients with a1 ARPKD diagnosis (not included in original training/testing cohort) and classify them as ARPKD or non-ARPKD.

Results: The key model selection features were number of visits with an ARPKD diagnosis code and presence of a hepatic fibrosis diagnosis code. Table 1 shows patient characteristics. Of 97 patients reviewed, clinicians excluded 5 as indeterminate, and classified 56 as non-ARPKD and 36 as ARPKD [positive predictive value (PPV) of a1 ARPKD diagnosis 39%]. The algorithm identified 23 true positives, 17 false positives,
13 false negatives, and 39 true negatives; model performance: sensitivity 64%; specificity 70%; PPV 58%; negative predictive value (NPV) 75%.

**Conclusions:** An EHR-based algorithm improves PPV for identifying patients with ARPKD compared to diagnosis code alone and has relatively good NPV for excluding ARPKD in non-ARPKD patients with an ARPKD diagnosis code in their chart. Further chart review of incorrectly classified patients will allow algorithm refinement to improve performance.

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**PUB257**

**Nitromethane Fuel Toxicity Causing False Elevation of Serum Creatinine**

**Vimal Master sankar rai**, Megan Narula, Joanna Harbia. University of Illinois College of Medicine at Peoria, Peoria, IL

**Introduction:** Nitromethane along with methanol is a common component of model airplane fuel, rocket fuel and race car fuel. Reports of nitromethane exposure causing falsely elevated creatinine by its interference with the Jaffé reaction analysis has been reported in adult literature with limited pediatric data being available.

**Case Description:** 12 year old male with past medical history significant for major depressive disorder on prozac, H/o medium chain acyl-CoA dehydrogenase (MCAD) deficiency on a low fat diet and levocarnitine. Patient had prior admissions for self-harm and presented after ingesting about a mouthful of Torco race fuel. On initial evaluation in outlying ER, he was hemodynamically stable with heart rate of 97 per minute, respiratory rate of 16/min with saturations of 97% on room air and BP recorded at 130/67. Initial lab check showed a normal creatinine at 0.69 mg/dl. Patient was transferred to our hospital for administration of fomepizole as methanol is a main component of Torco race fuel. On arrival, repeat labs in 5 hours showed an increase in creatinine to 1.73, which slowly started coming down to 1.39, 48 hours into admission. He remained normotensive and presented after ingesting about a mouthful of Torco race fuel. On initial evaluation in outlying ER, he was hemodynamically stable with heart rate of 97 per minute, respiratory rate of 16/min with saturations of 97% on room air and BP recorded at 130/67. Initial lab check showed a normal creatinine at 0.69 mg/dl. Patient was transferred to our hospital for administration of fomepizole as methanol is a main component of Torco race fuel. On arrival, repeat labs in 5 hours showed an increase in creatinine to 1.73, which slowly started coming down to 1.39, 48 hours into admission. He remained normotensive through the course of stay and further studies including urine studies for protein came back normal. No azotemia and blood urea nitrogen remained normal at 13-15 mg/dl through the length of stay. Cystatin C levels done on hospital transfer returned normal at 0.68 mg/L. With serum methanol levels returning negative, patient was transferred to inpatient psychiatry ward.

**Discussion:** This is a pediatric case report on Torco race fuel ingestion in which the ingredient nitromethane (CH₃NO₂) caused a false elevation of serum creatinine. The standard assay for creatinine uses the Jaffe reaction, which involves a reaction between creatinine and alkaline picrate producing a cromophore that closely resembles the creatinine picrate derivative resulting in falsely elevated creatinine. Nitromethane by its reactive methyl component interacts with alkaline picrate producing a cromophore that closely resembles the creatinine picrate derivative resulting in falsely elevated creatinine by its interference with the Jaffé reaction analysis. Nitromethane along with methanol is a common component of model airplane fuel, rocket fuel and race car fuel. Reports of nitromethane exposure causing falsely elevated creatinine by its interference with the Jaffé reaction analysis has been reported in adult literature with limited pediatric data being available.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

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**PUB259**

**Prevalence of Secondary Hypertension in Children with a New Diagnosis of Hypertension: A Meta-Analysis**

**James Nguyen**, Chelsea R. Young, Melissa C. Funaro, Lama Ghazi, Francis P. Wilson, Jason H. Greenberg. Yale University School of Medicine, New Haven, CT.

**Background:** Secondary hypertension (HTN) in children is associated with an increased risk of end organ damage and treatment resistance. For asymptomatic children with HTN identified on screening, the prevalence of secondary HTN is unknown.

**Methods:** MEDLINE, EMBASE, Web of Science, and Cochrane Library were searched for studies reporting rates of secondary HTN in children aged 0-19 years who underwent evaluation for HTN. We identified studies that diagnosed HTN based on at least 2 outpatient blood pressure readings and included children without any known comorbidities associated with HTN. Two authors independently extracted the study-specific prevalence of secondary HTN in children with HTN of unknown cause. Prevalence estimates were pooled in random effects meta-analysis.

**Results:** For the 18 prospective and 7 retrospective studies included, there was a median of 56 (range, 9-486) participants with HTN in each study. Although studies applied different diagnostic criteria for HTN, 20 of 25 studies used a blood pressure percentile-based approach. The pooled prevalence of secondary HTN was 8.2% (95% CI: 4.1-13.4%). Studies conducted in primary care or school settings reported a lower prevalence of secondary HTN (3.6% [95% CI: 1.0-7.4%]) than studies conducted in referral clinics (20.1% [95% CI: 11.5-30.3%]). When stratified by study setting, there were no significant subgroup differences according to study design, participant age range, intervention type, blood pressure device, or study quality.

**Conclusions:** The low prevalence of secondary HTN in otherwise healthy children with a new diagnosis of HTN reinforces current guidelines to avoid extensive diagnostic testing for secondary causes in most hypertensive children ≥6 years old.

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Improvement (QI) Approach for Health Care Transition (HCT)

We propose that implementation of the new standardized process including our 2-step transition clinic (n= 10) which was overall reassuring and had the highest patient satisfaction rating (above 95%). During this endeavor, our team was able to build a framework for transition that can be used in at least two different health care settings, pediatrics followed by adult medicine. This clinic provides patient interaction with their renal providers and multi-disciplinary team to discuss disease-related aspects and to ensure a comprehensive plan for transition. A pilot group of patients was proposed to lead this effort with initiation of a novel form of transition clinic; 2-step transition clinic to tackle lack of a dedicated transition clinic. Involved surveys to pediatric faculty (n = 14), who rated the current transition process. They found that the new approach was significantly better in terms of convenience and communication. Part of this assessment involved on-site observations and interviews with patients and their families. The next step is to implement the new standardized process including our 2-step transition clinic will result in enhanced patient satisfaction and HCT outcomes with potential areas for improvement.

Conclusions:
The on-site assessment underscores areas to target for intervention. We propose that implementation of the new standardized process including our 2-step transition clinic will result in enhanced patient satisfaction and HCT outcomes with potential areas for improvement.

PUB261
Clinicopathological Characteristics of Focal Segmental Glomerulosclerosis (FSGS) in a Pediatric Patient Population

Kenneth V. Lieberman,1 Clint Abner,2 Kerime Ararat,2 Patrick D. Walker,2 Amin Yakubu,3 Martin C. Bunke,4 Hackensack University Medical Center, Hackensack, NJ; 2Arkana Laboratories, Little Rock, AR; 3Genesis Research, LLC; Hoboken, NJ; 4Travere Therapeutics Inc, San Diego, CA.

Background: FSGS is a major cause of steroid resistant nephrotic syndrome and is a major cause of end stage renal disease in children. FSGS may progress to renal disease if untreated, however, treatment is only ameliorative. Few studies are available that characterize the histological and clinical features of FSGS in pediatric patients (pts) at time of kidney biopsy.

Methods: A retrospective cohort study was performed within the Arkana Biopsy database (January 1, 2016 to May 31, 2020) among pediatric pts who met the following study criteria: ≤17 years of age, ≥1 FSGS positive biopsy, and no prior kidney transplant. Outcomes evaluated included clinical and histologic characteristics.

Results: Of 3,157 renal biopsies performed among pts ≤17 years during the study period, 167 (5.3%) FSGS cases were identified, and 164 pts evaluated met study criteria. In this sample, 44.5% were female and mean (SD) age at biopsy was 11.4 (4.8) years. About one third of pts were White (33.5%), 25.6% African American, 12.2% Hispanic and 1.2% Asian. Median (Q1 - Q3) uric acid protein to creatinine ratio=24-hour urine protein for 61.0% of patients with available data was 3.0 (1.1 - 9) g/g, and approximately a third of pts (34.2%) had a diagnosis of hypertension. The majority of pts had a diagnosis of arteriolesclerosis (82.3%) and arteriolesclerosis (90.9%) and nearly half of FSGS pts (49.4%) had severe foot process effacement (≥80%). The most common FSGS type was "membranous" (71.1%), while 13.4% of pts had tip lesion, followed by perihilar (8.5%) and collapsing (6.7%) FSGS. Approximately 25.0% of pts had an interstitial fibrosis and tubular atrophy (IFTA), 52.4% had 1-<25% IFTA, 17.1% had IFTA 25-%<50% and 4.9% had IFTA ≥ 50%. Most pts (79.3%) exhibited <25% glomerular sclerosis while 9.2% had ≥50% GS.

Conclusions: FSGS in this pediatric population was associated with low degrees of glomerular sclerosis, interstitial fibrosis and tubular atrophy, but severe foot process effacement was common. When comparing to data reported in a companion abstract in adult pts with FSGS, the lower levels of sclerosis and fibrosis observed in this pediatric FSGS pts, suggest that early and effective intervention could potentially aid long term renal survival.

Funding: Commercial Support - Travere Therapeutics

PUB262
Impact of Hypertension on Health-Related Quality of Life in Childhood-Onset Systemic Lupus Erythematosus

Kristianna A. Singh,1 Marietta De guzman, Alisa A. Acosta, Cortney T. Zimmerman, Scott E. Wenderfer. Baylor College of Medicine, Houston, TX.

Background: Childhood onset SLE can significantly impact Health-related quality of life (HRQOL) due to disease manifestations and its associated therapies. Hypertension is another chronic disease that can impact the HRQOL in children despite its “silent nature.” In cSLE, secondary HTN can occur in up to 70%, due to nephritis and/or medications (i.e. steroids). We aim to assess the impact of HTN on HRQOL in patients diagnosed with active SLE aged 7-18 years in the Texas Children Hospital (TCH).

Methods: A total of 10 subjects met inclusion criteria: diagnosis of SLE as determined by a Pediatric Rheumatologist, age 7-18 years, new onset disease or flare from 11/2020 to 4/2021. Subjects were excluded if unable to complete the questionnaire, BMI >32, or eGFR<60. We classified hypertension using ambulatory BP monitoring (ABPM). HRQOL was measured by both patient and parent proxy using disease-specific SMILEY© (Simple Measure of Impact of Lupus in Youngsters) tool. We used Jamovi software to analyze demographic data.

Results: Median age was 17 (IQR 13-18) years. HTN was diagnosed in 40% by casual BP measurement and 70% by ABPM. Median Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score was 13(10-18). Median SMILEY score was 60 (57-64). Although there was no clinically significant differences in the parent report scores, patients with an attenuated nocturnal BP dipping had lower child reported scores (Table 1). Child reported SMILEY© scores correlated inversely with Mean 24hr systolic and diastolic load (r=0.7, r<0.9), mean wake SBP and DBP load (r=0.7, r<0.7), and sleep DBP load (r=0.76).

Conclusions: In cSLE, ambulatory BP patterns significantly impact HRQOL. These initial conclusions suggest that HTN may impact HRQOL in cSLE.

Table 1 Median SMILEY© scores stratified by nocturnal BP dipping status at enrollment.
Background: Elevated fibroblast growth factor 23 (FGF23) levels are associated with left ventricular hypertrophy (LVH) and diastolic dysfunction (DD). Recent preclinical and adult patients studies showed that parenteral iron (Fe) supplementation and erythropoietin (EPO) may increase FGF23 production and circulating levels. Whether treatment with EPO or Fe could increase FGF23 levels and adversely contribute to LVH and DD in pediatric patients maintaining hemodialysis (HD) remains largely unknown.

Methods: Adolescents (n=20, median age 16 years) maintained on HD (average dialysis vintage 30 ± 17 months) were studied. All were treated with EPO, with or without concomitant parenteral Fe sucrose and all received intravenous paricalcitol for secondary hyperparathyroidism. C-terminal FGF23 (cFGF23), biochemical markers, and sequential echocardiograms (conventional and tissue Doppler, ECHO) were analyzed longitudinally twice, 6 months apart. LV dimensions, including IVST (intraventricular septal thickness) and markers of diastolic function with peak early (E), late (A) diastolic flow velocities, and corresponding mitral annular velocities (Em, Am) were measured, and adjusted to Z-scores according to age and gender.

Results: Whereas the cumulative average EPO dose was similar in Fe-treated and untreated patients (10,056 ± 5,445 and 10,818 ± 7,935 Units/week/months, respectively), the initial and final cFGF23 levels remained similarly elevated in both groups. Prevalence of DD improved from 22% to 12% during the study period. LogFGF23 values correlated with Am (r = -0.7) and Em/Am (r = 0.7) Z-scores (both p<0.05) in Fe-treated patients. The doses of EPO and Fe did not correlate with markers of diastolic function, but EPO correlated with the IVST Z-score (r = 0.7, p<0.05). The cumulative paricalcitol dose did not correlate with markers of diastolic function but inversely correlated with IVST Z-score (r = -0.5, p<0.05)

Conclusions: Treatment with EPO, irrespective of parenteral Fe supplement, hemoglobin, and ferritin levels did not result in consistent elevations of cFGF23 levels. While cFGF23 levels correlated with worsen markers of diastolic function, the overall prevalence of DD improved overtime. The administration of paricalcitol may have contributed to the improvement of DD and the LVH.

Funding: Clinical Revenue Support

PUB264

Is It Time to Update the Age-Specific Pediatric Normative Serum Creatinine Ranges?

Background: Diagnosis of abnormal kidney function is routinely based on serum creatinine (SCr) value. SCr in children increases with growth and normative values therefore vary with age. However, due to lack of availability of large number of blood samples from healthy children, most laboratories combine the SCr reference ranges in up to 5-year age group blocks, resulting in an upper limit that can be 2.3 to 2.6 times higher than the lower limit for that age block. As a result, a child with subnormal kidney function (GFR < 90 mL/min/1.73m2) who is near or at the younger end of the age in a specific age group block, can still have SCr value below the upper limit of reference range and thus will remain unflagged on the reported result. This may result in a missed diagnosis of decreased kidney function. Similarly, a diagnosis of acute kidney injury (SCr increase >1.5 above baseline) can also be missed as the increased SCr value can still fall within the reference range for that age group. In research studies, missing baseline creatinine values are customarily back calculated from eGFR equations with a presumed GFR of 120 mL/min/1.73m2. Our objective was to calculate age specific SCr reference ranges for children 2 – 18 years, and compare them with current age group block reference ranges.

Methods: We used bedside Schwartz equation (eGFR = height*0.413/SCr, where 0.413 is the constant k) to calculate estimated creatinine (eCr) = height*0.413/GFR. We calculated the eCr reference ranges by inserting 3rd percentile for height and GFR of 120 mL/min/1.73m2 for the lower limit, and by inserting 97th percentile for height and GFR of 90 mL/min/1.73m2 for the upper limit. Height values for respective ages were obtained from the CDC reference charts.

Results: The calculated theoretical reference ranges are shown in the Table. The upper limit of eCr values are only 1.6 times higher than the lower limit in contrast to the current reference ranges where the upper limit is 2.3 to 2.6 times higher than the lower limit for its age group block.

Conclusions: We believe that by switching from age group blocks to age specific normative SCr ranges the possibility of missing subnormal kidney function will be minimized. The calculated values need to be further validated.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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PUB265

Are Mutations in the Alpha-Hydroxy Acid Oxidase (HAO1) Gene Not as Harmless as Described?
Bernd Hoppe,1 Luisa Averdunk,2 Kathrin Buder,2 Cristina Martin Higueras,1
1German Hyperoxaluria Center, Bonn, Germany; 2University Childrens Hospital Zurich, Zurich, Switzerland; 3University Childrens Hospital Dusseldorf, Dusseldorf, Germany.

Introduction: Alpha-hydroxy acid oxidase (HAO1) catalyzes the oxidation of glycolate into glyoxylate in hepatic peroxisomes. Patients with homozygous HAO1 mutations have massively elevated urinary glycolic acid excretion (Uglyc), but are said to be clinically asymptomatic.

Case Description: We present three pediatric patients, who either developed clinical sequelae, here arthrolithiasis (UL), or surprisingly had hyperoxaluria. First patient now 10 years of age, developed UL at age 6 years, which was treated by lithotripsy (stone analysis: 100% wheeelellite). Currently, he has 2 small stones in left kidney. Recent 24 h urine excluded elevated urinary oxalate excretion (UOx, 0.35-0.43), but high glycolate UGlyc (3.34-4.78 mmol/1.73m2/d). His grandfather also had recurrent UL, but normal Uox and Uglyc. Patient 2 was 6 months of age at diagnosis of elevated Uox and Uglyc (1.37 and 7.01 mmol/1.73m2/d, respectively). He has 3 relatives with a history of UL, elevated Uox/creatinine ratio was found in 2/3, and in the boys mother. Genetic evaluation for primary hyperoxaluria (PH) was negative. In patient 3 screening for organic acids detected elevated Uox: 1.56 and Uglyc: 7.04 mmol/1.73m2/d. Genetic testing for PH was negative. Vitamin B6 though let to decline in Uox. Uglyc remained significantly elevated. Homozygous (family) mutations in HAO1 were found also in parents, sister and in newborn brother. Father and sister also had elevated Uox (1.09 and 0.92) and Uglyc (4.19 and 4.75 mmol/1.73m2/d). The newborn has a massively elevated Uglyc/creatinine ratio, but no hyperoxaluria.

Discussion: In the contrary to current understanding, patients with HAO1 mutations can express a renal phenotype. We do not have an adequate explanation for UL in patient 1, as only Uglyc is elevated and no other risk factor is found. GO inhibition is used as therapeutic target in patients with PH1, which reduces Uox, but elevates Uglyc. Even more problematic to explain is the significant hyperoxaluria in patients 2 and 3 (after excluding secondary reasons). Therefore, the link between HAO1 (loss of function) mutations and UL, or hyperoxaluria, respectively, clearly needs further clarification.
More Than “Getting High.” Be Aware of Cannabis-Induced AKI: A Report of Two Pediatric Cases

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Background: Cannabinoids (synthetic ~ natural) can have deleterious effects on kidneys. We report 2 cases of cannabis-induced acute kidney injury (AKI) with acute tubular necrosis (ATN) and acute interstitial nephritis (AIN).

Methods: Case Series.

Results: Two adolescents were cared for in 2011, presented with elevated serum creatinine (S. Cr). At presentation S. Cr was 1.7- 5.4 mg/dL, peaked at 5.4-6.6 mg/dL. Both patients developed acidosis. Patient 2 had hypokalemia, hypophosphatemia, and hypomagnesemia. Urine drug screen was positive for cannabinoids. Both patients admitted to using natural cannabis predominantly and smoking cannabis joints daily for a few weeks- a month prior to admission. Urinalysis showed proteinuria, leukocyturia, heme+ without RBCs in urine, hyaline casts. Renal bladder sonogram: echogenic kidneys. Kidney biopsy revealed ATN in patient 1 and AIN in patient 2 (Fig 2). ATN was managed conservatively, while the patient with AIN received steroids. Both patients responded well and improvement in kidney function.

Conclusions: Though the endocannabinoid system (ECS) has been found to play a beneficial role in renal homeostasis and improvement of tubular cell survival, long-term stimulation and alterations to the ECS can lead to kidney damage as reported here. It is interesting to note that 2 patients predominantly used natural cannabis and reported that they assumed that natural cannabis is safe. A thorough history including drug use should be obtained in cases of AKI, particularly where the cause is not apparent and AKI does not improve with hydration. Awareness of this could lead to early diagnosis, management, and appropriate counseling, which might potentially decrease kidney damage and scarring.


PUB267

Involvement of Succinate Dehydrogenase (SDH) in Deceased Kidney Donors’ Inflammation

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Background: Succinate is a Krebs cycle intermediate that is converted to fumarate by succinate dehydrogenase (SDH). SDH activity depends indirectly on the oxygen availability. In deceased renal donation, hypoxia associated to ischemic process can increase renal succinate formation and induce the infiltration of immune cells producing TNF-α, increasing inflammation, renal epithelial apoptosis, as well as leukocyte recruitment, binding and migration, which can lead to renal graft damage. Moreover, increased levels of IL-1β promoting inflammation. We aim to demonstrate that succinate pathway is an important player in early and late inflammation in deceased kidney transplants.

Methods: Relative gene expression of SDH complex genes (SDHA, SDHB, SDHC and SDHD), HIF-1α and inflammatory factors were quantified by qPCR in RNA samples from deceased donors. Succinate levels were measured in serum from deceased kidney donors at the time of donation.

Results: Circulating succinate levels in serum from deceased donors were significantly higher than in healthy volunteers (p=0.002). In kidneys samples from deceased donors, gene expression of all four subunits of SDH complex were downregulated before transplantation (p<0.001 for all of them) whereas HIF-1α was increased compared to living donors (p<0.001). SDHA, SDHB and SDHD gene expression at 4 months after kidney transplantation is positively correlated with graft renal function (CKD-EPI). In kidneys from deceased and living donors, SDHA, SDHB and SDHD are negatively associated with recruitment (MCP-1), adhesion (ICAM-1) and activation (IL-1β) of monocyte.

Conclusions: Our results indicate that low expression of SDH in kidneys from deceased donors could result in reduced activity of SDH that would reduce the ability to transform succinate to fumarate resulting in succinate accumulation, increasing inflammation that can influence on kidney transplantation outcomes.

PUB269

Lymphoproliferative Disease After Kidney Transplantation: Describing Our Experience

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Background: Post-transplant lymphoproliferative disorders (PTLD) are one of the most common malignancies in kidney transplant (KT) recipients. Immunosuppressive therapy and Epstein Barr Virus (EBV) play a main role in their pathogenesis.

Methods: In this study we retrospectively analyze the characteristics, clinical evolution and treatments of a group of KT recipients performed between 1986 and 2020 in a single center.

Results: We included 31 patients (64.5% males). Polycystic kidney disease was the most frequent cause of renal failure. Before KT a 6.5% of the patients presented another malignancy, 10% were EBV seropositive and one received immunosuppressive therapy secondary to his primary disease. Mean age at KT was 43±12 years. 68% of the KT came from brain-dead donors. The most frequent immunosuppressive regime consisted in tacrolimus, mycophenolic acid and prednisone (61.5%). Basiliximab and Timoglobulin were used in the same proportion for the induction therapy (22.6%). Before PTLD appearance the immunosuppressive therapy was reduced in the 54.8% of the patients. 13% of them presented acute allograft rejection. The majority of PTLD were diagnosed between 2016 and 2020. Median time to develop PTLD was 13 years. 54.3% of the patients presented extranodal involvement. Although all the patients positivized EBV serology, 60% of them had undetectable EBV viral load. The main therapeutic strategy after PTLD consisted in a reduction of the immunosuppressive
therapy. In this way, 28.6% of the recipients was treated with monotherapy with a calcineurin inhibitor and 21.5% with monotherapy with a mTOR inhibitor. In other hand, 16.7% received a combination of tacrolimus with a mTOR inhibitor. Rejections were not observed in our group and all the patients presented a preserved kidney function at the end of follow up. Four recipients died because of PTLD. The remaining 27 presented a complete response or stabilization of the disease.

**Conclusions:** Most of the PTLD were detected between 2016-2020. The time from transplantation to PTLD appearance was long, being EBV viral load negative in the majority of the cases. Graft survival after chemotherapy and reduction of immunosuppressive therapy was excellent, with a low risk of rejection and a good prognosis for hematologic disease. It is possible that a reduction in immunosuppression in selected patients could prevent the development of PTLD.

**PUB270**

Shorter Antibody-Mediated Rejection-Free Survival in Persistence Preformed DSA vs. Clearance After Kidney Transplantation: A Single-Center 10-Year Experience in Thailand Theracrahi Thanamathanawat,1,2 Suwisin Udomkarnjananun,1,2 Yingyos Avihingsanool,1,2 Kearsiat Praditpornsilpa,1,2 Natavudh Townmachi,1,2 1Chulalongkorn University Faculty of Medicine, Bangkok, Thailand; 2Naresuan University Faculty of Medicine, Phitsanulok, Thailand; *Excellence Center for Solid Organ Transplantation King Chulalongkorn Memorial Hospital, Bangkok, Thailand.

**Background:** Preformed donor specific anti-HLA antibodies (pre-KT DSA) is one of the leading causes of post kidney transplant antibody mediated rejection (ABMR). Decrease level of pre-KT DSA by pre-transplant desensitization is one of the best available methods to lower risk of ABMR after transplantation. Post-transplant follows up of DSA to determine the persistence or clearance of DSA should reflect transplant outcomes. This study aimed to compared outcomes between patients who have persistence and patients who have clearance of DSA after kidney transplantation.

**Methods:** This retrospective cohort enrolled pre-KT DSA positive (CDC-A/HG negative) kidney transplant recipients (KTR) at King Chulalongkorn Memorial Hospital from 2009 to 2018. Post-transplant DSA was tested by Luminex single-antigen assays and divided patient in to two groups 1) DSA clearance (<1000 MFI) and 2) DSA persistence (>1000 MFI). The outcomes were evaluated that comprise biopsy-proven acute rejections, including acute antibody-mediated rejection (ABMR) and acute T cell-mediated rejection (TCMR), subclinical or borderline rejections, and graft loss clinical and mortality. Complications following KT and other associated risks were also assessed.

**Results:** There were 47 KT enrolled. The mean pre-KT DSA (MFI) level was 931.37. Sixty percent of patients underwent pre-transplant desensitization. The median follow-up time was 5.7 years after transplant. The persistence DSA group (n=17) had higher rate of ABMR than DSA clearance group (n=30), with hazard ratio (HR) of 4.47 (95% CI, 1.48 – 13.45, p=0.008). Factors associated with persistence DSA include the recipient's age of over 40 years old, higher number of HLA A/B/DR mismatch, and lower tacrolimus levels at six months.

**Conclusions:** DSA should be monitored in kidney transplant patient with pre-KT DSA. The persistence of pre-KT DSA after kidney transplantation is associated with higher rate of ABMR. Surveillance allograft biopsy should be performed in patient with persistence DSA for early detection of rejection.

**PUB271**

Angiosarcoma in a Kidney Transplant Recipient with Fibrillary Glomerulonephritis Mohammad Atari, Jessica Friedman, Anil S. Paramesh, Sixto G. Giusti. Tulane University School of Medicine, New Orleans, LA.

**Introduction:** Kidney transplant recipients are at increased of developing malignancy. Angiosarcoma (AS) are aggressive tumors arising in either blood or lymphatic vessels. Fibrillary glomerulonephritis (FGN) has been described in the setting of malignancies. Here we present a case of metastatic angiosarcoma that developed in a patient with a history of end-stage kidney disease (ESKD) secondary to FGN.

**Case Description:** A 66-year-old female with ESKD secondary to FGN underwent a five-antigens mismatch living unrelated donor kidney transplant with thromboglobulin and methylprednisolone induction. Pre-transplant workup showed no malignancy. Immunosuppression included tacrolimus, mycophenolate mofetil, and prednisone. Three months post-transplant, she had a scalp lesion diagnosed as eczema, which improved partially with topical steroids. Four months post-transplant, the lesion increased in size and developed abdominal discomfort with distention. Imaging showed widespread lymphadenopathy, numerous liver lesions, splenomegaly, and ascites. An excisional lymph node biopsy from the neck revealed AS. She developed acute kidney injury with gross hematuria. Urine microscopy revealed numerous intact RBCs but no other abnormal findings. Due to volume overload with low serum albumin (2 g/dl), she was given intravenous albumin and furosemide, and her creatinine improved. Tacrolimus and mycophenolate were stopped, and sirolimus was started. Weekly paclitaxel was initiated, but she developed febrile neutropenia and deconditioning after the second dose, for which she opted out for further chemotherapy. Nine months post-transplant, follow-up showed dramatic clinical improvement with complete resolution of scalp lesions. Imaging showed many partially decreased conspicuous low attenuation observations in the liver and a marked decrease in mesenteric and retroperitoneal lymphadenopathy. Kidney function remained at baseline.

**Discussion:** Angiosarcoma is a rare yet aggressive tumor with a poor prognosis in kidney transplant recipients. Here, the dramatic response may have resulted from lowering immunosuppressive drugs and starting chemotherapy. However, the anti-angiogenic activity of mTOR inhibitors is a possible explanation. Most reported AS cases developed from arteriovenous fistulas in kidney transplant patients. This is the first case of AS with FGN with an unexpected dramatic improvement.

**PUB272**

Recurrent of Scleroderma Renal Crisis After Kidney Transplantation Juan P. Portocarrero Caceres, Cybele Ghoseein, Yashpal S. Kanwar. Northwestern University Feinberg School of Medicine, Chicago, IL.

**Introduction:** Diffuse cutaneous Systemic Sclerosis (dcSSc) is a disease of generalized inflammation, vascular damage, and organ fibrosis. Scleroderma Renal Crisis (SRC), one of the most devastating complications of dcSSc occurs in 5-20% of patients and leads to end stage renal disease (ESRD) 20-50% of the time. SRC is characterized by malignant hypertension and acute kidney injury (AKI). Thrombotic microangiopathic anemia (TMA) and heart failure (HF) can also be seen. SRC patients with ESRD can undergo kidney transplantation (KT) with excellent graft survival. Recurrence of SRC in KT is very rare presumably because the renal vasculature is from a donor kidney without dSSc. We report a case of SRC in a patient post KT.

**Case Description:** A 52-year-old male-to-female transgender patient with a history of ESRD due to SRC, who had a living unrelated KT 2 months prior to admission was admitted with hypertension and pulmonary edema. She was found to have reduced ejection fraction (37%) and new pericardial effusion and AKI. Kidney biopsy showed arterioles with thickened walls, bland arteriolsitis with semi occlusive changes. She was diuresed and discharged home. She returned 2 weeks later with microangiopathic hemolytic anemia, thrombocytopenia, and worsening kidney function. Repeat kidney biopsy was consistent with TMA. Given her clinical presentation and her biopsy findings, a presumptive diagnosis of SRC was made. The patient was also found to have an antibody-mediated graft rejection. She received captopril, multiple sessions of PLEX, eculizumab, and belatacept, without response. She was initiated on dialysis where she remains today.

**Discussion:** SRC post KT is unusual but should be considered in the differential of AKI in the right clinical setting. Active dcSSc disease, use of steroids and calcineurin inhibitors may increase the risk of post transplant SRC.

**PUB273**

Kidneys with Kidney Donor Profile Index (KDPI) >85% Can Be Used Successfully in Older Recipients Muna Alnaimi. University of California Davis, Davis, CA.

**Background:** Kidneys with KDPI>85% have high discard rate approaching 50%, transplanted elderly patients over the age of 55 have lower risk of all cause mortality and death caused by cardiovascular disease compared to their counterparts on dialysis. We present one year clinical outcomes of High KDPI > 85% kidneys when transplanted in elderly recipients.

**Methods:** Retrospective analysis of kidneys with KDPI >85% transplanted in UC Davis Medical Center between 1/1/2016 and 12/30/2018.

**Results:** 67 patients received kidneys with KDPI >85% between 1/1/2016 and 12/30/2018. 77.5% were males, 52.2% diabetics, mean recipient age was 64.3years, 41.8% developed delayed graft function staying on dialysis for a mean of 17 days, 82% were alive after one year, 3 kidneys failed 81.5 % of kidneys were functioning after one years with mean creatinine of 1.4mg/dl.

**Conclusions:** KDPI >85% kidneys can be used successfully in older kidney recipients avoiding dialysis exposure and expanding the donor pool.
Risk Factors and Outcomes of BK Viremia Among Deceased Donor Kidney Transplant Recipients Based on Donor Characteristics

Isabel C. Bryan, Ban E. Dodin, Arjjang Djamali, Margaret R. Jorgenson, Neetika Garg, Fahad Aziz, Maha A. Mohamed, Didier A. Mandelbrot, Sandesh Parajuli. University of Wisconsin School of Medicine and Public Health, Madison, WI.

Background: BK polyomavirus (BKV) and BKV nephropathy (BKN) are common infections among kidney transplant recipients (KTRs). Risk factors and outcomes based on donor characteristics remain largely unknown, although some studies suggest BKV is donor derived. In particular, outcomes based on concordance or discordance for BK viremia between the pair: “no BK-group” if neither KTR developed BKV, “discordant” if one KTR developed BKV but not the other and “concordant” if both KTRs developed BKV. Acute rejection (AR), graft failure and BKN were outcomes of interest.

Methods: This was a retrospective study including all adult deceased donor KTRs at our center between 01/2014 and 12/2019 in which both donor kidneys were transplanted to two different recipients. Recipient pairs from each donor were divided into three groups based on concordance or discordance for BK viremia between the pair: “no BK-group” if neither KTR developed BKV, “discordant” if one KTR developed BKV but not the other and “concordant” if both KTRs developed BKV. Acute rejection (AR), graft failure and BKN were outcomes of interest.

Results: Of 78 KTRs (36 (58%) were in no BK-group, 17 (30%) were discordant and 66 (11%) were concordant. Donors in the concordant group were younger, had lower KDPI, were less likely to be DCD, and had lower cPRA. Most of the recipient baseline characteristics were similar in all groups. In a multivariate analysis (MA) adjusting for significant factors, KTRs who had a donor with a higher BMI (HR: 0.97; 95% CI: 0.95-0.99; p=0.009) were less likely to develop BKV and those who received depleting induction were more likely to develop BKV (HR: 1.77; 95% CI: 1.26-2.51; p=0.001). There was no difference in the rate of AR, death censored graft failure (DCGF) or BKN among the groups. In MA, concordance was not associated with AR (HR: 0.83; 95% CI: 0.51-1.34; p=0.45), DCGF (HR: 1.77; 95% CI: 0.42-7.50; p=0.43) or BKN (HR: 1.02; 95% CI: 0.51-2.03; p=0.96). By K-M survival analysis, uncensored and DCGF were significantly lower in the concordant group (p=0.009 and 0.04 respectively), but not affecting BKV or grafts that were lost within one year post-transplant. There was no difference in AR or BKN across the groups.

Conclusions: In this large study of 578 deceased donor KTRs, we identified donor BMI and depleting induction to be associated with BKV. Interestingly, concordance or discordance for BKV was not associated with detrimental outcomes.

Risk of Rejection, Graft Failure, and Patient Death After Knee or Hip Replacement Surgery in Kidney Transplant Recipients


Background: There remains a large debate about the timing of hip and knee replacement surgery (joint replacement) in the context of patients with end-stage renal disease (ESRD). Few studies have assessed the surgical complications of knee and hip joint replacement surgery after kidney transplantation; however, there is a lack of data regarding risk factors leading to joint-replacement surgery, as well as transplant outcomes. More studies are needed to assess the risk factors of joint replacement on transplanted kidneys in patients with ESRD.

Methods: This was a retrospective study analyzing all adult kidney transplant recipients (KTRs) at our university hospital who underwent hip or knee replacement between 2001 and 2017. Among KTRs with multiple joint replacements, only the first transplanted kidneys in patients with ESRD.

Results: A total of 101 KTRs underwent joint replacement surgery during the study period. Although we attempted to select controls at a 1:3 ratio, this was not possible in all cases. However for each case, at least one control was selected, resulting in a total of 281 controls. The mean interval from KT to joint replacement was 3.9±3.1 yrs. Patients needing joint replacements were older at transplant on KT (56±11.7 vs 50±7.2, p<0.011) and White (94.1% vs 84%, p=0.01). In regression analysis, only older age was associated with an increased risk of needing joint replacements (HR: 1.04; 95% CI: 1.01-1.06; p=0.01). In multivariable analyses, the need for replacement was not associated with patient death (HR: 0.79; 95% CI: 0.52-1.18, p=0.25), death-censored graft failure (HR: 0.87; 95% CI: 0.48-1.56; p=0.64) or rejection (HR: 1.59; 95% CI: 0.77-3.29; p=0.21).

Conclusion: Our observational study suggests that hip or knee joint replacement after kidney transplantation is not a risk factor for acute rejection, graft failure, or patient death. Further studies are required to determine the risks of complications after joint replacement surgery.

Utilization of Donor-Derived Cell-Free DNA and Total Cell-Free DNA to Inform Treatment Decisions in a Pancreas Transplant Recipient with COVID-19 Infection and Rejection

Ty Dunn,1 Kerry Gaj,2 Behdad Besharatin,1 Robert R. Redfield,1 Mary Kaminski,1 Heather Wade,2 Philippe Gauthier,1 Penn Medicine, Philadelphia, PA; 2Natera, Inc., San Carlos, CA.

Introduction: Donor derived cell-free DNA (dd-cfDNA) is an established noninvasive biomarker for immunologic rejection of donor tissue in organ transplant recipients. The Prospera™ test, a SNP-based nmpPCR methodology, evaluates dd-cfDNA levels as a fraction of total cfDNA. Atypical elevations in total cfDNA, as seen in immunologic responses, could affect the assessment of active rejection (AR). dd-cfDNA has been analyzed in patients undergoing kidney transplants, however, early data suggests that dd-cfDNA behaves similarly following pancreas transplant. Here we present the clinical course of a pancreas transplant recipient with COVID-19 infection for whom, serial dd-cfDNA testing was performed.

Case Description: A 51-year-old female received a deceased donor pancreas transplant in August, 2020. The patient was maintained on a triple immunosuppressive (IS) therapy regime, had stable amylase and lipase levels and no episodes of rejection. Six months later, the patient received the first dose of a COVID-19 vaccine. Two weeks later, the patient was negative for COVID-19 and was resumed. The dd-cfDNA fraction at this time was 1.59%, and total cfDNA decreased to 1.1 MoM. Subsequent weekly Prospera tests indicated dd-cfDNA fractions of 1.03%, 0.54%, and 0.81% with total cfDNA levels of 1.4 MoM, 1.3 MoM, and 0.94 MoM. We eventually found 5 reports and 6 cases of RHUC in KT from a literature review based on past case reports on MEDLINE. According to the literature review, the incidence of urinary stone and EIAK in either KT recipients or donors with RHUC were not determined due to a small number of patients in previous studies. However, we should focus on preventing these complications based on the evidence obtained from the general population, since both the recipient and the donor have a single kidney with significant hypouricemia, which potentially can be high risk for these complications. RHUC in donors transmits in recipients, which raise the caution for potential kidney stones or EIAK in both recipients/donors after KT.
**PUB278**

**No Benefit of Prophylactic Surgical Drainage in Combined Liver and Kidney Transplantation: Our Experience**

**Paolo Vincenzi**, Miami Transplant Institute, Liver/GI Transplant Surgery and Kidney/Pancreas Transplant Surgery Miami Transplant Institute, Miami, FL.

**Background:** Contrasting results have emerged from limited studies investigating the role of prophylactic surgical drainage in preventing wound morbidity after liver and kidney transplantation. This retrospective study analyzes the use of surgical drain and the incidence of wound complications in combined liver and kidney transplant recipients.

**Methods:** A total of 55 patients aged >18 years were divided into two groups: the drain group (D) (n=35) and the drain-free group (DF) (n=20). Discretion to place a drain was based exclusively on surgeon preference. The primary outcome was the development of superficial/deep wound complications during the study follow-up. Secondary outcomes included the development of delayed graft function (DGF) of the transplanted kidney, primary non function (PNF) and early allograft dysfunction (EAD) of the transplanted liver, graft failure, graft and patient survival, overall postoperative morbidity rate and length of hospital stay.

**Results:** With a median follow-up of 14.4 months after transplant, no difference in the incidence of superficial/deep wound complications, except for hematomas, in collections size, intervention rate, PNF, EAD, graft failure and patient survival, was observed between the two groups. Significantly lower level of platelets, higher INR values, length of hospital stay, DGF and morbidity rates were reported postoperatively in the D group. Preoperative hypoalbuminemia and longer CIT were included in the propensity score for receiving a drain and were associated with a significantly higher rate of developing a hematoma post-transplant.

**Conclusions:** Absence of the surgical drain did not appear to adversely affect wound morbidity compared to the prophylactic use of drains in renal transplant patients during CLKTx.

**PUB279**

**Albumin Preceding Simple Plasma Exchange in ABO-Incompatible Kidney Transplantation**

**Toshihide Uchida**, Osaka City University, Osaka, Japan

**Background:** At present, the use of simple plasma exchange (PEx) for ABO-incompatible kidney transplantation (CLKTx) is limited. Some groups have reported cases of successful PEx with albumin in ABO-incompatible kidney transplantation recipients. The aim of this study is to report the outcomes of ABO-incompatible kidney transplantation recipients who underwent PEx with albumin.

**Methods:** A total of 55 patients aged >18 years were divided into two groups: the drain group (D) (n=35) and the drain-free group (DF) (n=20). Discretion to place a drain was based exclusively on surgeon preference. The primary outcome was the development of superficial/deep wound complications during the study follow-up. Secondary outcomes included the development of delayed graft function (DGF) of the transplanted kidney, primary non function (PNF) and early allograft dysfunction (EAD) of the transplanted liver, graft failure, graft and patient survival, overall postoperative morbidity rate and length of hospital stay.

**Results:** With a median follow-up of 14.4 months after transplant, no difference in the incidence of superficial/deep wound complications, except for hematomas, in collections size, intervention rate, PNF, EAD, graft failure and patient survival, was observed between the two groups. Significantly lower level of platelets, higher INR values, length of hospital stay, DGF and morbidity rates were reported postoperatively in the D group. Preoperative hypoalbuminemia and longer CIT were included in the propensity score for receiving a drain and were associated with a significantly higher rate of developing a hematoma post-transplant.

**Conclusions:** Absence of the surgical drain did not appear to adversely affect wound morbidity compared to the prophylactic use of drains in renal transplant patients during CLKTx.

**PUB280**

**Post-Transplant Nephrocalcinosis: A Single-Center Case Series**

**Aileen Wang, Vivek Charu, Colin R. Lenihan**, Stanford University School of Medicine, Stanford, CA

**Background:** Nephrocalcinosis is characterized by multifocal renal tubular and interstitial abnormalities. Few studies describe the clinical presentation of post-transplant nephrocalcinosis. The goal of this study was to describe the characteristics of patients with nephrocalcinosis diagnosed on kidney transplant biopsy at our center.

**Methods:** We searched all adult kidney transplant biopsy reports between January 2010 and May 2021. We identified biopsies performed on ABO-incompatible kidney and with a concurrent acute rejection or glomerulonephritis diagnosis. We identified 13 patients with nephrocalcinosis as a principle histological diagnosis.

**Results:** Patient characteristics and laboratory findings are shown in Table 1. Mean age was 49±13 years, 69.2% were male and 53.8% Caucasian. Time from transplant to biopsy was 15±18 months. Post-transplant nadir creatinine was 1.25±0.55 mg/dL. Creatinine at the time of biopsy was 1.9±0.72 mg/dL. Creatinine measured at mean of 28 months post-biopsy was 1.89±0.61 mg/dL. Pre- and post-transplant parathyroid hormone levels were 1516±1192 and 264±190 pg/mL respectively. 4 patients underwent post-transplant parathyroidectomy for a parathyroid adenoma in all cases. 7 and 9 patients were prescribed calcinealcalce pre- and post-transplant respectively. Hypocitraturia was found in all 5 patients with available urine studies.

**Conclusions:** Long duration vialysis, markedly elevated pre-transplant parathyroid hormone level, and calcinaculate use were common in patients with post-transplant nephrocalcinosis. Further study is required to identify risk factors and treatments for post-transplant nephrocalcinosis.

**Funding:** Other NIH Support - National Institute of Allergy and Infectious Diseases, Grant/Award Number 1R25AI147369-01.

**Table 1**

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**PUB281**

**Adenovirus and Clostridium difficile Coinfection in a Kidney Transplant Recipient**

**Katherine Rizzolo**, Scott Davis, University of Colorado, Denver, CO

**Introduction:** Adenovirus infection is associated with AKI (hemorrhagic cystitis, tubulointerstitial nephritis, or obstructive uropathy), fevers, and non-glomerular hematuria. Severe adenovirus infections are rare in solid organ transplants, manifesting within the first year of transplant. In this case, we report fever, AKI, and hematuria one year post kidney transplant due to co-infection of *Clostridium difficile* and adenovirus.

**Case Description:** 65 yo male status post deceased donor kidney transplant one year prior presented with five days of diarrhea and fever. Blood work revealed an acute kidney injury (AKI) from a baseline serum creatinine of 1.5 mg/dL to 2.3 mg/dL. He was found to have *Clostridium difficile* toxin positive and started on PO vancomycin and IV fluid. On hospital day 4, he began having high grade fevers to 40C, worsening creatinine to 5.9 mg/dL, and gross hematuria despite resolution of diarrhea. Urine microscopy revealed non-normorphic red blood cells. Adenovirus blood and urine PCR returned positive >1 million copies/mL. Remainder of workup was negative. Biopsy was unable to be performed due to persistent bowel overlying the kidney. Tacrolimus was reduced to target a range of 4-7 ng/mL, mycophenolate was discontinued, prednisone was increased to 20 mg.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
He received 5 days of 400 mg/kg IVIG with declining levels of adenovirus and resolution of fever. Adenovirus became undetectable after four months and creatinine stabilized to 1.3 mg/dL.

**Discussion:** This is the first case reported to our knowledge of *Clostridium difficile* coinfection with adenovirus. It is unclear whether the coinfection we report is due to viral immunomodulation or over-immunosuppression, further research will be needed in this area. Detection methods include direct antigen detection, molecular methods, viral culture, or histopathology. Kidney biopsy reveals acute tubular injury, necrosis, interstitial nephritis with pleomorphic infiltrate, viral cytopathic changes. Treatment is reduction of immunosuppression; cases may be treated with antivirals, ribavirin, or IVIG. IVIG was used for our patient given its good safety profile compared with antiviral therapies, and theoretical rationale for reducing immunosuppression.

**Results:** No differences were observed in patient survival/surviving graft function. Graft survival with HR of 2.56 (95% CI: 1.03 – 6.35, p<0.04) and one-year acute rejection with HR of 1.73 (95% CI: 1.35 – 2.21, p<0.01) were worse in AA compared to non-AA after adjusting for age, sex, diabetes and donor type.

**Conclusions:** In this sizeable cohort with ethnic diversity, AA were at higher risk for graft failure outcomes even in the early post-transplant period compared to non-AA. Further studies evaluating factors including socio-economic determinants of health are needed to mitigate against poorer allograft outcomes.

Comparison of Allograft/Patient Survival at one year between African Americans and non-African Americans

**PUB284**

Assessment of Donor-Derived Cell-Free DNA for Allograft Rejection in Kidney Transplant Patients More Than 1 Year from Transplant: Implications for Clinical Management

**Mike Morgan, Sarah McCormick, Philippe Gauthier. Natera, Inc., San Carlos, CA.**

**Background:** Detection of acute rejection in patients more than a year from kidney transplant (KT) relies on monitoring kidney function tests such as creatinine (SCR), BUN, protein/creatinine reactions and periodic assessment of donor specific antibody levels. Unfortunately, these metrics are lagging indicators of rejection and other injuries that may contribute to declining allograft function over time. In this setting, regular monitoring of donor-derived cell-free DNA (dd-cfDNA) can enhance the nephrologist's ability to detect and monitor acute changes in the allograft and to detect early injury caused by immunosuppression (IS) non-adherence. Here we examined the results of the Prospera™ test, a non-invasive single nucleotide polymorphism-based mmPCR methodology to evaluate dd-cfDNA levels, that was performed on patients >1 year from KT.

**Methods:** We contacted clinics with high-risk Proserpa test results (dd-cfDNA >1%) for patients >1 year from KT. Based on the clinical follow-up, we classified the results as rejection, other injury, IS non-adherence or chronically elevated dd-cfDNA for an unknown reason.

**Results:** We identified 403 patients with Proserpa tests performed between 366 and 14,554 days post-KT with a median time of 1445 days. Among test results, the median dd-cfDNA fraction was 2.19% (range: 1-20.73). Clinical follow-up was available for 115 cases with biopsy-matched results available for 24. Biopsy revealed rejection in 33.3% (8/24) of the cases: ABMR (62.5%, 5/8) and TCMR (37.5%, 3/8). An additional 8 biopsies showed pathological findings consistent with other allograft injury including diabetic/ hypertensive nephropathy, BK nephropathy, interstitial fibrosis and tubular atrophy and other injury not classified as rejection. Elevated dd-cfDNA test results in patients without biopsy were attributed to IS non-adherence in 4 cases, as assessed by the physician, and to viral infection (1 CMV, 3 BK virus) in the remaining 4 cases. These findings resulted in referral to the transplant center for 3 patients, treatment for rejection for 1 patient, and serial testing and increased monitoring for 16 patients.

**Conclusions:** These findings provide real-world data that supports Proserpa’s utility in identifying allografts at high-risk for injury in patients more than 1 year from transplant.

**PUB285**

Subclinical Rejections on Kidney Transplant Recipients After COVID-19

Enzo C. Vasquez Jimenez,1 Bernardo Moguel,1 Cesar Flores Gama.1 Instituto Nacional de Cardiologia Ignacio Chavez, Mexico, Mexico; Instituto de Seguridad Social del Estado de Mexico y Municipios, Toluca, Mexico.

**Background:** The outcomes after COVID-19 and the associated immunosuppressive agents modification in kidney graft is unknown. We evaluated the presence of de-novo DSA and histopathologic findings in a group of kidney recipients after COVID-19 infection.

**Methods:** Kidney recipients recovered from COVID-19 infection from March 31, 2020 to December 8, 2020 in a single transplant center in Mexico were enrolled. Four weeks after COVID-19 diagnosis, DSA and kidney graft biopsy were performed.

**Results:** A total of 20 kidney transplant recipients were enrolled. Immunosuppressive regimen was modified in 60% of patients, the most common modification was MMF reduction or withdrawn (35%). Allograft biopsy revealed that 70% had rejection; 20% were classified as active chronic rejection, 15% active ABMR, 20% mixed ABMR/TCMR rejection, 10% borderline for acute TCMR and 5% acute TCMR. Among allografts diagnosed with graft rejection, 5% were considered as subclinical. All borderline for acute TCMR and active ABMR with dnDSA were subclinical.

**Conclusions:** The unusually high rate of acute rejections and the high number detected without allograft dysfunction in recipients recovered from COVID-19 should be an alert to others transplant centers to monitorize alloimmune response after COVID-19.
**PUB286**

**Challenges Treating Discordant Rejection in Simultaneous Kidney Pancreas Transplant (SPKT)**

Fizza Abbas, Linyuan Wang, Arpita Basu. Emory University, Atlanta, GA.

**Introduction:** Discordant rejection in SPKT are uncommon with limited data on outcomes. We present 2 cases of severe discordant acute rejections of the pancreas presenting early post-transplant (PTx).

**Case Description:** Patient 1 46-year-old lady underwent SPKT. 4 months PTx she was admitted, with abdominal pain and elevated pancreatic enzymes. CT abdomen was suggestive of transplant pancreatitis. She was treated for presumed pancreas rejection with IV Solumedrol. She was re-admitted 10 days later with significant rise in amylase and lipase. Pancreas biopsy showed moderate acute cellular rejection treated with IV Solumedrol and ATG. Patient was readmitted 1 week later with elevated pancreatic enzymes and additional ATG was administered. In the following months while pancreatic enzymes normalized, she developed hyperglycemia needing insulin therapy. 9 months PTx she was on an oral hypoglycemic agent. Patient 2 35-year-old lady underwent SPKT. 9 months PTx she was admitted with fever, elevated pancreatic enzymes elevation and acute kidney injury. Kidney biopsy showed no rejection. CT abdomen showed transplant pancreatitis. She was treated for presumed pancreas rejection with IV Solumedrol. Patient was readmitted 4 days later with worsening pancreatic enzyme elevation. Pancreas biopsy showed severe acute cellular rejection which was treated with ATG. 12 months PTx, pancreas and kidney allograft function are normal, however, blood sugars are elevated and being monitored without medications.

**Discussion:** Treatment of discordant acute pancreas rejection is difficult, particularly with congruent viremia. Large studies assessing allograft and patient outcomes post discordant rejection is needed to better care for this cohort.
Light Chain Deposition Disease (LCDD) Recurrence Post Kidney Transplant

Introduction: Advanced Renal disease from LCDD does benefit from renal transplant but allograft survival may be limited by LCDD recurrence. We report a case to support this.

Case Description: 57-yr old male with history of multiple myeloma status post autologous peripheral blood stem cell transplantation (PBSCT) and ESRD due to IgG Kappa LCDD who got a deceased donor kidney transplant (DDKT) and developed recurrence of LCDD. Patient evaluated 4 years prior for creatinine 3.43 mg/dL, proteinuria 7.4 g/day, kappa light chain (KLC) 118.2 mg/dL, lambda light chain (LLC) 13.8 mg/dL, K/L ratio 8.5, serum protein electrophoresis (SPEP) with M-spike in gamma region, UPEP showed selective glomerular proteinuria, urine immunofixation with 2% of total protein being IgG kappa. Kidney biopsy showed diffuse tubular and glomerular basement membrane staining for kappa light chain (KLC) 3+, weak basement membrane staining for IgG and albumin 1+, moderate -severe fibrosis, negative amyloid. Bone marrow biopsy: 30-40%, hypocellularity, atypical plasmacytosis, plasma cells with CD38 + up to 5% of marrow cellularity, CD56 +, and KLC restricted. Had 3 cycles of chemotherapy with partial response and autologous PBSCT to achieve complete response 1. Two years later, bone marrow and Kidney biopsies showed evidence of disease relapse. Had another cycle of chemotherapy and salvage PBSCT, follow up bone marrow biopsy negative for plasma cell abnormality. Started on PD due to worsening renal function. Allograft biopsy 9 months post DDKT done due to elevated serum creatinine and proteinuria showed recurrent LCDD (tubular basement membrane thickening and mesangial expansion with nodular accentuation, 3+ Linear staining for KLC, negative for lambda, focal glomerular staining for albumin 1+, Electron dense fine granular deposits along glomerular basement membrane) similar to native kidney biopsy prior to PBSCT. SPEP with M-spike 0.4 g/dL K/L elevated at 11. He was started on chemotherapy for LCDD recurrence. Renal Allograft failed at 10 months post-DDKT and patient returned to Hemodialysis.

Discussion: This case illustrates that renal allograft survival is reduced in LCDD patients no matter the treatment used to achieve sustained hematologic response and this supports the need for more studies to establish the pathophysiologic mechanisms underlying LCDD recurrence in renal allograft which may serve as therapeutic targets.

Hypocalbuminemia Is a Risk Factor for Invasive Fungal Infections and Worse Outcomes in Infected Kidney Transplant Recipients
Aniruddha Srivastava, Fauzia Osamn, Ashad N. Khan, Margaret R. Jorgenson, Neetika Garg, Fahad Aziz, Maha A. Mohamed, Didier A. Mandelbrot, Arjang Djamali, Sandesh Parajuli. University of Wisconsin School of Medicine and Public Health, Madison, WI.

Background: Serum albumin is a marker of overall health status. It is unknown if kidney transplant recipients (KTRs) with hypocalbuminemia are at an increased risk of invasive fungal infection (IFI) specifically, blastomycosis, coccidiosis, histoplasmosis, aspergillosis, and cryptococcus.

Methods: In this retrospective observational cohort study, all adult KTRs transplanted between 01/01/2001 and 12/31/2017 were included with serum albumin measured 3-6 months before selected IFIs and compared to matched controls using incident density sampling. KTRs were stratified into three pre-infectional albumin levels: normal albumin a4-0 g/dL, mild hypocalbuminemia 3.0-4< g/dL, and significant hypocalbuminemia <3.0 g/dL. Incidence models per 100 person-years and Cox proportional hazards were used to compare outcomes between groups.

Results: 113 KTRs with IFI and 348 controls were included in the study. Mean serum albumin level at the time of IFI was 3.1±0.62 g/dL. The majority of infected KTRs had aspergillosis (48.7%) followed by endemic fungal and cryptococcus infections. Infected KTRs were older at transplant (56x11 vs 53a14 years, p=0.02) with a higher incidence of delayed graft function (23.9% vs 5.8%, p<0.001). Basalimibinah induction was more common in those with IFI (55.8% vs 47.4%, p=0.02). Calcineurin-inhibitor maintenance immunosuppression prevailed overall, but differed (85.9% vs 96.9%, p=0.001). Infected KTRs had lower serum albumin level with 71% normal, 50.4% mild, and 42.5% significant hypocalbuminemia; while in controls 18.7% had normal, 75.9% mild and only 5.5% significant hypocalbuminemia (p<0.001). The incidence rate of IFIs among normal, mild, and significant hypocalbuminemia was 3.6/100, 8.7/100, and 29.3 person-years, respectively. After multivariate analysis, mild hypocalbuminemia (HR: 2.2, 95%CI: 1.02-4.7) and significant hypocalbuminemia (HR: 5.0 95%CI: 2.3-11.2) had a significantly higher risk of IFI than normal albumin. A similar pattern of mortality and graft failure with hypocalbuminemia after IFI was observed.

Conclusions: These results suggest that hypocalbuminemia is associated with an increased risk of IFI as well as subsequent graft loss and mortality.
Symptoms and Occurrence of Hepatitis E in Solid-Organ Recipients: A Single-Center Experience of the Last Five Years


Background: The Hepatitis E virus (HEV) can be found worldwide and the transmission is mainly fecal-oral. In Germany, transplantation ocusses especially from pork or beef, where genotype 3 is predominant. While most infections are asymptomatic, under immunosuppressive therapy a chronic (and fatal) course of Hepatitis E is possible. Regular testing is often missing due to lack of experience. Therefore, we retrospectively evaluated all solid-organ transplant patients in our tertiary care center with a positive diagnosis of Hepatitis E in the last five years.

Methods: All solid-organ recipients with positive HEV-RNA replication in the blood in the last 5 years were retrospectively analysed regarding disease manifestation, immunosuppressive therapy, and course of HEV infection. HEV-IgG or IgM alone were not sufficient for diagnosis.

Results: From 2015 to 2020 14 solid-organ transplant patients (4x kidney, 5x heart, 4x liver, 1x lung) were diagnosed with HEV in our center. All patients showed elevated transaminases before diagnosis. In total 3 patients experienced abdominal pain, two presenting with acute liver failure. Overall, HEV infection occurred after a median of 8.6 years after transplant, however 3 patients developed HEV within the first year after transplantation. The transmission path remained uncertain in all cases. Blood transfusions were a prevalent associated contaminant and/or undercooked meat was the most likely cause, especially as none of the patients were vegetarian. Regarding immunosuppressive therapy, 92 % (N=13) had a tacrolimus based regimen combined with either mycophenolic acid or because of the severe course of the disease. In 4 patients HEV infection disappeared without specific treatment due to the reduction of immunosuppressive therapy. One patient developed a chronic HEV infection, which resolved after Ribavirin therapy.

Conclusions: HEV-E is a common cause of elevated transaminases in solid-organ recipients and should be considered for differential diagnosis. Therefore, we suggest a more precise instruction – even years after transplantation – regarding cooking rules.

Vancomycin Nephrotoxicity Causing Renal Transplant AKI
Luan D. Truong, Sean Hebert, Ngonbena Tantranont. The HoustonMethodist Hospital, Houston, TX.

Introduction: Nephrotoxicity is a rather frequent side effect of vancomycin treatment. Attributes of vancomycin nephrotoxicity (VN) are well documented including immunosuppressive therapy, and course of HEV infection, and variable responses of patients to treatment. Attributes of vancomycin nephrotoxicity (VN) are well documented including immunosuppressive therapy, and course of HEV infection, and variable responses of patients to treatment.

Case Description: We herein reported the first three such cases. In each of these cases acute kidney injury developed concurrently with vancomycin treatment and resolved after its cessation. As compared with the general population VN in the renal transplant setting displayed some unusual clinical behaviors. Its development was rather capricious, being noted in some treatment episodes, but not others even in the same patient. Acute kidney injury developed gradually in conjunction with a protracted vancomycin treatment, in contrast to a precipitous course in the non-transplant setting. However, renal transplant biopsies showed typical features of VN in each case

Discussion: VN is an exceptional but well documented cause of acute kidney injury in renal transplant recipients. VN in this setting may display some atypical features setting it apart from that in the general population. However, renal transplant biopsy changes are characteristic and amenable to a definitive diagnosis.

A Comparative Exploration of Patient-Provider Communication Challenges After a Kidney Transplant

Background: Kidney transplantation is a life-altering treatment, but symptoms and drug side effects persist for many patients post-transplantation. Effective communication with the healthcare team (HCT) is key to address these, yet research shows patients find that challenging. Ineffective communication may lead to inadequate assessment and management of symptoms. Although communication is among patients’ top research priorities, less than 5% of articles in the two leading transplant journals address it. To fill this gap, we conducted a qualitative exploration of communication challenges from recipients’ perspective.

Methods: Within a larger study, we used Qualitative Description methodology to understand the quality of communication between patients and HCT post-transplantation. Purposeful recruitment was done via flyers (Jun-Dec 2020). Patients with significant cognitive impairment or insufficient English were excluded. In-depth, semi-structured, individual interviews were recorded and transcribed verbatim. Directed content analysis framed the iterative development of codes.

Results: 7 recipients (4 males, ages 51-75, 4-15.5 years post-transplant) and 1 caregiver participated. Findings indicate a range of experiences, from regular contact with HCT to infrequent or uninformative communication to no communication in-between clinic visits. Compared to pre-transplant care, communication was less frequent and many patients felt isolated, making it difficult for them to know where and how to seek information and support. Instead, patients relied on searching for information online, visiting family doctors or the emergency room. Some used phone/voicemail to reach HCT, but these were not always timely or efficient. Patients also raised the need for HCT to consider the uniqueness of each patient and their broader context, in addition to quantitative measures, in assessing their health. The diverse communication experiences also relate to patients’ comfort with self-advocacy. While some proactively initiated conversation, others are more reserved.

Conclusions: Communication challenges between kidney transplant recipients and HCT contribute to feelings of isolation and difficulties navigating post-transplant life. Tailoring communication to individual preferences may improve patient-centered care.

CMV-Associated Thrombosis in a Kidney Transplant Recipient
Young C. Hsu,1,2 Lin Wang,1,2 Thanh Cao,2 Neeraj Sharma,2 University of Southern California, Los Angeles, CA; 3Keck Hospital of USC, Los Angeles, CA.

Introduction: Cytomegalovirus (CMV) infection is a common infectious complication after kidney transplantation. Indirect effects of CMV infection include an increased risk of secondary infections, increased risk of acute rejection and chronic allograft dysfunction, and well known to CMV may lead to a blood clotting disorder. Cytomegalovirus (CMV) infection is a common infectious complication after kidney transplantation. Indirect effects of CMV infection include an increased risk of secondary infections, increased risk of acute rejection and chronic allograft dysfunction, and well known to CMV may lead to a blood clotting disorder.

Case Description: A 64 year old male presented with 4 weeks of sore throat, cough, subjective fevers, chills, right thigh pain, fatigue, 3 weeks prior, he presented to an outside hospital with flu-like symptoms and complaints of right calf pain. Imaging showed the right leg with totally thrombosed posterior tibial and peroneal veins as well as acute partially thrombosed popliteal vein. The patient was subsequently admitted to the hospital and found with a CMV PCR of 35,900 IU/ml, after which he underwent an esophagogastroduodenoscopy (EGD) and colonoscopy with biopsies confirming CMV in the lower esophagus consistent with CMV esophagitis. IV ganciclovir treatment was initiated with appropriate response seen.

Conclusions: CMV belongs to the herpesvirus family that establishes latent infection following a primary infection. For patients who are CMV seropositive, the risk of CMV reactivation is highest in the setting of systemic immunosuppression. CMV infections may present with a wide array of syndromes ranging from meningoencephalitis to enteritis/colitis and hepatitis. In addition, CMV infection has been associated with thromboembolic events. Kidney transplant recipients show a high prevalence of thrombotic events compared with the general population. In short, acute CMV infection should be considered as a risk factor for venous thromboembolism. Therefore, diagnosis of acute CMV infection in patients with an acute thrombosis should redefine the thrombotic event as provoked rather than unprovoked, limiting the duration of anticoagulation treatment.

Comparison of the Efficacy and Safety Between Anti-Thymocyte Globulin (ATG) and Basiliximab in Deceased Donor Kidney Transplantation: A Multicenter Study
Suveen Hong,1,2 Chul Woo Yang,1 Byung cha Chung,1 Woo Yeong Park,2 Kyubok Jin,3 Seungyup Han.1 1The CatholicUniversity of Korea, Seoul S.Mary’sHospital, Seoul, Seoul, Republic of Korea; 2The Catholic University of Korea, Uijeonbu S.Mary’s Hospital, Uijeonbu, Gyeounggido, Republic of Korea; 3Keimyung University School of Medicine, Daegu, Daegu, Republic of Korea.

Background: Induction immunosuppressant is decided upon the condition of deceased donors and recipients in deceased donor transplantation (DDKT). Although anti-thymocyte globulin (ATG) is preferred in immunologically high risk patients, there is no clear evidence for the efficacy and safety of induction agent in DDKT. This study aims to compare the efficacy and safety between ATG and basiliximab (BSX) in deceased donor kidney transplantation (DDKT).

Methods: A total of 724 kidney transplant recipients (KTRs) from 3 transplant centers were enrolled and ATG-DDKT group was 252 and BSX-DDKT group was 472. We investigated the impact of induction therapy based on donor age of 60, donor kidney with acute kidney injury (AKI) and kidney donor profile index (KDIP) score of 65% on post-transplant clinical outcomes in delayed graft function (DFG), acute rejection (AR), infectious complications, allograft and patient survivals.

Results: ATG-DDKT group had poor donor condition and highly sensitized recipients than BSX-DDKT group. DGF did not show statistically significant differences according to induction agent in terms of elderly/donors age, AKI/non-AKI, and high-KDIP/low-KDIP subgroups. Acute rejection and infection rate did not show meaningful differences. Death-censored allograft survival and patient survival rate between induction agents were also statistically irrelevant.
Conclusions: Our results suggest that though ATG was more frequently applied to poor donor condition and highly sensitized recipients, ATG was not inferior to BSX not only in aspect of survival rate but also DGF, AR and infection aspects. Therefore, as an induction agent, ATG should be considered in preference to BSX, especially in high-risk DDRT.

Funding: Government Support - Non-U.S.

Table 5. Risk factors for allograft failure in deceased donor kidney transplantation

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted HR (95% C.I.)</th>
<th>P</th>
<th>Adjusted HR* (95% C.I.)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction therapy</td>
<td></td>
<td></td>
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<tr>
<td>2006-2008</td>
<td>1.229 (0.737-2.040)</td>
<td>0.490</td>
<td>0.713 (0.390-1.343)</td>
<td>0.332</td>
</tr>
<tr>
<td>2009-2010</td>
<td>0.798 (0.482-1.346)</td>
<td>0.364</td>
<td>0.910 (0.528-1.553)</td>
<td>0.753</td>
</tr>
</tbody>
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PUB297

Longitudinal Urinary Inflammatory Profile During Renal Transplantation

Elizabeth Spizak, Corina Nailescu, Andrew L. Schwaderer. Indiana University School of Medicine, Indianapolis, IN.

Background: In the year 2020, more than 5,000 living donor kidney transplants were performed in the United States. Kidney transplant recipients are subjected to several types of immunosuppressants in order to prevent rejection of the graft. Over-immunosuppression increases the risk of infectious complications and these patients require a delicate balance. Inflammatory profiles from the urine can help identify which biomarkers may guide clinicians in balancing over vs. under-immunosuppression.

Methods: Urine samples were obtained from 12 kidney donor-recipient pairs at a pre-operative visit ~1 week prior to or at time of transplant and then for the recipients, ~3 months following transplantation. The urine samples were analyzed using inflammatory urine biomarker profiles (Mesoscale Discovery). Urine levels were then normalized to urine creatinine values. Differences were noted between groups using the mixed-measures ANOVA, corrected for multiple comparisons with the Tukey test to get adjusted p-values.

Results: Results are presented in the figure, but it was identified that eotaxin urine levels were higher in post-transplant samples compared to donor samples; interleukin-15 levels were higher in pre-transplant samples compared to their post-transplant samples.

Conclusions: The urine inflammatory profile evolves over the transplant course between donors, pre-transplant recipients and transplant recipients. Although the transplant itself is typically accepted as a pro-inflammatory event, levels of biomarkers in the urine tend to decrease post-transplant. Immunosuppression regimens may influence inflammatory profiles and warrant further investigation.

Funding: NIDDK Support

PUB298

A Study of Outcomes of Renal Transplantation from Deceased Donors in a Tertiary Care Centre from Southern India

Vishnu K. Kotha, nephrology NP1 UNIT Nizam’s Institute of Medical Sciences, Hyderabad, India.

Background: In India, there are large number of end stage renal disease patients awaiting renal transplantation. Deceased donor renal transplantation (DDRT) is one possible solution to this. So this study aimed to determine the outcomes of DDRT.

Methods: Total 126 DDRT recipients in a tertiary care hospital in southern India, between 2013 and 2020 were taken in to the study and the outcomes were retrospectively analysed.

Results: Out of 339 renal transplants, 126(37%) were DDRT in the study period. Mean age at transplant was 58.3 years.77.7% were males and 22.3 % were females. 73.8% patients received basiliximab, 26.2% received antithymocyte globulin for induction. Steroids, calcineurine inhibitors and mycophenolate mofetil were used for maintenance immunosuppression. Over a mean follow up of 3.6 years, patient and graft survival rates were 85% and 92.6%, respectively, with a median serum creatine of 1.32 mg/dl. The incidence of delayed graft function (DGF) was 54.3%. The incidence of slow graft function was 33.4%. The incidence of immediate graft function was 12.3%. Prolonged cold ischaemia time was risk factor for DGF. Mean cold ischemia time was 4.2 hours.

Conclusions: Outcomes of DDRT showed successful results. So DDRT has a potential to expand donor pool and shorten the waiting list for renal transplantation. Increasing public awareness and good communication and a well trained team of transplant coordinators can help in improving the number of organ donations.

PUB299

Pressure Natriuresis and Diuresis Are Differentially Regulated Depending on Age and Sex

Yang gwan Kim, Sangho Lee, Ju young Moon. Kyung Hee University Hospital at Gangdong, Gangdong-gu, Seoul, Republic of Korea.

Background: The renal capacity for handling salt and water is linked to hypertension. This study aimed to clarify the sex- and age-related natriuretic and diuretic differences in blood pressure (BP) regulation.

Methods: We analyzed two datasets: one from the E-SPECIAL trial, which evaluated the effect of a low-salt diet (LSD) on lowering albuminuria in 235 patients with nondiabetic chronic kidney disease, and the other from the Korean Genome and Epidemiology Study (KoGES), including 4,937 subjects.

Results: In the E-SPECIAL trial, BP was lower in premenopausal women (Pre) than in younger men (Y), and the gap disappeared between postmenopausal women (Post) and older men (O). LSD decreased urine sodium in Y, Post, and O but did not mitigate urine sodium in Pre. A positive correlation between BP and urine sodium was
observed only in the younger groups (Pre, Y). Urine volume was greater in Pre than in the other groups. Misoprostol was not detectable in Pre. Her urine volume was positively correlated with BP in Pre and negatively associated with BP in other groups. Urine volume and urine sodium were the most decisive factors for predicting BP in Pre. In the KoGES, BP was lowest in Pre. Urine sodium increased in Pre compared with Post, although sodium intake was not different. The correlation between BP and urine sodium augmented in younger groups (Pre, Y).

Conclusions: The pressure-natriuretic and pressure-diuretic responses were well conserved in Pre and mitigated in Post. Augmented natriuresis and diuresis might contribute to lower BP in Pre.

PB302
Urinary Dickkopf-3 (Dkk3) Uncovers Unapparent Progressive Kidney Injury in Patients with Chronic Obstructive Pulmonary Disease: An Etiological Study and Experimental Validation
Stefan J. Schunk, Danilo Fiser, Thimoteus Speer. Universitätsklinikum des Saarlandes und Medizinische Fakultät der Universität des Saarlandes, Homburg, Germany.

Background: Chronic kidney disease (CKD) and chronic obstructive pulmonary disease (COPD) represent global public health problems with high disease-related morbidity and mortality. However, the interaction between both diseases remains unclear.

Methods: In a novel murine model, cigarette smoke (CS)-induced lung injury was combined with a CKD model (CS-CKD model). In 2,314 patients of the prospective multi-center COSYCONET study, urinary Dickkopf-3 (Dkk3), a renal tubular stress marker, was investigated. The association between urinary Dkk3 and trajectories of FEV1, and estimated glomerular filtration rate (eGFR), exercise capacity, risk of exacerbation, and mortality was determined (follow-up 37.1 months).

Results: In the CS-CKD model, CKD was associated with higher systemic and pulmonary inflammation, and the combination of CKD and CS significantly agGRAvated kidney inflammation as well as fibrosis and increased renal expression of Dkk3. Abrogation of Dkk3 attenuated kidney injury and pulmonary inflammation alike. In COPD patients, higher urinary Dkk3 was associated with rapidly declining FEV1 (OR 3.36, P<0.0001), higher risk for exacerbation, lower 6-minute walking distance, and higher all-cause mortality (HR 1.49, P=0.015). Importantly, higher urinary Dkk3 was also associated with declining eGFR during follow-up (OR 2.23, P=0.0005). Neither eGFR nor proteinuria were associated with lung or kidney dysfunction during follow-up.

Conclusions: In summary, the present study identified a strong pathophysiologi cal link between lung and kidney dysfunction, which is at least partially mediated by Dkk3. Urinary Dkk3 allows identification of COPD patients at increased risk for deteriorating pulmonary and kidney function as well as adverse outcomes. These patients might particularly benefit from preventive therapeutic strategies as a personalized-medicine approach.

PB303
Outpatient Treatment Patterns of Hyperkalemia in the United States: The Design and Initial Findings from ZORA, an Observational Study
Eva Lešen,1 Abiy Agiro,2 Alaster Allum,3 Jonatan Hedberg,1 Mina Khezrian,4 Krister Järbrink,1 1AstraZeneca, Gothenburg, Sweden; 2AstraZeneca US, Wilmington, DE; 3AstraZeneca, Cambridge, United Kingdom.

Background: Hyperkalemia (HK) is a potentially life-threatening disorder due to alterations in cardiac conduction, which may result in arrhythmias and sudden death. Potassium binders is a key pillar in the outpatient treatment of HK, but conventional binders, including sodium polystyrene sulfonate (SPS), are generally poorly tolerated, lack palatability and have limited long-term efficacy – with suboptimal use as a consequence. New potassium binders (patiromer and sodium zirconium cyclosilicate [SZC]) with a more beneficial tolerability profile have become available, but contemporary real-world evidence on outpatient treatment patterns including these new therapeutic options is scarce.

Purpose: To describe the characteristics and treatment patterns among patients with outpatient potassium binder treatment in the US.

Methods: This is an observational study including patients who filled an outpatient prescription for SPS, patiromer or SZC between 1 Jan 2018 and 30 Jun 2020, as identified in HealthVerity claims data linked with Quest Diagnostics laboratory data. Patient characteristics and binder treatment patterns will be described using standard descriptive statistics and survival analysis.

Results: The data set includes a random sample of 20,000 patients with a filled prescription for SPS, and approximately 20,000 patients with a filled prescription for a new binder (patiromer or SZC), over a data capture period of 30 months for patiromer and 12 months for SZC. Analyses on patient characteristics (such as demographics, HK severity, comorbidities, treatment history etc.) and their associations with outpatient treatment choice, as well as binder treatment patterns and trends over time, are ongoing and will be presented.

Conclusions: This study will identify important insights into the characteristics and binder treatment patterns among US patients with HK, and provide useful guidance to improve adherence to guidelines and optimize patient care.

Funding: Commercial Support - AstraZeneca
eGFR calculation Without the Race Coefficient Obscures Obesity-Related Glomerulopathy in Female Adolescents

Dana Bielopolski,1 Odah S. Bentur,2 David M. Charytan,3 Jonathan N. Tobin,4 The Rockefeller University, New York, NY; NYU Langone Health, New York, NY; New York University Grossman School of Medicine, New York, NY; Clinical Directors Network Inc, New York, NY.

Background: Obesity is more prevalent among minorities, increasing the risk for cardiovascular morbidity. We explored interactions between race, body mass index (BMI), and the risk of hyperfiltration associated with Obesity Related Glomerulopathy (ORG).

Methods: We created a cohort of women and girls ages 12-21 from the New York area using their longitudinal electronic health records (EHR). Glomerular filtration rate (GFR) was estimated in two ways: I) using the standard age recommended formulae, and II) eGFRr –without a race-specific coefficient. Multivariate logistic regression was used to analyze the correlation of risk factors for ORG associated hyperfiltration, defined by a threshold of a 135ml/min/1.73m².

Results: 7315 Black and 15,102 non-Black women and girls were evaluated for kidney function in parallel to body measures. Hyperfiltration was more frequent in Black compared to non-Black individuals when using standard eGFR but was lower after eliminating the race-specific coefficient. Black race was independently associated with hyperfiltration with standard eGFR calculation (OR=3.43, 95% CI 2.95-3.99) but the association was reversed when estimated by eGFRr (OR=0.56, 95% CI 0.45-0.70). Risk of hyperfiltration was higher for Black individuals across all BMI strata with standard eGFR estimates, but when estimated as eGFRr hyperfiltration filtration risk was reduced for overweight (OR=0.70 95% CI 0.54-0.89) and obese (OR=0.47, 95% CI 0.37-0.60) participants.

Conclusions: Estimated CKD prevalence among Black adolescents and young adults increases following removal of the race coefficient while fewer have evidence of obesity associated hyperfiltration. In the CKD-range of GFR we should consider a gradual increase in the race coefficient to avoid underestimation of obesity related glomerulopathy in the high normal range of GFR.

Funding: Other NIH Support - This project was supported in part by the National Center for Advancing Translational Sciences, National Institutes of Health, through The Rockefeller University, Grant #UL1 TR001866, The Sackler Center for Biomedicine at The Rockefeller University, The Sackler Institute for Nutrition Science at the New York Academy of Sciences, and the Patient-Centered Outcomes Research Institute (PCORI) PCORNet Contract # CDKN-1306-03961., Private Foundation Support

Hyperfiltration rates according to race and the different formulae in Black individuals vs. non-black individuals. Panel A – hyperfiltration calculated by eGFR according to BMI groups in Black (orange) and non-Black individuals (blue). Panel B hyperfiltration rates according to eGFRr in blacks (orange) and non-Black (blue) individuals.

Inside CKD: Projecting the Global Clinical Burden of CKD Using Patient-Level Microsimulation

Juan Jose Garcia Sanchez,1 Claudia S. Cabrera,1 Joshua Card-Gowers,4 Steven J. Chadban,1 Timothy Coker,1 Stephen Nolan,2 Albert J. Power,3 Lise Retal,4 Navdeep Tangri,1 Juan Vagasa,4 Laura Webber,4 Michael Xu,4 Inside CKD 1Royal Prince Alfred Hospital Department of Neurology and Stroke, Camperdown, NSW, Australia; 2AstraZeneca UK Ltd, Cambridge, United Kingdom; 3University of Manitoba Faculty of Health Sciences, Winnipeg, MB, Canada; 4HealthLumen Ltd, London, United Kingdom; 4AstraZeneca, Gothenburg, Sweden; 1North Bristol NHS Trust, Westbury on Trym, United Kingdom.

Background: Chronic kidney disease (CKD) affects ~10% of the global population and disease progression is associated with increased risk of cardiovascular events, renal replacement therapy (RRT) and premature death. The trajectory of CKD and related costs are critical considerations for public health and policy planning. Using country-specific, patient-level microsimulations, Inside CKD models the global clinical and economic burden of CKD from 2021 to 2026.

Methods: We used the Inside CKD microsimulation to project the clinical burden of CKD in Canada, the UK and the US. We constructed a virtual general population for each country using national survey data and relevant published literature. Data inputs included country demographics and the prevalence of CKD, RRT, comorbidities, and complications. CKD stages were defined as discrete health states consistent with Kidney Disease: Improving Global Outcomes (KDIGO) 2012 recommendations. We conducted model validation and calibration using established methods for health economic modelling. Analyses from additional countries in the Americas, Asia-Pacific and European regions are underway.

Results: Preliminary results show that the prevalence of CKD stages 1–5 is projected to increase from 13.35% to 14.22% in Canada, from 13.48% to 13.98% in the UK, and from 14.88% to 15.57% in the US from 2021 to 2026 (Table). The number of patients receiving RRT annually is projected to increase from 42,064 to 47,582 in Canada, from 69,796 to 75,051 in the UK, and from 797,638 to 823,050 in the US, between 2021 and 2026 (Table).

Conclusions: Inside CKD projects that the prevalence of CKD will continue to rise in Canada, the UK and the US over the period 2021–2026 with a corresponding increase in the annual RRT burden. These data demonstrate that CKD continues to pose a significant global challenge to public health and demonstrates the continued need for national policies aimed at early intervention.

Funding: Commercial Support - AstraZeneca

Projected increase in CKD stages 1–5 (including undiagnosed) and RRT from 2021 to 2026

*Percentages expressed as a proportion of total projected country population

Peer Support as an Intervention for Kidney Disease: A Systematic Review

Jennifer Taylor, Supritha Prasad, Talar Markossian, Holly J. Kramer. Loyola University Chicago, Chicago, IL.

Background: Peer support may help improve chronic kidney disease (CKD) self-management because patients who share experiences can provide unique resources including passage, encouragement and advice unlike any other provider. The objective of this systematic review is to assess the published data on peer support as an intervention to improve health outcomes for patients with CKD.

Methods: This systematic review was guided by the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P). The electronic search for studies was done using Medline, Psychological Information Database (PsychINFO), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Central Register of Controlled Trials and Web of Science Core Collection. Medical Subject Heading (MeSH) terms and free text terms were modified as appropriate into each database. Eligibility criteria was based on the Problem or Population, Interventions, Comparisons, Outcomes and Study design (PICOS) framework. Study quality was evaluated using the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies and the Mixed Methods Appraisal Tool (MMAT).

Results: A total of 319 articles were identified and 10 clinical trials, 8 observational studies, and 1 mixed method study met inclusion criteria. Clinical trials showed medium to high quality while observational studies showed medium to low quality. The mixed-methods study showed high quality. Studies covered a broad range of CKD stages and problems relating to kidney disease. Only 2 articles of low quality focused on peer support as an intervention to slow CKD progression.

Conclusions: This systematic review shows a need for more research on peer support especially for peer support as an intervention to slow CKD progression.

Funding: Private Foundation Support

Figure shows quality assessment in 10 clinical trials (right) and 8 observational studies (left). Quality assessment ratings: dark grey-strong; medium grey-moderate; light grey-weak;
RISK OF PULMONARY EMBOLI IN PATIENTS WITH RENAL FAILURE

Abhishek Pulia, Arsalan Zahid, Jonathan Paul, Stephanie Besser, Mary S. Hammes. University of Chicago Division of the Biological Sciences, Chicago, IL.

Background: There are 2 million cases of deep vein thrombosis and 200,000 deaths due to pulmonary embolism (PE) each year in US. The LITE study showed a relative risk of 2.1 (95% CI 1.5-3.0) for venous thromboembolic events in advanced renal failure with limitations as patients with ESRD were not included, renal function at time of event was not defined, and no definition or clot burden or cardiac function. The objective of the current study was to characterize the thrombotic event and details of cardiac function in patients who develop PE, stratifying for renal failure along with determination if demographic data or medical history can predict the outcome or severity of a PE.

Methods: This was a retrospective review conducted at a single-center in an urban community. Charts were reviewed from patients who were referred to the Pulmonary Embolus Response Team (PERT) for treatment of a PE. Demographic data, medical history, and labs including serologic markers of renal and cardiac were reviewed. Patients were stratified based on renal function. Controls had an eGFR > 60 ml/min as compared to patients with AKI or a history of CKD. PE severity was defined by 2019 ESC guidelines with the most severe classification (4) having hemodynamic instability. Cardioembolic parameters reviewed included echocardiograms and CT scans.

Results: Charts were reviewed for 170 patients who were admitted for a PE with PERT team activation between 2017 through 2020. There were 45 patients included with AKI, 37 with Stage 3 CKD, 20 with Stage 4-6 CKD, 69 in the control group defined as a eGFR > 60 ml/min. The control group was younger with a lower incidence of coronary artery disease and hypertension (p <0.05). Mortality associated with a PE was stratified for renal function with a higher in-hospital mortality in patients with AKI and advanced CKD when compared to controls (p=0.052). Logistic regression was performed to ascertain the relationship of the severity of the PE and renal failure with an OR 9.26 SE 0.97 (95% CI 2.1,40.6) p= 0.003. Patients had a 9-fold increased risk of PE Severity Class 4 if they had renal failure when compared to controls.

Conclusions: Patients with advanced CKD or AKI tend to have a higher PE severity with a higher mortality. Efforts to triage aggressively treat patients with renal failure who present with PE may improve outcomes.

PUB308

EFFECTS OF AIR POLLUTANTS ON MORTALITY OF PATIENTS WITH CKD LIVING IN GREEN SPACES IN SEOUL, KOREA: A LARGE OBSERVATIONAL STUDY

Jiyun Jung,1 Jangwook Lee,1 Yong Chul Kim,1 Jung Pyo Lee,1 Yon Su Kim,1 Sung Joon Shin,1 Jae Yoon Park.1 Dongguk University Ilsan Hospital, Goyang, Gyeonggi-do, Republic of Korea; 2 Seoul National University College of Medicine, Seoul, Republic of Korea.

Background: Owing to increasing air pollution, the association between green spaces and health outcomes has become a global health concern. The relationship between air pollution and the survival of patients with chronic kidney disease while considering residential greenness remains to be elucidated.

Methods: Time-varying survival analysis was conducted to investigate the association between long-term exposure to air pollutants (PM_{2.5}, PM_{10}, NO_{2}, SO_{2}, CO, and O_{3}) and mortality in 29 602 chronic kidney disease patients living in residential environments with low and high green infrastructure. Low and high green infrastructure was defined as continuous (0.3, 0.35, and 0.4) and percentile (50%, 75%, and 90%) thresholds using satellite data derived average normalized difference vegetation index within 250 m and 1250 m around the residence.

Results: During the average 6.14 ± 3.96 observation period, 3 863 (14%) deaths occurred. The effect of exposure to air pollution on mortality was stronger in the low index group compared to the high index group. Particularly, SO_{2} was significantly associated with increased mortality risk in the low index group regardless of the threshold. Conclusion: The results were observed in the co-pollutant models.

Conclusions: Exposure to high greenness significantly reduced the mortality risk associated with air pollution. Our results emphasize the need for creating environmental infrastructure considering green spaces.

PUB309

IMPACT OF INPATIENT EDUCATIONAL PROGRAMS ON MORTALITY AFTER THE INTRODUCTION OF DIALYSIS THERAPY

Keisuke Yoshida,1 Yohei Kita,1 Wei Han,2 Sayaka Shimizu,1 Yugo Shibagaki,1 Tsutomu Sakurada.1 1Sei Marianna Ika Daigaku, Kawasaki, Japan; 2Kyoto Daigaku Daigakuin Igaku Kenkyou Igakubu, Kyoto, Japan.

Background: Although inpatient educational programs (IEPs) for non-dialysis-dependent chronic kidney disease (CKD) have been reported to slow disease progression, its effect on prognosis after the introduction of dialysis therapy is unclear.

Methods: Consecutive patients who started dialysis therapy between January 1, 2011 and December 31, 2018 were included in this study. The patients were divided into two groups according to whether or not they received IEPs before dialysis introduction, and their background characteristics were compared. The survival rate for each group was calculated using the Kaplan-Meier method and compared by the log-rank test. Furthermore, the hazard ratio (HR) adjusted for confounding factors associated with mortality (age, sex, BMI, CCI, eGFR, albumin, ADL, smoking, welfare patient and emergency hospitalization) was calculated using a Cox regression analysis.

Results: Of the 489 subjects (mean age 68 years, 71.0% male), 129 patients (26.4%) received IEP. Compared with the non-IEP group, the IEP group had higher serum albumin (p <0.001) and lower total cholesterol levels (p =0.0078), and the proportion of patients with a history of smoking in their daily living activities was high (p = 0.0057). The mean observation period was 3.8 years, and 153 people (31.3%) died. The 5-year survival rates[A1] [A2] [A3] were 81.0% and 61.4% in the IEP and non-IEP groups, respectively (p = 0.015). From the Cox regression analysis,[A4] [A5] [A6] the HR for the IEP group was 0.56 (95% CI: 0.36–0.88).

Conclusions: IEPs for CKD patients were associated with a more favorable prognosis after induction of dialysis.

PUB310

THE PREVALENCE OF ADVERSE CHILDHOOD EXPERIENCES IN ADULTS WITH CKD

Kira Clark, Amira Al-Uzri. Oregon Health & Science University, Portland, OR.

Background: Adverse childhood experiences (ACE) are traumatic events of physical and emotional neglect and abuse, sexual abuse, household dysfunction, caregiver instability, community violence, and collective trauma. Previous research shows the prevalence of ACEs is higher in people with chronic disease, but limited data is available on the prevalence of ACEs in people experiencing chronic kidney disease (CKD).

Methods: This case-control study used the Adverse Childhood Experiences International Questionnaire to compare the ACE prevalence of people diagnosed with CKD (case) to people without CKD (control). ACE scores consisted of 13 trauma subtypes and were coded on a scale from 0-13 for an overall score. Fisher’s exact test was used to compare the difference between groups within a 95% confidence interval. Logistic regression examined group differences for each ACE sub-type and adjusted for sociodemographic confounders.

Results: The analysis included 34 people with CKD and 29 controls. Subjects were predominantly female (64.1%), white (84.1%), had a college degree (73.0%), were employed full-time (54.0%), and had a M age of 36.1 (± 8.6) years old. Subjects with CKD were diagnosed around 25.5 (± 13.6) years old with a mean eGFR of 38.5mL/min/1.73m². ACE scores for CKD (M = 6.7, SD = 3.2) compared to control group (M = 5.0, SD = 3.0) demonstrated significantly higher ACE scores, (61) = 2.4, p < .02. People with CKD had a higher prevalence in 11 of the 13 ACE trauma sub-types with the highest reported categories including bullying (91.2%), emotional abuse (82.4%), physical abuse (70.6%), household violence (70.3%), and caregiver mental illness (64.7%). Statistically significant (p <0.05) differences in prevalence occurred with exposure to emotional neglect, caregiver mental illness, and sexual abuse. Odds ratios for having a CKD diagnosis were significant (p <.05) for emotional neglect (OR: 8.84), caregiver mental illness (OR: 4.81), sexual abuse (OR: 4.52), and bullying (OR: 5.55).

Conclusions: This pilot research indicates that adults with CKD experienced every trauma sub-type of ACE and at higher frequencies than a control population. Cumulative exposure to ACEs and experiencing specific trauma sub-types increased the odds of having a CKD diagnosis. Further research is needed to explore how ACEs affect disease occurrence and management of people with CKD.
as a contributor to morbidity / mortality. The BMG analysis suggests there are possible nephrotoxic effects of uranium exposure, though more studies are needed to improve precision.

**Funding:** Clinical Revenue Support

**PUB312**

**Nephrology eConsultation: A Progress Update**

David S. Levy, Rickinder Grewal, Monica L. Ranaalta, Stephanie Lempeka, Thu H. Le. University of Rochester Medical Center, Rochester, NY.

**Background:** Given the high demand for nephrology consultation at the University of Rochester, with an average of 30 - 40 new outpatient consultation requests per week, based on the AAMC (Association of American Medical Colleges) Project CORE (Coordinating Optimal Referral Experiences) model, we developed an eConsultation program for primary care providers (PCPs) across the University’s health network to receive subspecialty advice in a prompt and efficient manner in lieu of formal face-to-face nephrology consultation.

**Methods:** Here, we report our experience with time and value-based metrics of our eConsultation program from September 2019 through March 2021. eConsult requests were placed by PCPs for renal-related issues such as mild to moderate acute kidney injury, CKD, electrolyte disturbances, and proteinuria. The nephrologist electronically communicated with the PCP who then conveyed the subspecialty recommendations with their patient.

**Results:** Between September 2019 and March 2021, 338 eConsult requests were received, averaging 17.8 eConsults/month. Of these, 47% were deemed medically appropriate and completed, 34% were converted to in-person visits and 4% were declined. The majority – 63% of eConsults were completed between 11 - 20 minutes, 35% were completed between 5-10 minutes, and only 2% required more than 20 minutes to complete the consult. From a financial perspective, between September 2019 and March 2021, the nephrology eConsult program has generated over $6500 in revenue, translating to ~$38 per encounter, the equivalent of 0.7 RVUs.

**Conclusions:** Our nephrology eConsultation program has provided timely and remote subspecialty guidance for PCPs within our University’s health network and has overall been well-received by patients and PCPs. This model has the ability to decrease wait time for more complex patients requiring in-person consultation thereby improving the overall quality of care we provide to all of our patients, while still maintaining, if not improving, financial feasibility. Further expansion of the program to involve non-University affiliated PCPs may further improve the program’s ability to provide prompt quality care and better access for patients in more remote areas.

**Funding:** Clinical Revenue Support

**PUB313**

**eGFR Trajectory and Risks of Cardiovascular Events and ESKD in CKD Patients**

Kohei Ohorij, Maiko Kokubu, Masaru Matsui. Nara Prefecture General Medical Center, Nara, Japan.

**Background:** Growing evidence has shown the eGFR level is an established predictor of cardiovascular events, but the association of eGFR trajectory with cardiovascular and renal events remained limited.

**Methods:** We conducted a retrospective cohort study on 276 CKD patients in whom at least two measurements of eGFR levels to calculate eGFR slope were confirmed. We conducted a retrospective cohort study on 276 CKD patients in whom at least two measurements of eGFR levels to calculate eGFR slope were confirmed. From an access standpoint, eConsults were generally completed within 1-2 business days whereas the average wait time for an in-person consultation from referral creation was 33.8 ± 3.7 days.

**Conclusions:** Our nephrology eConsultation program has provided timely and remote subspecialty guidance for PCPs within our University’s health network and has overall been well-received by patients and PCPs. This model has the ability to decrease wait time for more complex patients requiring in-person consultation thereby improving the overall quality of care we provide to all of our patients, while still maintaining, if not improving, financial feasibility. Further expansion of the program to involve non-University affiliated PCPs may further improve the program’s ability to provide prompt quality care and better access for patients in more remote areas.

**Funding:** Clinical Revenue Support

**PUB314**

**Baseline Renal Characteristics and Trial Design for MIRROR RCT, Randomized Trial of Pegloticase with or Without Methotrexate for Uncontrolled Gout**

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**Background:** Twenty four percent of patients with gout1 and 49% of patients with uncontrolled gout (UCG)2 patients have CKD. Pegloticase (a pegylated recombinant uricase which rapidly dissolves urate) is associated with a 42% response rate,3 however preliminary evidence suggests co-therapy with immunomodulation such as methotrexate (MTX)5 may increase this response.3 The ongoing MIRROR randomized controlled trial (RCT) directly compares pegloticase w/wo MTX for UCG. We describe study design and baseline renal characteristics.

**Methods:** Enrolled patients had a serum urate [SU]>7 mg/dL, urate lowering therapy failure or intolerance, and ANV disposable tophs, recurrent flares, or chronic gouty arthropathy. Chronic immunosuppression, eGFR<40 ml/min/1.73m2, and GOF deficiency were key exclusion criteria. Patients who tolerated a 2-wk 5 mg/wk oral MTX run-in were randomized 2:1 to receive MTX or placebo (PBO). After a 4-wk MTX or PBO period, patients received 52 wks of p Pegloticase with weekly MTX MTX or PBO. Primary endpoint is 6-month response rate (pts with SU<6 mg/dL for at least 24% during Month 6).

**Results:** 42 US sites randomized 152 adults (54.7±12.6 yrs, 89% men, BMI 32.6±6.5 kg/m2) with UCG (SU 8.9±1.9 mg/dL, 13.9±1.0 g/yr gout history, 68% with clinical tophi). 21% had prior kidney stones. Mean eGFR was 69±17.8 ml/min/1.73m2 with 32% having eGFR<60 ml/min/1.73m2. Gout burden became more severe as CKD stage increased, as indicated by Physician Global Assessment, Health Assessment Questionnaire (HAQ), and affected joint count.


**Funding:** Commercial Support - Horizon Therapeutics plc

Mean values of gout severity assessments

**PUB315**

**Clinical Outcomes Associated with Systemic Lupus Erythematosus (SLE) over the 5 Years Prior to ESKD Diagnosis**

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**Background:** Lupus nephritis affects up to 38% of patients (pts) with SLE, many of whom may progress to ESKD.1 Despite high disease burden, data on clinical characteristics of pts with SLE in the years leading to ESKD diagnosis are limited. This study describes and compares the clinical outcomes of pts with SLE in the 5 years prior to ESKD diagnosis.

**Methods:** This retrospective analysis (GSK Study 215295) of United States administrative claims data (from IBM MarketScan database) included adult pts with SLE newly diagnosed with ESKD (International Classification of Diseases codes ICD-9-10) from March 2012 to December 2018. Study results focus on clinical outcomes in pts with 5-year continuous enrollment pre ESKD diagnosis.

**Results:** Of 1356 pts with SLE and ESKD identified, 81.8% were female; mean (standard deviation, SD) age was 46.7 (12.3) years. Of these pts, 616 had 5 years of continuous enrollment pre ESKD. Over the 5-year period pre ESKD, mean (SD) Quan-Chang Comorbidity scores increased from 1.8 (1.5) in Year 5 to 3.1 (2.0) in Year 1 prior to ESKD. The proportion of pts with severe disease also increased from 31.3% in Year 5 to 51.1% in Year 1 pre ESKD, and more pts experienced SLE flares (80.5% in Year 5 and 94.8% in Year 1 pre ESKD), particularly severe flares (Year 5: 11.9%; Year 1: 13.3%). Renal outcomes worsened each year for the 5-year period (Figure).

**Conclusions:** Prior to ESKD diagnosis, pts with SLE had high disease burden, particularly renal-related, which increased in the years leading to ESKD.

**Funding:** Commercial Support - GlaxoSmithKline
Gout in Advanced CKD Patients: Prevalence and Impact on Patient Health

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Background: Gout is associated with higher mortality risk,1 multiple comorbidities,2,3 and decreased quality of life.4 Impaired renal function increases gout risk,4 but gout prevalence and impact on advanced CKD patients have not been thoroughly described. This study reports health burden of gout in CKD patients under the care of nephrologists.

Methods: Nephrologists provided chart data on random Stage 3-5 CKD patients. Criteria to identify gout in this study: gout listed as comorbidity, urate-lowering therapy (ULT) use, or visible tophi/gout flare noted. Uncontrolled gout (UCG) was defined as serum urate >6 mg/dL, with visible tophi, ≥2 flares in past year, or ≥1 swollen/tender joint. Gout prevalence was examined with patients and without gout were compared.

Results: 111 physicians reported on 746 patients (55% male, 56.2 ± 11.7 yrs, BMI: 31.4 ± 10.9 kg/m²) with Stage 3-5 CKD (duration: 4.0 ± 4.8 yrs, eGFR: 32.2 ± 15.5 ml/min/1.73 m²). 173 (23%) met gout criteria, with highest frequency in Stage 3b and 4 (both 28%). Of gout patients, 13% had UCG, 29% had no formal gout diagnosis, and 38% were not using a ULT. Compared to those without gout, gout patients more often sought acute medical care (30% vs 7% in prior yr) and, at presentation, more often had urination changes (15% vs 7%) and shortness of breath (21% vs 14%; all p<0.02). Gout patients had more diagnoses of CKD-mineral bone disorder, ischemic heart disease, CHF, peripheral vascular disease, and chronic pain. Compared to controlled gout patients, UCG patients more often had pulmonary hypertension, joint issues, chronic pain, febriculost use, and anemic urose use.


Funding: Commercial Support - Horizon Therapeutics plc

Claims-Based Evaluation of Pegloticase Use in Gout Patients with a History of Kidney Transplant

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Background: Kidney transplant (KT) recipients have a high occurrence of gout due to reduced GFR and medications associated with hyperuricemia. Impaired renal function and drug interactions can make it challenging to effectively lower urate in this population. Pegloticase (pegylated recombinant uricase) rapidly metabolizes urate and has known efficacy for managing uncontrolled gout. However, clinical trials excluded organ transplant recipients and few cases of use in transplant recipients have been reported. This study examined pegloticase use in KT patients with uncontrolled gout in a large claims database.

Methods: The IQVIA database was used to identify pts with a history of KT (± ICD or POS code) receiving a pegloticase infusion. The number and type of concomitant immunosuppression (IM) prescriptions within 3 mo prior to/during pegloticase use were collected and the number of pegloticase infusions was evaluated. Pts were excluded if they returned to dialysis before the first pegloticase infusion because of graft failure or rejection.

Results: 91 pts were identified between 2015 and 2020. Pts with reported demographics (n=85) were predominately male (81%) and 58 ± 11 yrs old at the time of first pegloticase infusion. The most common comorbidities were hypertension (84%), hyperlipidemia (48%), anemia (46%), type 2 diabetes mellitus (40%), and heart failure (34%). Compared to 1st pegloticase claim, the 1st transplant code was 2.6 ± 1.7 yrs (mean ± SD) earlier and 1st gout code was 2.1 ± 1.7 yrs earlier. 61 pts (67%) had a tophaceous gout code. Transplant IM medication codes were available for 67 pts (74%), with the majority receiving tacrolimus (n=34), mycophenolate mofetil (n=33), and or cyclosporine (n=29). Pts received a mean of 13 ± 16 pegloticase infusions (median: 6; Q1: Q3: 4, 15), with 38% receiving ≥12 infusions and 20% receiving ≥20 infusions.

Conclusions: This real-world dataset demonstrated that KT patients with uncontrolled gout are being treated with pegloticase. A main consideration with pegloticase efficacy is potential development of anti-drug antibodies (ADAs). Given that solid-organ transplant patients are on IMs medications to preserve their grafted organ, this likely contributed to prevention of ADAs indicated by the longer average duration of therapy compared to other real-world pegloticase datasets.

Funding: Commercial Support - Horizon Therapeutics plc

Prediction of Mortality Among Patients with CKD: A Systematic Review

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Background: Chronic kidney disease (CKD) is a common medical condition with an increasing prevalence. To date, several clinical characteristics have been shown to be associated with mortality in CKD patients from regression analyses. However, the accuracy of mortality prediction has not been clearly elucidated. Thus, we aimed to demonstrate the predicting factors for mortality among CKD patients by utilizing the area under the receiver operating characteristic curve (AUC) analysis.
Methods: Ovid MEDLINE, EMBASE, and the Cochrane Library were searched through January 2021. Inclusion criteria were: 1) observational studies; 2) populations were non-transplant CKD at any stage; and 3) results were presented with AUC analysis with 95% confidence interval. AUC of 0.70-0.79 is considered acceptable, 0.80-0.89 is considered excellent, and more than 0.90 is considered outstanding.

Results: A total of 18 studies (n = 14,579) were included in the systematic review. 832 patients had non-dialysis CKD and 13,747 patients had dialysis-dependent CKD (2,160 hemodialysis, 370 peritoneal dialysis, and 11,217 non-differentiated mode of dialysis). Of 24 mortality predicting factors, none were deemed outstanding for mortality prediction. 7 factors were excellent predictors for mortality (NT-proBNP, BNP, soluble urokinase plasminogen activator receptor [suPAR], augmentation index, left atrial reservoir strain, C-reactive protein, and systolic pulmonary artery pressure). 17 predictive factors were in the acceptable range; two of which were echocardiographic factors (Image 1).

Conclusions: Several factors were predictive of mortality among CKD patients. Most of these factors could be identified by echocardiography, which may serve as an practical tool for mortality prediction in this population.

| Table 1 Characteristics of HF patients with CRS vs. those without CRS. |
|-----------------------------|-----------------------------|-----------------------------|
| Variable                   | CRS HF patients (n=77)      | Non-CRS HF patients (n=430) |
| Age (years)                | 60.0±11.2                   | 58.4±10.1                   |
| Male gender                | 25%                         | 56%                         |
| Diabetes                   | 42%                         | 45%                         |
| Hypertension               | 88%                         | 64%                         |
| Hypothyroidism             | 55%                         | 55%                         |
| Diabetic nephropathy       | 22%                         | 14%                         |
| Albuminuria                | 47%                         | 47%                         |
| Smoking                    | 47%                         | 28%                         |
| incubation index           | 35.7%                       | 33.9%                       |
| C-reactive protein         | 15.8±3.0                    | 12.3±11.3                   |
| Baseline vital signs       | 2.4±0.2                     | 2.4±0.3                     |
| Serum sodium (milli eq/l)  | 1.1±0.3                     | 1.03±0.2                    |
| Medications                | 1.609                      | 0.892                       |

Conclusions: RAASi are underutilized in CRS patients, a multidisciplinary approach is required to increase RAASi utilization in this population.

PUB321

Renal Function Outcomes at 5 Years from Radical and Partial Nephrectomies in Normal Renal Function Patients: An Insidious Tale of Failed Renal Hydropfiltrations

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Background: CKD represents a major postoperative long-term complication in renal surgery, both in radical (RN) than in partial nephrectomy (PN). Aim of our study was to compare the eGFR decay over time from pre-operative time surgery to 5 years follow up in RN and PN in normal renal function pts.

Methods: A multicentric cohort-study of 269 consecutive pts who underwent RN or PN due to the presence of a kidney mass was enrolled. A group of 42 kidney living donors was considered as control. We evaluated eGFR variation at the pre-surgical visit, hospital dismissal, 6,12,24,36,48,60 months. eGFR categories were created according to K-DIGO system. Comparisons between groups were performed using Kruskal-Wallis ranks sum test for numerical variables and Pearson’s Chi square test for categorical variables.

Results: Descriptive analysis is reported in table1. Two-way ANOVA underlined a significative difference for the type of surgery(p<0.001). The analysis showed the presence of a variation over time of the eGFR(p<0.001) that depends also on the surgery type(p<0.001).

Conclusions: RN and PN harbor a solid risk of post-operative CKD even in normal renal function pts. PN pts tend to vicariate the acute loss of nephron mass with an increase of eGFR over time, while PN renal function remains stable in time without hyperfiltration effect.
PUB322
Outcomes of Educational Initiatives for Advanced CKD

Background: Timing of kidney replacement therapy (KRT) and transplant referral in chronic kidney disease (CKD) G4 and G5 is a difficult topic. The COVID-19 pandemic has disrupted nearly all aspects of healthcare, including the process of KRT plan. This study examined if the addition of a Transition Coordinator (TC) improved KRT plan transition despite the pandemic.

Methods: Retrospective descriptive study examining patients at single academic practice with eGFR <20 that completed CKD educational program (CKDEP). Control Group: 5/1/19-1/31/20 with virtual or in-person CKDEP, no TC. Intervention Group (IG): 5/1/20-1/31/21 with virtual or in-person CKDEP with addition of TC. TC called patient monthly to assess barriers to KRT planning, assist with scheduling, and communicate with Nephrologist. “Success” was defined as having a KRT plan. Failure was defined as either urgent start dialysis via dialysis catheter (DC) or patients without KRT plan.

Results: CG had n=15 while IG had n=47. Both groups were evenly distributed with age, average eGFR (15). The CG had slightly higher rates of urgent starts and patients without KRT plan compared to IG (Table 1). Patients were referred for Vascular access +/- Transplant 20% (3) in CG and 23% in IG. PD +/- Transplant was chosen in 6.7% (1) of CG and 36% (17) of IG. Success and Failure rates were similar in both groups (Table 2).

Conclusions: Despite the pandemic, there was no overall change in rate of failure (urgent start or lack of KRT plan), however, individual decreases in these groups were noted. This could indicate that TC may improve outcomes when the pandemic is controlled. Increased interest in PD was noted which could indicate greater understanding via follow up provided by TC.

Table 1. Percentage of Urgent KRT vs no KRT plan due to intervention

<table>
<thead>
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<tbody>
<tr>
<td>Urgent start KRT</td>
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<tr>
<td>2 (13.3%)</td>
<td>1 (8.5%)</td>
</tr>
<tr>
<td>No KRT plan</td>
<td></td>
</tr>
<tr>
<td>2 (13.3%)</td>
<td>8 (17.3%)</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
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<td></td>
<td>47</td>
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Table 2

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<tr>
<th>Control Group Outcomes</th>
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<tbody>
<tr>
<td>Failure</td>
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<tr>
<td>Success</td>
</tr>
<tr>
<td>Total</td>
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PUB324
Inhibition of Old Astrocyte Specifically Induced Substance (OASIS) in Myofibroblasts Suppressed Kidney Fibrosis
Ayaha Yamamoto,1 Masanori Obana,1 Yoshiaki Miyake,1 Shota Tanaka,1 Makiko Maeda,1 Kazunori Imazumi,1 Yasushi Fujio,1 Osaka Daigaku, Suita, Japan; Hiroshima Daigaku, Higashihiroshima, Japan.

Background: Although kidney fibrosis is a critical event for the onset of renal failure, molecular mechanisms are not fully understood. Previously, we found that Old astrocyte specifically induced substance (OASIS), a transcription factor, exacerbated kidney fibrosis in part by increased bone marrow stromal cell antigen 2 (B2u), using conventional knockout mice; however, the cell specificity of OASIS function in kidney fibrosis remains to be elucidated. In this study, we focused on the role of OASIS in myofibroblasts to elucidate novel mechanisms of kidney fibrosis.

Methods: OASIS expression in human kidneys was examined by immunohistochemistry with anti-OASIS and α-SMA antibodies. Cultured myofibroblasts were treated with AEBSF, an inhibitor of OASIS activation. In addition, C37BL/6 mice were intraperitoneally injected with AEBSF for 9 consecutive days starting 2 days before unilateral ureteral obstruction (UUO) surgery. To examine the effects of OASIS in myofibroblasts on kidney fibrosis, myofibroblast-specific OASIS knockout (cKO) mice were subjected to UUO. Day 7 after UUO, kidney fibrosis was examined by Sirius Red staining, hydroxyproline assay and immunofluorescence analysis. Isolated murine myofibroblasts were treated with TGF-β1 for 24 hours and chromatin immunoprecipitation assay was conducted to test whether OASIS directly regulates the transcription of Collagen I and IIa.

Results: OASIS was increased in myofibroblasts in human fibrotic kidneys. AEBSF suppressed OASIS activation in myofibroblasts and reduced kidney fibrosis after UUO. Importantly, kidney fibrosis was attenuated in OASIS cKO mice compared with control mice (Sirius Red positive area (%): Control-contralateral:2.4±0.9, Control-UUO:23.4±2.9, cKO-contralateral:3.1±1.0, cKO-UUO:18.8±2.0, n=9-11). In addition, OASIS cKO mice showed reduced number of Ki-67-positive proliferative myofibroblasts in fibrotic kidneys. Finally, mRNA levels of Collagen I and IIa were decreased in the kidneys of OASIS cKO mice after UUO and OASIS directly bound to the promoter region of these genes in murine kidney myofibroblasts.

Conclusions: OASIS in myofibroblasts contributes to the development of kidney fibrosis. Suppression of OASIS signaling in myofibroblasts could be a novel therapeutic strategy against fibrotic kidney disease.

PUB325
Salvianolic Acid C Activates PPAR Signaling Pathway and Ameliorates Renal Fibrosis in Obstructive Kidneys
Junyan Lin, Ming Wu, Dongping Chen, Chaoyang Ye. Shuguang Hospital, Shanghai, China.

Background: Salvianolic acid C (SAC) is a component of Danshen, a widely used herbal medicine for the treatment of renal cardiovascular diseases. Renal interstitial fibrosis is a common pathway of all kinds of chronic kidney diseases progressing to the end stage of renal diseases. We aimed to study the effect of SAC on renal fibrosis and its underlying mechanisms.
Methods: After sham or unilateral ureteral obstruction (UOU) operation, 20-25g male C57BL/6J mice were treated with vehicle or SAC (10mg/kg) for 14 days. Moreover, normal rat kidney interstitial fibroblasts (NRK-49F) were treated with various concentrations of SAC (10 mM to 100 mM). Protein samples from in vivo and in vitro experiments were collected to assess renal fibrosis.

Results: Treatment with SAC reduced the deposition of interstitial matrix proteins in UOU kidneys as shown by Masson staining. The expression of Fibronectin, collagen-1 and α smooth muscle actin (αSMA) were increased in UOU induced fibrotic kidneys, which were down-regulated in SAC treated UOU kidneys. In parallel, treatment with SAC increased expression of fibronectin and collagen-1 in NRK-49F cells. RNA sequence analysis showed that multiple genes belong to the PPAR (peroxisome proliferator-activated receptor) signaling pathway were up-regulated by SAC treatment in UOU kidneys.

Conclusions: SAC inhibits renal fibrosis in obstructed kidneys possibly through activation of the PPAR signaling pathway.

Funding: Government Support - Non-U.S.

PUB326

Role of PAR-1 in Immune Activation and Tubulointerstitial Fibrosis During AKI-to-CKD transition
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Background: The high-affinity thrombin receptor protease-activated receptor-1 (PAR-1) has been recognized as a therapeutic target for cardiovascular intervention. Emerging evidence suggests that the coagulation cascade is activated in the kidney interstitium during AKI. Yet, the role of PAR-1 signaling in AKI to CKD transition remains largely unexplored.

Methods: We investigated the effect of PAR-1 deficiency in a longitudinal kidney fibrotic murine AKI to CKD transition model. PAR-1-/- and wild type mice were subjected to unilateral ischemia-reperfusion injury (UIRI) for 7, 14 and 28 days. Uninephrectomy of the contralateral kidney was performed one day before sacrifice to assess renal injury.

Results: After 14 or 28 days of UIRI, BUN was significantly lower in PAR-1-/- vs wild type mice. PAR-1-/- mice showed diminished kidney fibrosis with reduced ECM accumulation and expression of fibronectin, α-smooth muscle actin and collagen via TGF-β/Smad signaling after UIRI. Macrophage infiltration and inflammation was alleviated in PAR-1-/- ischemic kidneys in which macrophage M1-polarization and its secretory cytokine TNF-α were attenuated.

Conclusions: PAR-1 deficiency confers renoprotection by suppressing M1 macrophage activation, inflammatory and profibrotic responses during AKI and its subsequent transition to CKD. Funding: Health and Medical Research Fund (HMRF) of Hong Kong (grant no. 05163596), Research Grants Council of Hong Kong (General Research Fund, grant no. 17118720), and Hong Kong Society of Nephrology/HR Kidney Foundation Research Grant 2018.

PUB327

Increased Serum ApoCIII Levels in CKD Patients May Underlie the Impaired Delivery of Cholesterol to Hepatocytes and Increased Cardiovascular Disease (CVD) Risk
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Background: Increased CVD risk underlies the mortality in CKD patients but the underlying mechanisms are not completely defined. We reported earlier that the serum from CKD patients displayed an impaired ability to deliver cholesterol to hepatocytes demonstrating a likely defect in hepatic elimination of cholesterol (as bile acids and biliary cholesterol) returning to the liver from the peripheral tissues via lipoproteins (e.g., VLDL or HDL). Apolipoprotein C-III (ApoCIII) is associated with VLDL and HDL and, not only inhibits lipoprotein lipase and hepatic lipase, but inhibits the uptake of VLDL and HDL by hepatic lipoprotein receptors. Herein we examined the hypothesis that impaired ability of serum from CKD subjects to deliver cholesterol to hepatocytes was associated with increased serum ApoCIII.

Methods: ApoCIII levels were determined by ELISA in serum samples from 32 patients with CKD [stage 3 (N=15) and stage 4+5 (N=17)], 15 patients with established CAD and 15 healthy subjects from our earlier study. One-way ANOVA with Multiple group comparisons was used to determine significance of observed differences.

Results: While ApoCIII levels in healthy subjects and patients with established CAD were not significantly different, significantly higher ApoCIII levels were seen in patients with CKD 3 and CKD 4+5 (See Figure) compared to healthy subjects as well as compared to patients with CAD. This is consistent with the reported decrease in hepatocyte uptake of lipoprotein cholesterol from serum of CKD patients.

Conclusions: Circulating ApoCIII, the catabolism of which is related to kidney function, is increased in CKD and likely impairs the ability of VLDL and HDL uptake by hepatocytes. Using ApoCIII transgenic mice, the mechanistic details are currently under investigation.
endothelium
dendrotoysis
erythropoietin
epithelial sodium transport
endothelial cells
ESRD (end-stage renal disease)
endothelium
eosinophilia
epidemiology and outcomes
ethnic minority
extracellular matrix
Fabry disease
Fabry family history
fibroblast
fibronectin
fibrosis
gastrointestinal complications
gastrointestinal medications
gender difference
gene expression
gene therapy
gastrointestinal disease
gene transcription
genetic renal disease
genetics and development
gentamicin
generic nephropathy
glomerular disease
J Am Soc Nephrol 32: 2021
glomerulopathy (continued) .......... PO1446, PO1457, PO1458, PO1459, PO1465, PO1468, PO1474, PO1479, PO1480, PO1492, PO1501, PO1502, PO1503, PO1504, PO1514, PO1518, PO1519, PO1523, PO1524, PO1528, PO1529, PO1530, PO1531, PO1532, PO1536, PO1537, PO1541, PO1546, PO1554, PO1556, PO1560, PO1561, PO1566, PO1568, PO1571, PO1572, PO1573, PO1577, PO1580, PO1583, PO1603, PO1611, PO1614, PO1628, PO1644, PO1651, PO1653, PO1661, PO1662, PO1677, PO1710, PO1717, PO1882, PO1885, PO1886, PO1900, PO1915, PO1925, PO2215, PO2232, PO2233, PUB003, PUB172, PUB196, PUB198, PUB199, PUB226, PUB240, PUB241, PUB261

glomerular endothelial cells .......... TH-OR52, FR-OR15, FR-OR40, PO0510, PO0626, PO0645, PO0660, PO0664, PO1705, PUB244

glomerular epithelial cells .......... PO1398, PO1671, PO1715

glomerular filtration rate ............. TH-OR61, TH-OR62, TH-OR64, TH-OR65, TH-OR66, TH-OR67, FR-OR42, FR-OR41, FR-OR54, FR-OR58, SA-OR24, PO0531, PO0531, PO0537, PO0507, PO1006, PO1299, PO1307, PO1330, PO1578, PO1691, PO1735, PO1782, PO1827, PO1884, PO1888, PO1925, PO1934, PO1974, PO1975, PO2015, PO2069, PO2103, PO2233, PO2267, PO2278, PO2285, PO2289, PO2313, PO2317, PO2318, PO2319, PO2321, PO2322, PO2323, PO2324, PO2325, PO2328, PO2331, PO2332, PO2333, PO2342, PO2344, PO2347, PO2358, PO2362, PO2368, PO2388, PO2389, PO2390, PO2412, PO2419, PO2430, PO2431, PO2508, PO2518, PUB264

glomerular hyperfiltration .......... PUB304

glomerulonephritis .......... FR-OR37, FR-OR49, SA-OR33, SA-OR50, PO0110, PO1006, PO1019, PO2084, PO2089, PO3036, PO1159, PO1407, PO1415, PO1417, PO1420, PO1423, PO1424, PO1438, PO1460, PO1461, PO1463, PO1464, PO1480, PO1481, PO1489, PO1490, PO1491, PO1494, PO1495, PO1497, PO1498, PO1502, PO1504, PO1507, PO1515, PO1525, PO1525, PO1548, PO1551, PO1555, PO1558, PO1562, PO1564, PO1565, PO1573, PO1607, PO1615, PO1616, PO1618, PO1619, PO1890, PO1896, PO1939, PO2076, PO2158, PO2213, PO2216, PO2244, PO2246, PO2473, PUB156, PUB187, PUB189, PUB190, PUB192, PUB195, PUB199, PUB200, PUB201, PUB205, PUB206, PUB209, PUB213, PUB215, PUB217, PUB223

glomerulopathy .......... PO0733, PO1397, PO1408, PO1469, PO1482, PO1485, PO1508, PO1519, PO1547, PO1574, PO1576,
nephron

nephropathy

nephrotic syndrome

nitric oxide

nutrition

obesity

obstructive uropathy

organ transplant

osmolality

osteopontin

outcomes

peritoneal dialysis

peritoneal membrane

pharmacokinetics

phosphate binders

phosphate uptake

platelets

podoocyte

polyactic acid

polycystic kidney disease

polymerase chain reaction

polymorphisms

poxivirus infection

prec ponderance

pregnancy

priming

pulmonary hypertension

primary hyperparathyroidism

primary hyperoxaluria

primary hyperuricemia

primary sclerosing cholangitis

product design

protein degradation

protein expression

protein synthesis

protein turnover

protein ubiquitination

proteinuria

prophylaxis

posium

psychiatric disorders

psychomotor retardation

psychosocial factors

puberty

puberty

puberty

puberty

puberty

puberty

puberty

puberty

puberty