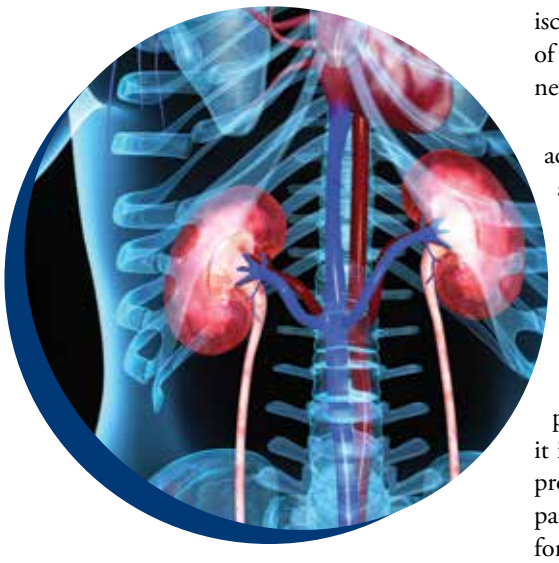
ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

ASN 50 years

Kidney News

May 2016 | Vol. 8, Number 5

Basic Science Research Yields Possible New Treatment Targets for AKI



Basic science research into the underlying mechanisms of acute kidney injury (AKI) poses unique challenges, making it difficult to identify promising new targets for prevention and treatment. This month, *The Journal of Clinical Investigation* presents three new and unique basic science studies exploring differing mechanisms of AKI and ischemia-reperfusion injury (IRI)—each of which identifies a potentially useful new therapeutic target.

"There is increasing awareness that acute kidney injury is both a major source of immediate morbidity and mortality and has a long-term impact on the development of chronic kidney disease," said Raymond Harris, MD, FASN, President of the American Society of Nephrology. "Unfortunately, we still lack effective therapies to prevent or treat AKI. Therefore, it is encouraging that these three studies provide important new insights into the pathogenesis and offer potential avenues for prevention and treatment of AKI."

Possible protective effect of vagal nerve stimulation

Previous research has suggested that ultrasound preconditioning of adrenergic neurons innervating the spleen has an anti-inflammatory effect—including protection against severe sepsis-induced AKI in a mouse model. Those studies identified the cholinergic anti-inflammatory pathway (CAP) as the central mechanism of protection.

In a new study, Tsuyoshi Inoue, MD, PhD, Chikara Abe, MD, and colleagues at the University of Virginia School of Medicine in Charlottesville sought to build on that knowledge by testing whether similar protective effects could be induced by ultrasound stimulation of the vagus nerve. In their mouse model, vagal nerve stimulation (VNS) ameliorated renal IRI via the same CAP activated by ultrasound. The findings included evidence that vagal efferents were the common pathway activating the CAP.

The results highlight the importance of neuroimmunomodulatory mechanisms of AKI—for example, the "interorgan crosstalk" by which injury to one kidney affects the response of the other kidney.

"In the setting of multiorgan failure, such neural mechanisms are likely to be even more important," writes Simon J. Atkinson, PhD, Vice Chancellor of Research at Indiana University–Purdue University, Indianapolis, in an accompa-

Continued on page 2

Climate Change May Contribute to Rising Rates of Chronic Kidney Disease of Unknown Origin

By Tracy Hampton

Chronic, severe dehydration linked to working in hot, humid climates for long hours may be accelerating rates of chronic kidney disease (CKD). Research published in the *Clinical Journal of the American Society of Nephrology (CJASN)* suggests that a condition called heat stress nephropathy may represent a disease of neglected populations, but one that may emerge as a major cause of poor kidney health as the climate continues to change (Glaser J, et al. *Clin J Am Soc Nephrol*. doi: 10.2215/CJN.13841215 [published online May 5, 2016]).

Over the next century, climate change and resulting water shortages are likely to affect a wide variety of health issues related to dehydration and heat stress—with risks increasing for cognitive dysfunction, malnutrition, waterborne infectious diseases, CKD, and other conditions. Some health situations, such as a great geographic spread of tropical and infectious diseases, may be more noticeable than gradual changes such as incremental increases in pollen counts that could lead to longer allergy seasons and worse asthma cases. In

Continued on page 3

Inside

AKI

Continued from page 1

nying commentary. "This is a relatively neglected aspect of AKI and one that, as this new work clearly demonstrates, deserves much more attention."

Dr. Atkinson said the findings of VNS and ultrasound show promise as a "practical preventative clinical strategy" for AKI—although, unfortunately, likely not for treatment of AKI that has already started to progress. "Given the risk and benefit profile of this strategy, one could imagine this approach being employed widely in critical care settings to reduce the risk of the serious consequences of AKI," he said.

Drs. Inoue and Abe and colleagues note that VNS is already clinically used for treatment of drug-resistant epilepsy and depression, and is being studied for use in inflammatory disorders such as rheumatoid arthritis and inflammatory bowel disease. They predict that future studies will inform the use of therapeutic ultrasound, as a less-invasive alternative to VNS, to prevent acute injury to the kidneys as well as other organs.

Estrogen and sugar blockade as potential AKI targets

Two additional papers provide evidence of other novel mechanisms and possible therapeutic targets for AKI and IRI. Wuding Zhou, MD, PhD, and Steven H. Sacks, MD, PhD, of King's College London led research on the contribution of C-type lectin collectin-11 (CL-11), a recently described innate immune factor, in the development of AKI. In a mouse model of ischemic injury, they found that CL-11 interacts with the stress-induced ligand L-fucose, triggering renal epithelial cell injury.

The findings clearly showed that the proximal tubule cell was the source of CL-11 responsible for mediating postischemic renal injury. The researchers also found that CL-11 binding to targeted epithelial cells was easily blocked by soluble monosaccharide inhibitors—suggesting a "physiological control mechanism that merits further exploration and exploitation" of CL-11 as a therapeutic target for hypoxic renal injury. Drs. Zhou and Sacks and colleagues add, "The broad expression of CL-11 and its putative ligands makes it possible that CL-11 operates on a wider scale, promoting inflammation and immunity in other organs and conditions."

David D. Aufhauser, Jr., MD, and Zhonglin Wang, MD, of the University of Pennsylvania performed a study to explore the previous finding of improved recovery from IRI in females compared to males. In a mouse model of renal ischemia, the researchers found that tolerance of IRI was "profoundly increased" in females versus males. They also noted an "intermediate phenotype" of IRI tolerance after neutering of either sex.

Further experiments found that renal IRI was greater in female estrogen receptor-α knockout mice, as well as a protective effect of supplemental estrogen administration to female mice before induction of ischemia.

Are the findings relevant to human transplant recipients? Analysis of United Network for Organ Sharing data on deceased-donor kidney recipients found a stronger association with delayed graft function in male versus female recipients. "We demonstrated that both donor and recipient hormonal milieus contribute to renal IRI tolerance," the researchers write. "Recipient effects are dominant in human transplant outcomes, while donor effects appear somewhat stronger in mice."

Obviously, more research will be needed to explore the clinical ramifications of the findings. But for now, Drs. Aufhauser and Wang and coauthors conclude, "[O]ur results demonstrate that sex affects renal IRI tolerance in mice and humans and indicate that estrogen administration has potential as a therapeutic intervention to clinically improve ischemia tolerance."

If the protective effects of estrogen are supported by further studies, there may be important implications for protecting against AKI as well, according to an accompanying editorial by Dr. Sanjeev Noel and colleagues of Johns Hopkins University. Coronary artery bypass graft surgery and other scenarios associated with a high risk of AKI "are excellent opportunities to examine the role of sex-specific differences in IRI and determine whether estrogen therapy can be beneficial toward protecting the kidney," they write.

New Site Extends Kidney News into Digital Space, Expanding Resources, Context

The American Society of Nephrology (ASN) has launched a new website, www.kidneynews.org, that extends *ASN Kidney News* as a digital platform for daily updates on news, context, and resources for all stakeholders in the kidney community.

Kidney News has been tremendously successful since launching in 2008. Thanks to its broad scope, *Kidney News* has amassed the largest audience of any ASN publication. Building on that success, this new site uses new digital tools to expand commentary and resources with a focus on developing an interactive presence for everyone interested in and affected by kidney health issues. The thoughtful perspectives and long-form content that have made the print version so popular will continue, while the new digital platform affords the ability to develop online coverage into a diverse resource updated daily, allowing more interactivity, and enabling users to personalize the site according to their interests.

A wealth of new content

Every month, Raymond C. Harris, MD, FASN, will share his thoughts on issues important to nephrology in a new column. Other contributions will reflect the diversity and dynamics of the profession, including a series on the nephrology fellowship experience, interviews with clinicians who will share experiences "from the field," insights from all members of the kidney care team, and podcast discussions with ASN research grant recipients.

Perspective pieces include a look at gaps in medical education curricula and how nephrology can address them, insights on the leadership qualities physicians need for career success, an up-close look at the advantages of training in smaller fellowship programs, and how priority areas in kidney health differ in various regions of the world. One of the most rapidly changing areas within the kidney community involves public policy. Kidney News Online will highlight policy issues relevant to all members of the global kidney community. Marking ASN's 50th anniversary is a series of contributions from ASN members recalling their observations from the first ASN annual meeting they attended.

The site also contains an archive of past *ASN Kidney News* articles, now available by article (instead of by issue only). The site includes all content from 2014 through the current day, and will continue to build the archive so all past content from *Kidney News* will be easily searchable and accessible. Other resources focus on information key to nephrology professionals, making it easy to find current and relevant information on ICD-10, MACRA, telemedicine, and other priority areas.

Kidney News Online also offers users the ability to personalize their experience by providing content that matters most to individual users. While access to the site is freely available without login or registration, the site can be integrated with ASN member profiles, or profiles nonmembers set up by registering on the site, allowing users to segment and prioritize new items based on their indicated interest. Those who want to personalize their content can then log in and the displayed content will be automatically updated according to the interest areas selected. Areas of interest can be modified at any time by visiting http://www.asn-online.org/myasn.

Serving the readers' interests

The site includes a feedback button on every page, and every section invites readers to send in suggestions for coverage to info@kidneynews.org. Suggestions from readers, combined with closely tracking analytics to see what sections are popular (or not) with users, will guide ASN as it evolves the site to meet the interests of users as well as the rapidly changing worlds of medicine, science, education, and health policy.

Climate Change

Continued from page 1

this latest *CJASN* research, investigators found that CKD that is not associated with traditional risk factors (CKDu) also appears to be increasing in rural hot communities as worldwide temperature progressively rises.

The researchers believe the risk for heat stress nephropathy—or CKD consistent with heat stress—has increased owing to global warming and an increase in heat waves, and it is having a disproportionate impact on vulnerable populations, such as agricultural workers.

"So far, the profile for impacted communities seems to be extreme heat and heavy labor. As you leave these extremely hot areas, there are far fewer cases recorded to date even though some of the other proposed risk factors remain relatively unchanged," said lead author Jason Glaser, of La Isla Foundation, in Nicaragua and the US. Decreasing precipitation exacerbates this epidemic by reducing the water supply and water quality as temperatures climb.

"We were able to connect increased rates of chronic kidney disease in different areas to an underlying mechanism—heat stress and dehydration—and to climate," said senior author Richard Johnson, MD, of the University of Colorado School of Medicine. "A new type of kidney disease, occurring throughout the world in hot areas, is linked with temperature and climate and may be one of the first epidemics due to global warming."

Mechanistically, dehydration may inhibit an individual's ability to excrete toxins as effectively as those who are well hydrated, leading to higher concentrations in the blood and kidney. Dehydration also results in the kidney concentrating the urine. While this is a healthy process that is normally protective in the acute setting, repeated dehydration appears to carry a cost to the kidney, according to Johnson. "Specifically, recurrent dehydration can lead to chronic elevations in vasopressin that may induce kidney damage," he said. "It can also activate processes that lead to fructose generation in the kidney that can cause local oxidative stress. High concentrations of uric acid can also precipitate in the concentrated urine and may exacerbate injury. These processes may be amplified by rehydrating with drinks high in sugar or high fructose corn syrup."

Earlier studies by the investigators in Nicaragua and El Salvador revealed a remarkable decrease of kidney function in male sugarcane cutters after high-intensity harvesting in hot conditions (García-Trabanino R, et al. *Environ Res* 2015; 142:746–755; Wesseling C, et al. *Environ Res* 2016; 147:125–132). Other studies have uncovered similar hotspots in other parts of Central America, as well as in South Asia, North and South America, Africa, and the Middle East.

"I don't think this disease is new—I think it has been with us for some time, and is more recognized due to increasing surveillance but also because the factors that put people at risk are exacerbated by extreme demands at the workplace to meet production needs," said Glaser. "The result is over 40,000 dead in the last 10 years in Mesoamerica and Sri Lanka alone. Of course, we think that due to surveillance being so inadequate for these at-risk populations, the disease is much more widespread."

To address the problem, interventions—such as those proposed in La Isla's and Solidaridad's Worker Health and Efficiency (WE) Program (www.weprogram.org)—are needed to improve worksite conditions and ensure adequate hydration. In addition, governments and scientists should work together to conduct epidemiological and clinical studies to document the presence of these epidemics and their magnitude. To this end, the World Health Organization, in collaboration with the Sri Lankan government, called together approximately 45 global experts from various organizations, institutions, and disciplines in late April. Also, Johnson is working with Glaser and others on a simple and practical protocol to estimate distributions of kidney function in rural communities globally. The Disadvantaged populations estimated glomerular filtration rate (eGFR) epidemiology study (DEGREE) will provide key information to inform hypotheses and to guide further research into the sources of CKDu.

ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

ASN 50 years

Kidney News

Editorial Staff
Editor-in-Chief: Richard Lafayette, MD
Executive Editor: Dawn McCoy
Design: Lisa Cain Design
Communications Assistant: Sara Leeds

Editorial Board:
Joseph Mattana, Winthrop University Hospital, New York, NY
Linda McCann, RD, RCN, Satellite Dialysis, San Jose, CA
Andrew King, MD, Scripps, San Diego, CA
Pascale Lane, MD, FASN, University of Oklahoma Health Sciences
Edgar V. Lerma, MD, FASN, University of Illinois – Chicago /Associates in Nephrology, SC
Uday S. Nori, MD, Ohio State University Wexner Medical Center
Glenda Payne, MS, RN, CNN, Nephrology Clinical Solutions
Jeffrey Petersen, MD, Amgen
Amy Williams, MD, Mayo Clinic, Rochester, MN

Advertising Sales:
The Walchli Tauber Group
2225 Old Emmorton Road, Suite 201, Bel Air, MD 21015
443-252-0571 Mobile
443-512-8899 *115 Phone
christine.kenney@wt-group.com

ASN Council:
President: Raymond C. Harris, MD, FASN
President-elect: Eleanor D. Lederer, MD, FASN
Past-President: Jonathan Himmelfarb, MD, FASN
Secretary-Treasurer: John R. Sedor, MD, FASN
Councilors: Mark D. Okusa, MD, FASN, Mark E. Rosenberg, MD, FASN, Anupam Agarwal, MD, FASN, Susan E. Quaggin, MD

Executive Vice President: Tod Ibrahim
Director of Communications: Robert Henkel

ASN Kidney News is published by the American Society of Nephrology
1510 H Street NW, Suite 800, Washington, DC 20005. Phone: 202-640-4660

www.asn-online.org

Postmaster: Please send address changes to *ASN Kidney News*, c/o Customer Service, American Society of Nephrology 1510 H Street NW, Suite 800, Washington, DC 20005.

Publications mail agreement No. 40624074. Return undeliverable Canadian addresses to PO Box 503, RPO West Beaver Creek, Richmond Hill ON L4B 4R6

ASN Kidney News (ISSN print 1943-8044 and online 1943-8052) is an official publication of the American Society of Nephrology, 1510 H Street NW #800, Washington DC 20005, and is published monthly. Periodicals postage paid at Washington, DC and at additional mailing offices. Subscription rates: $12 per year. To order, please email bhenkel@asn-online.org. Subscription prices subject to change. Annual ASN membership dues include $12 for *ASN Kidney News* subscription.

ASN President's Column

By Raymond C. Harris, MD, FASN

Raymond C. Harris, MD, FASN

Fifty years ago this year, a group of illustrious Nephrologists and prominent Internists met to form the American Society of Nephrology. Nephrology as a subspecialty had arisen both from studies of renal physiology and from studies and clinical activities related to metabolic and hemodynamic alterations related to kidney failure. As a field, it had clinical roots in cardiology. Indeed, the first renal society in the United States was the Renal Section of the Circulation Council of the American Heart Association. Although Nephrology was already an accepted subspecialty, the formation of the ASN signaled that in the United States, nephrology would no longer be considered only a branch or an offshoot of cardiology.

Now in 2016, our discipline is so varied and so complex that it is difficult to think of us as only related to cardiology (we all know that the major role of the heart is to pump blood to the kidney, anyway). Nephrologists are as much physiologists, endocrinologists, immunologists, rheumatologists, and microbiologists as we are "cardiologists." It is one of the strengths and the appeals of our profession that we encompass so many aspects of medical science in our care of our patients and in our study of the mechanisms of kidney function and diseases.

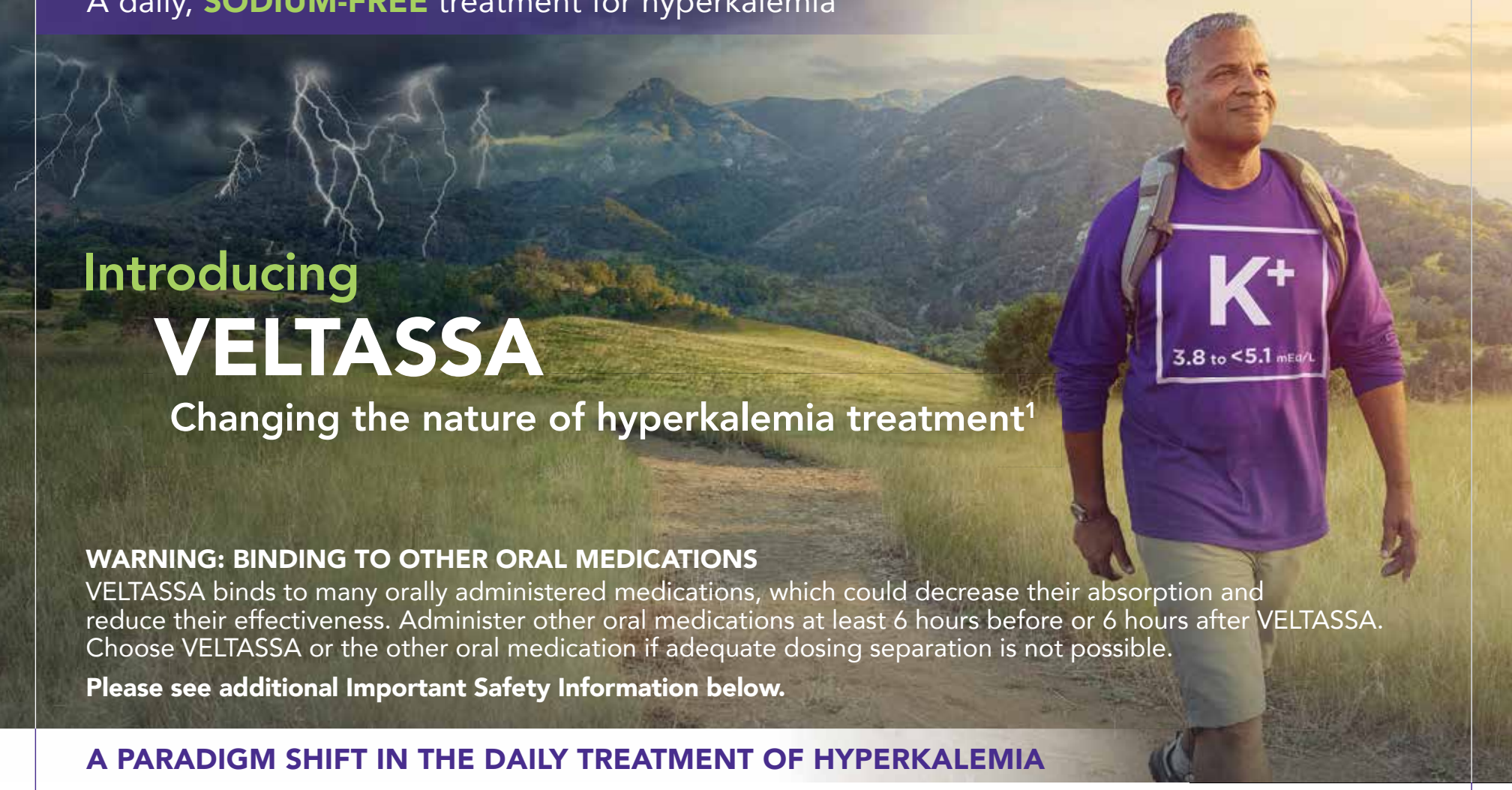
Currently, there seems to be a pervasive feeling of gloom and doom about Nephrology as a profession, and it is easy to pinpoint many of the reasons for this malaise: decreased interest in Nephrology careers by trainees, a perceived lack of job opportunities and a sense that Nephrologists may work too hard for too little pay, inadequate funding by NIH and other funding agencies, and increasing federal regulation on the one hand and encroachment of Nephrology's turf by other subspecialties on the other hand.

"It is one of the strengths and the appeals of our profession that we encompass so many aspects of medical science in our care of our patients and in our study of the mechanisms of kidney function and diseases."

All of these challenges are real and cannot be minimized. However, not every thing is so dreary. Surveys indicate that the majority of nephrologists in practice enjoy their work and are engaged and fulfilled; similarly, a majority of our trainees are happy that they chose Nephrology as a profession. Although funding for kidney research still remains inadequate, we have seen some significant breakthroughs in our understanding of the causes of many kidney diseases, while venture capital and industry are increasingly viewing kidney disease as a new frontier, so we can hope to have new treatments for our patients in the near future.

The ASN President's Column also appears in Kidney News Online at www.kidneynews.org.

A daily, **SODIUM-FREE** treatment for hyperkalemia



Introducing VELTASSA

Changing the nature of hyperkalemia treatment[1]

WARNING: BINDING TO OTHER ORAL MEDICATIONS

VELTASSA binds to many orally administered medications, which could decrease their absorption and reduce their effectiveness. Administer other oral medications at least 6 hours before or 6 hours after VELTASSA. Choose VELTASSA or the other oral medication if adequate dosing separation is not possible.

Please see additional Important Safety Information below.

A PARADIGM SHIFT IN THE DAILY TREATMENT OF HYPERKALEMIA

POWERFUL AND SUSTAINED SERUM K^+ REDUCTION

Up to 95% of patients with moderate hyperkalemia sustained serum K^+ within target range over a 1-year study†

SODIUM-FREE FORMULATION

Sodium-free non-absorbed polymer exchanges K^+ for calcium; 90 mL of water used for administration

WELL-STUDIED SAFETY PROFILE*

Most common adverse reactions leading to discontinuation were GI related (2.7%)

Indication and Limitation of Use

VELTASSA is indicated for the treatment of hyperkalemia.

VELTASSA should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action.

Important Safety Information

Contraindications: VELTASSA is contraindicated in patients with a history of a hypersensitivity reaction to VELTASSA or any of its components.

Worsening of Gastrointestinal Motility: Avoid use of VELTASSA in patients with severe constipation, bowel obstruction or impaction, including abnormal post-operative bowel motility disorders, because VELTASSA may be ineffective and may worsen gastrointestinal conditions. Patients with a history of bowel obstruction or major gastrointestinal surgery, severe gastrointestinal disorders, or swallowing disorders were not included in clinical studies.

Hypomagnesemia: VELTASSA binds to magnesium in the colon, which can lead to hypomagnesemia. In clinical studies, hypomagnesemia was reported as an adverse reaction in 5.3% of patients treated with VELTASSA. Approximately 9% of patients in clinical trials developed hypomagnesemia with a serum magnesium value <1.4 mg/dL. Monitor serum magnesium. Consider magnesium supplementation in patients who develop low serum magnesium levels.

Adverse Reactions: The most common adverse reactions (incidence ≥2%) are constipation, hypomagnesemia, diarrhea, nausea, abdominal discomfort and flatulence. Mild to moderate hypersensitivity reactions were reported in 0.3% of patients treated with VELTASSA and included edema of the lips.

Please see Brief Summary of Prescribing Information on following page, and full Prescribing Information at VELTASSAhcp.com.

*Across 4 studies up to 1 year.

†Approximately 69% of all patients studied completed treatment at 52 weeks.

Reference: 1. Bakris GL, Pitt B, Weir MR, et al; for AMETHYST-DN Investigators. Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease: the AMETHYST-DN randomized clinical trial. *JAMA*. 2015;314(2):151-161.

NOW AVAILABLE

Veltassa® (patiromer) for oral suspension

8.4g | 16.8g | 25.2g

relypsa

VELTASSAhcp.com

Findings

No Benefit of Adjuvant Antiangiogenic Drugs in Renal Cell Carcinoma

Adjuvant treatment with the oral antiangiogenic drugs sorafenib and sunitinib doesn't improve survival after complete resection of non-metastatic renal cell carcinoma (RCC), reports a placebo-controlled trial in *The Lancet*.

The study included 1943 patients with completely resected, non-metastatic clear-cell or non-clear cell RCC considered at high risk of recurrence. After stratification for recurrence risk and other characteristics, patients were randomly assigned to 54 weeks of treatment with sunitinib, sorafenib, or placebo. Disease-free survival was assessed by intention to treat.

The two active treatments had high rates of discontinuation related to toxic effects: 44 percent with sunitinib and 45 percent with sorafenib. This prompted reduction in the starting doses, which were then titrated up to the original full doses. However, toxicity remained high even at the reduced dosing regimen.

The trial was halted early owing to low conditional power for the primary endpoint. Disease-free survival was not significantly different between groups: median 5.8 years with sunitinib, 6.1 years with sorafenib, and 6.6 years with placebo. Frequent grade 3 adverse events included hypertension, hand-foot syndrome, rash, and fatigue. There were five deaths either related to treatment or occurring within 30 days after the end of treatment.

Renal cell carcinoma is a highly vascular tumor, proliferating via dysregulation of the vascular endothelial growth factor pathway. Sunitinib and sorafenib have been shown to improve survival in patients with advanced renal cell carcinoma [Haas NB, et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN e2805): a double-blind, placebo-controlled, randomised, phase 3 trial. *Lancet*. 2016; Mar 8. pii: S0140-6736(16)00559-6. doi: 10.1016/S0140-6736(16)00559-6].

Incompatible Live-Donor Kidney Transplant Improves Survival, Compared to Waiting

Patients who receive a kidney from an HLA-incompatible live donor have better survival than those who receive a deceased-donor transplant or who remain on the waiting list, concludes a study in *The New England Journal of Medicine*.

The study included 1025 adults who received kidney transplants from HLA-incompatible live donors at 22 US centers between 1997 and 2011. They were matched to control groups of patients who either remained on the waiting list or received a kidney from a deceased donor, and patients who remained on the waiting list without receiving a transplant.

One-year survival was 95.0 percent for patients who received kidneys from HLA-incompatible live donors versus 94.0 percent for waiting-list-or-transplant controls and 89.6 percent for the waiting-list-only controls. The differences remained significant through 8 years, when survival was 76.5, 62.9, and 43.9 percent, respectively.

The 8-year survival advantage of live-donor kidney transplant remained significant at all donor-specific antibody levels. For patients with a positive Luminex assay but a negative flow-cytometric cross-match, transplant from an incompatible live donor increased survival by 24.2 percentage points compared to waiting-list-or-transplant controls and by 42.1 percentage points for waiting-list-alone controls. The differences were 13.0 and 33.3 percentage points for patients with a positive flow-cytometric cross-match but a negative cytotoxic cross-match, and 9.5 and 27.3 percentage points for those with a positive cytotoxic cross-match, respectively. The findings were similar on sensitivity analysis excluding patients from the highest-volume center [Orandi BJ, et al. Survival benefit with kidney transplants from HLA-incompatible live donors. *N Engl J Med* 2016; 374: 940–950].

73%

OF NEPHROLOGISTS CHOOSE TO PRESCRIBE TRIFERIC OVER IV IRON[1]

Based upon:

- Maintaining hemoglobin without increasing iron stores
- Iron binding directly to transferrin and bypassing the reticuloendothelial system
- No anaphylaxis in over 100,000 patient administrations
- A decrease in blood transfusions
- No direct nursing time required for individual administration

TRIFERIC®
ferric pyrophosphate citrate

Replaces Iron and Maintains Hemoglobin without Increasing Iron Stores

www.triferic.com

Call 800-449-3353

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving parenteral iron products. Patients may present with shock, clinically significant hypotension, loss of consciousness, and/or collapse. Monitor patients for signs and symptoms of hypersensitivity during and after hemodialysis until clinically stable. Personnel and therapies should be immediately available for the treatment of serious hypersensitivity reactions. Hypersensitivity reactions have been reported in 1 (0.3%) of 292 patients receiving Triferic in two randomized clinical trials.

Iron status should be determined on pre-dialysis blood samples. Post dialysis serum iron parameters may overestimate serum iron and transferrin saturation.

Adverse Reactions

The most common adverse reactions (≥3% and at least 1% greater than placebo) in controlled clinical studies include: procedural hypotension (21.6%), muscle spasms (9.6%), headache (9.2%), pain in extremity (6.8%), peripheral edema (6.8%), dyspnea (5.8%), back pain (4.5%), pyrexia (4.5%), urinary tract infection (4.5%), asthenia (4.1%), fatigue (3.8%), arteriovenous (AV) fistula thrombosis (3.4%), and AV fistula site hemorrhage (3.4%).

References: 1. Rockwell Medical, Inc. Data on File. Independent Market Research Study Conducted in August 2015 with 103 U.S. Based Nephrologists – Based upon efficacy, safety, most appealing aspect, contrast to IV iron and choice between Triferic and IV iron.

ROCKWELL MEDICAL

TRIFERIC® (ferric pyrophosphate citrate) solution, for addition to bicarbonate concentrate

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE: Triferic is indicated for the replacement of iron to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD). **Limitation of Use.** Triferic is not intended for use in patients receiving peritoneal dialysis. Triferic has not been studied in patients receiving home hemodialysis.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS: Hypersensitivity Reactions. Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving parenteral iron products. Patients may present with shock, clinically significant hypotension, loss of consciousness, and/or collapse. Monitor patients for signs and symptoms of hypersensitivity during and after hemodialysis until clinically stable. Personnel and therapies should be immediately available for the treatment of serious hypersensitivity reactions *[see Adverse Reactions].* Hypersensitivity reactions have been reported in 1 (0.3%) of 292 patients receiving Triferic in two randomized clinical trials. **Iron Laboratory Testing.** Iron status should be determined on pre-dialysis blood samples. Post dialysis serum iron parameters may overestimate serum iron and transferrin saturation.

ADVERSE REACTIONS: The following adverse reactions are described below and elsewhere in the labeling: Hypersensitivity Reactions *[see Warnings and Precautions].* **Clinical Trials Experience.** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug may not reflect the rates observed in practice. In two randomized, placebo-controlled clinical trials, a total of 292 patients were administered Triferic for periods of up to 1 year *[see Clinical Studies in the Full Prescribing Information].* The mean total exposure in the randomized treatment period was 5 months. A total of 296 patients received placebo treatment for a similar time period. In the two studies, 64% were male and 54% were Caucasian. The median age of patients was 60 years (range, 20 to 89 years). Adverse events occurring in 3% or greater of patients treated with Triferic in the randomized clinical trials are listed in Table 1.

Table 1: Adverse Reactions Reported in Two Clinical Trials in at Least 3% of Patients Receiving Triferic and at an Incidence at least 1% Greater than Placebo

System organ class Preferred term	**Triferic N=292 n (%)**	**Placebo N=296 n (%)**
Number of patients with at least one adverse reaction	229 (78.4)	223 (75.3)
General Disorders and Administration Site Conditions		
Peripheral edema	20 (6.8)	11 (3.7)
Pyrexia	13 (4.5)	9 (3.0)
Asthenia	12 (4.1)	9 (3.0)
Fatigue	11 (3.8)	6 (2.0)
Infections and Infestations		
Urinary tract infection	13 (4.5)	4 (1.4)
Injury, Poisoning, and Procedural Complications		
Procedural hypotension	63 (21.6)	57 (19.3)
Arteriovenous fistula thrombosis	10 (3.4)	6 (2.0)
Arteriovenous fistula site hemorrhage	10 (3.4)	5 (1.7)
Musculoskeletal and Connective Tissue Disorders		
Muscle spasms	28 (9.6)	24 (8.1)
Pain in extremity	20 (6.8)	17 (5.7)
Back pain	13 (4.5)	10 (3.4)
Nervous System Disorders		
Headache	27 (9.2)	16 (5.4)
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	17 (5.8)	13 (4.4)

Adverse Reactions Leading to Treatment Discontinuation. In clinical trials, adverse reactions leading to treatment discontinuation included headache, asthenia, dizziness, constipation, nausea, hypersensitivity reactions, intradialytic hypotension, pruritus, and pyrexia. Adverse reactions reported in the treatment extension period were similar to those observed in the randomized clinical studies.

USE IN SPECIFIC POPULATIONS: Pregnancy. Pregnancy Category C. *Risk Summary:* There are no adequate and well-controlled studies of Triferic in pregnant women. In pregnant rats and rabbits, ferric pyrophosphate citrate caused developmental toxicity at maternally toxic dose levels that were higher than the maximum theoretical amount of iron transferred to patients from Triferic. The incidence of major malformations in human pregnancies has not been established for Triferic. However, all pregnancies regardless of exposure to any drug have a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. Use Triferic during pregnancy only if the potential benefit justifies the potential risk to the fetus. *Animal Data:* In a fertility and early embryonic development study in female rats, the maternally toxic ferric pyrophosphate citrate dose of 40 mg/kg administered three times per week by intravenous (IV) infusion was not toxic to the developing embryo. In embryo-fetal developmental toxicity studies, ferric pyrophosphate citrate was administered during the period of organogenesis as a one-hour IV infusion to pregnant rats and rabbits. No maternal or developmental toxicity was observed at doses up to 30 mg/kg/day in rats and 20 mg/kg/day in rabbits. Maternally toxic doses affected embryo-fetal development, resulting in post-implantation loss due to early resorptions, abnormal placentae, decreased fetal body weight and fetal head and vertebral malformations at 90 mg/kg/day in rats and vertebral malformations at 40 mg/kg/day in rabbits. A pre-and post-natal development study was conducted in pregnant rats with intravenous doses of ferric pyrophosphate citrate up to 90 mg/kg/day. The maternally toxic dose of 90 mg/kg/day resulted in reductions in the number of live offspring and lower offspring body weights. There were no adverse effects on survival of offspring at doses up to 30 mg/kg/day, or on behavior, sexual maturation or reproductive parameters of offspring at any dose level. **Nursing Mothers.** It is not known if ferric pyrophosphate citrate is present in human milk. Because many drugs are excreted in human milk and because of the potential for adverse events in nursing infants, a decision should be made whether to discontinue nursing or to avoid Triferic, taking into account the importance of iron to the mother and the known benefits of nursing. **Pediatric Use.** Safety and effectiveness have not been established in pediatric patients. **Geriatric Use.** In controlled clinical trials, 99 (28.6%) patients ≥ 65 years of age were treated with Triferic. No overall differences in safety and efficacy were observed between older and younger patients in these trials *[see Clinical Studies in the Full Prescribing Information].*

OVERDOSAGE: No data are available regarding overdosage of Triferic in humans.

NONCLINICAL TOXICOLOGY: Carcinogenesis, Mutagenesis, Impairment of Fertility. Studies examining the carcinogenic potential of ferric pyrophosphate citrate have not been conducted. Ferric pyrophosphate citrate was clastogenic in the in vitro chromosomal aberration assay in CHO cells in the presence of metabolic activation. Ferric pyrophosphate citrate was not mutagenic in the in vitro bacterial reverse mutation (Ames) test or clastogenic in the in vitro chromosomal aberration assay in CHO cells in the absence of metabolic activation or in the in vivo mouse micronucleus assay. In a combined male and female fertility study in rats, ferric pyrophosphate citrate was administered intravenously over one hour three times per week at doses of up to 40 mg/kg. No adverse effects on fertility or reproduction were noted.

Manufactured for
Rockwell Medical, Inc.
Wixom, MI 48393

Version: 09/2015

ROCKWELL MEDICAL

Complement-Mediated Glomerular Diseases

By Andrew Bomback

Why are nephrologists, particularly in the realm of glomerular diseases, talking about complement so much lately?

For years, many of the primary forms of glomerular diseases have been labeled idiopathic without a clear explanation of etiology other than a vague idea of autoimmunity. Focusing on the role of complement activation in the pathogenesis of glomerular lesions has allowed nephrologists to approach an answer to the question so often asked by patients: "Why did this happen to me?"

What should nephrologists know about complement?

The complement system is divided into three initiating pathways—the classical, lectin, and alternative pathways (Figure 1). Proper functioning of each pathway is required for coordinated activity of innate and acquired immunity (1), and each of these pathways has been implicated in the pathogenesis of glomerular disease. The three initiating pathways all converge at C3 to generate an enzyme complex known as C3 convertase that cleaves C3 into C3a and C3b. The association of C3b with C3 convertase results in generation of C5 convertase, which cleaves C5 into C5a and C5b. This cleavage triggers the terminal complement cascade, which is comprised of C5b, C6, C7, C8, C9, and regulators of these terminal complement proteins, such as clusterin and vitronectin. The terminal complement cascade culminates in the assembly of the membrane attack complex (also known as C5b-9) and subsequent cell lysis.

The classical complement pathway, which plays a major role in humoral immunity, is triggered into action by either IgG or IgM antibodies bound to antigen. This immune complex formation of antigen and antibody exposes a binding site on the immunoglobulin (Ig) for the first component of the classical pathway: C1. The lectin pathway is initiated by the binding of mannose binding lectin to the polysaccharide surface of pathogenic bacteria. This binding results in the formation of a trimolecular complex with two serine proteases and subsequent cleavage of C4 and C2, the next complement proteins in the cascade. The alternative pathway begins at the level of C3. Although microbial antigens can activate this pathway, the alternative pathway is also constitutively active via spontaneous hydrolysis of C3 to C3b, which binds factor B to yield the C3 convertase (C3bBb) of this pathway.

This distinction between the constitutively active alternative pathway and the triggered classical and lectin pathways manifests on immunofluorescence (IF) studies of kidney biopsies. Specifically, the presence of Ig staining (IgG, IgM, and/or IgA) alongside complement on IF microscopy implies that immune complexes of antigen/antibody have triggered consumption of the classical (Figure 2a) and/or lectin pathway proteins, whereas the presence of C3 staining alone without Ig (Figure 2b) suggests that the glomerular lesion is mediated by complement alone in an antibody-independent fashion, implicating the alternative complement pathway (2). For the treating nephrologist, these IF patterns, in turn, focus the workup and treatment of the glomerular disease on 1) the trigger in classical or lectin pathway-mediated injuries, with attention toward infectious, autoimmune, or malignant etiologies, versus 2) the dysregulation of the constitutively active alternative pathway in C3-mediated lesions, with attention toward genetic mutations or autoantibodies targeted at components of the alternative pathway (3).

What is an example of a complement-mediated glomerular disease?

A genetic or acquired (i.e., via autoantibodies or monoclonal gammopathies) defect in either the activation or modulation of the alternative pathway C3 convertase could lead to a transformation from low-grade physiologic activity ("tickover") to unrestrained hyperactivity (diseases of complement dysregulation). This loss of alternative pathway control can result in GN that, on IF, stains only (or dominantly) for C3, with complement proteins (and not immune complexes) mediating the glomerular injury. The term C3 glomerulopathy has been proposed as an umbrella classification for any GN with isolated or dominant C3 staining that, in turn, signals an etiology rooted in dysregulation of the alternative complement pathway (4). This term encompasses both dense deposit disease (formerly known as membranoproliferative GN type 2) and C3GN (formerly known as membranoproliferative GN type 1 or type 3 with isolated C3 staining). Carla Nester, MD, will review these disease states in more depth in an upcoming issue of *Kidney News*.

Are there more common glomerular diseases influenced by complement?

IgA nephropathy, the most common primary GN in the world, seems to be a disease mediated by both the lectin and alternative complement pathways. A multihit pathogenesis model of IgA nephropathy has emerged. Polymeric IgA1 with deficient O-linked glycosylation at the hinge region (galactose-deficient IgA1) forms immune complexes with IgG antibodies directed at the abnormal hinge region (antiglycan antibodies). These immune complexes then deposit in the mesangium (5). On light microscopy, mesangial proliferation and matrix expansion are the typical findings of IgA nephropathy, and diagnosis is established by dominant IgA staining on IF microscopy. The IF microscopy can also show subdominant staining of IgG, C3, C4d, and C5b-9 that colocalizes with IgA; C1q staining, however, is generally absent, suggesting no role of the classical complement pathway in the pathogenesis of disease. Instead, these IF findings suggest a potentially important contribution from the alternative and lectin complement pathways (6). IgA1 can activate both pathways in *vitro*, and pathway components are present in the mesangial deposits, including properdin and factor H in the alternative pathway and mannan binding lectin, mannan binding lectin-associated serine proteases 1 and 2, and C4d in the lectin pathway. Indeed, intensity of C3 staining and deposition of mannose binding lectin (as well as increases in urine complement components) have been shown in small studies to correlate with severity of IgA nephropathy (7–9).

How can these new findings affect treatment?

A better understanding of the role of complement in glomerular diseases, in turn, yields questions about targeting therapies at the complement pathways (10). The most logical target of therapy for diseases mediated by classical complement pathway activity is the trigger or inciting event that led to complement consumption—a documented infection, for example. In patients whose trigger is not apparent or in glomerular lesions where the lectin or alternative pathways seem to be playing the dominant role, complement-directed therapies may offer a more precise route of treatment than traditional use of nonspecific immunosuppression. Anticomplement therapies, such as eculizumab, a mAb that targets C5 and prevents the generation of membrane attack complex, have already shown benefit in atypical hemolytic uremic syndrome and some forms of C3 glomerulopathies. Other complement-targeting therapies are currently being studied in a variety of glomerular diseases, including lupus nephritis, IgA nephropathy, and antineutrophil cytoplasmic antibody-associated GN. The advent of therapies aimed at the complement cascade, now in the earliest phases, may promise breakthroughs in disease-specific treatments that will change the natural history of disease.

Andrew Bomback, MD, MPH, is assistant professor of medicine in the division of nephrology at Columbia University Medical Center in New York, NY.

References

1. Chen M, Daha MR, Kallenberg CG. The complement system in systemic autoimmune disease. *J Autoimmun* 2010; 34:J276–J286.
2. Sethi S. Etiology-based diagnostic approach to proliferative glomerulonephritis. *Am J Kidney Dis* 2014; 63:561–566.
3. Sethi S, Fervenza FC. Membranoproliferative glomerulonephritis—a new look at an old entity. *N Engl J Med* 2012; 366:1119–1131.
4. Fakhouri F, et al. C3 glomerulopathy: A new classification. *Nat Rev Nephrol* 2010; 6:494–499.
5. Suzuki H, et al. The pathophysiology of IgA nephropathy. *J Am Soc Nephrol* 2011; 22:1795–1803.
6. Maillard N, et al. Current understanding of the role of complement in IgA nephropathy. *J Am Soc Nephrol* 2015; 26:1503–1512.
7. Espinosa M, et al. Association of C4d deposition with clinical outcomes in IgA nephropathy. *Clin J Am Soc Nephrol* 2014; 9:897–904.
8. Liu LL, et al. Glomerular mannose-binding lectin deposition is a useful prognostic predictor in immunoglobulin A nephropathy. *Clin Exp Immunol* 2013; 174:152–160.
9. Liu L, et al. C3a, C5a renal expression and their receptors are correlated to severity of IgA nephropathy. *J Clin Immunol* 2014; 34:224–232.
10. Bomback AS. Anti-complement therapy for glomerular diseases. *Adv Chronic Kidney Disease* 2014; 21:152–158.

Continued on page 8

Continued on page 7

Figure 1
Overview of the complement cascade

The classical mannose-binding lectin and alternative complement pathways converge at C3 to generate an enzyme complex known as C3 convertase that cleaves C3 into C3a and C3b. However, the pathways are distinct in their points of origin. The classical complement pathway is activated by either IgG or IgM antibodies bound to antigen. The lectin pathway is initiated by the binding of mannose-binding lectin (MBL) to the polysaccharide surface of pathogenic bacteria. The alternative pathway begins at the level of C3 and is constitutively active via spontaneous hydrolysis of C3 to C3b, which binds factor B to yield the C3 convertase (C3bBb) of this pathway.

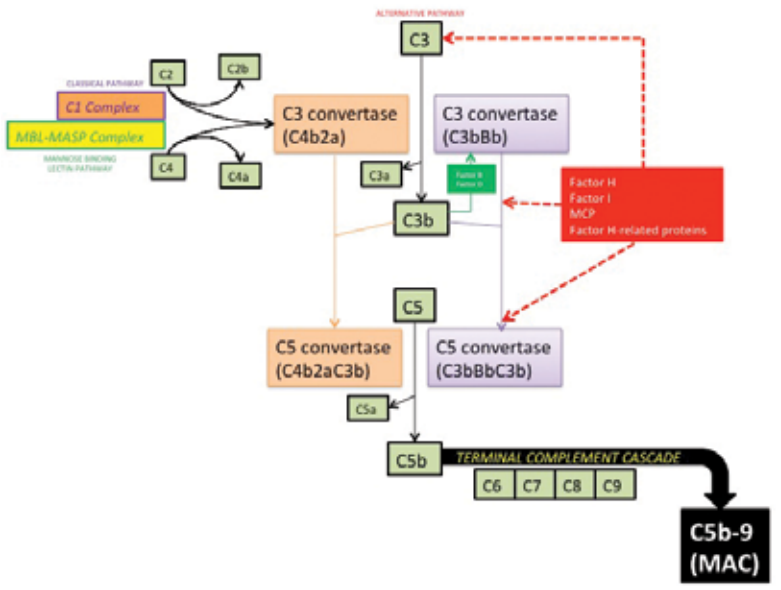
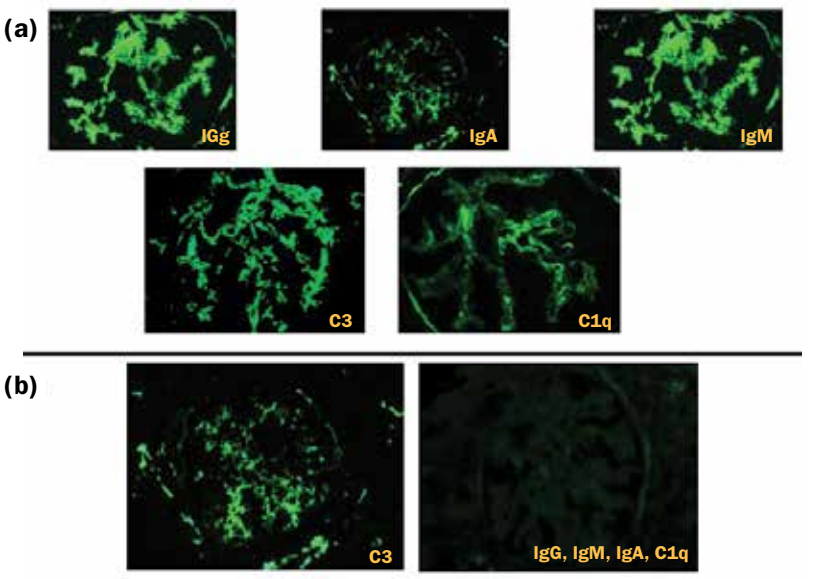


Figure 2
Immunofluorescence studies in kidney biopsies of (a) lupus nephritis and (b) C3GN

(a) The hallmark staining in lupus nephritis, termed a "full house," is positive for C1q, C3, IgA, IgM, and IgG. The presence of Igs and C1q denotes activation of the classical complement pathway by immune complexes of antigen and antibody. (b) In C3GN, C3 is the sole (or dominant) staining, suggesting that complement deposition is antibody independent and therefore, caused by activity of the alternative pathway.



Kidney Care: A Model for Transforming Medical Education

By Mark E. Rosenberg, MD, FASN, and Rachel N. Meyer

Rapid changes are occurring in the healthcare environment, with greater emphasis placed on the care experience, its value/cost, and health outcomes. These changes are outpacing educational reforms, leading to growing gaps between medical education and clinical practice. Particularly concerning is trainee readiness for such gap areas as systems redesign, quality improvement and patient safety, population health, and interprofessional practice. Medical education must continue to evolve to address these gaps, and nephrology is at the cutting edge of these transformations.

Greater attention is being paid to the continuum of medical education and the competencies needed to advance from undergraduate medical education (UME; medical students) to graduate medical education (GME; residents and fellows) to clinical practice. Competency-based assessment of entrustable professional activities such as ability to perform a history and physical, or form a differential diagnosis, is becoming the preferred method of assessing performance. As a consequence there is a move from the traditional block rotation of clinical clerkships to more longitudinal clinical experiences.

The classic Flexnerian model of UME with two years of foundational knowledge (anatomy, genetics, biochemistry, histology, and others) followed by two years of clinical education, is changing to earlier and more meaningful clinical education experiences, a shorter time for learning the foundational knowledge, and greater integration of basic and clinical science across all years of medical school. Incorporating public health, health policy, quality improvement, and interprofessional practice into the curriculum is narrowing gaps between medical education and clinical practice.

Integrating basic and clinical science

Nephrology exemplifies how the understanding of basic science can greatly inform the clinical approach to patients. For example, understanding the action of antidiuretic hormone in the cortical collecting duct, or the trafficking of aquaporin 2 can inform the differential diagnosis of diabetes insipidus or the approach to hyponatremia. Part of the teaching of clinical fluid and electrolyte disorders is simultaneous re-education in renal physiology. Similarly, renal histology informs the interpretation of kidney biopsies, and understanding the basics of complement regulation can help with the approach to glomerular diseases.

Focusing on population health

In the US, funding for the treatment of patients with end-stage renal disease (ESRD) is unique in that every American with kidney failure is eligible for Medicare coverage under the Medicare End-Stage Renal Disease (ESRD) Program, regardless of age or income. As a consequence, ESRD is a disease that is monitored closely. The United States Renal Data System (USRDS) established in 1988 is the national data registry that collects, analyzes, and reports information on ESRD patients in the US. USRDS reports on the epidemiology of ESRD including incidence and prevalence, trends in mortality, and demographic characteristics of the ESRD population. This data enables investigation into relationships among demographics, treatment modalities, and clinical

outcomes. More recently patients with chronic kidney disease (CKD) not on dialysis, and patients with acute kidney injury are reported and studied.

Social determinants of health play a prominent role in CKD. A population health approach enhances understanding of the epidemiology, case detection, therapy, and outcomes of CKD and can inform similar efforts in other fields.

Incorporating bundled payment, pay-for-performance, and accountable care into practice

The costs for Medicare coverage of ESRD have presented unforeseen challenges as the ESRD population has grown in numbers and increased in complexity. ESRD beneficiaries comprise <1% of the Medicare population but account for about 7% of total Medicare spending. Unique opportunities and motivations exist to test new models of payment and care for ESRD patients.

The Monthly Capitated Payment (MCP) code that compensated nephrologists for the outpatient care of dialysis patients was the first bundled or "global" physician payment structure and models today's shift toward global payments. The ESRD Prospective Payment System (PPS) implemented in 2011 provides a single payment to ESRD facilities for renal dialysis services. This is the first fully bundled (with the exception of certain oral-only medications) mandatory payment system, intended to keep costs down by shifting risk and reward to providers. The Quality Incentive Program (QIP) was the first mandatory "pay-for-performance" system designed to promote high quality care of dialysis patients. The ESRD Seamless Care Organization (ESCO) program is a new payment and service delivery model launched in 2015. This is the first disease-specific accountable care model. In the ESCO, coordinated care is provided for beneficiaries by dialysis clinics, nephrologists, and other providers. ESCOs are accountable for both clinical and financial outcomes.

Nephrology has also broken ground in the area of immigration policy. The Emergency Medical Treatment and Active Labor Act (EMTALA) requires hospital Emergency Departments that accept payment from Medicare to provide appropriate medical screening examination to patients seeking treatment regardless of citizenship, legal status, or ability to pay. When such treatment is administered there are no provisions for reimbursement. For undocumented immigrants with ESRD, EMTALA requires that patients receive dialysis as an emergency measure. In some states, patients rely on emergency dialysis care as a routine way of getting access to dialysis. Nephrologists are confronted with conflicting mandates of trying to provide high quality, high value care but bound by the limitations raised by the undocumented immigrant status of patients.

Applying quality improvement measures to improve patient safety

Nephrology was one of the first specialties to develop clinical practice guidelines with the Kidney Disease Outcomes Quality Initiative (KDOQI) and the international Kidney Disease Improving Global Outcomes (KDIGO) evidence-based care algorithms.

Clinical performance measures have informed quality improvement, public reporting, and payment. In the dialysis unit, an interprofessional team reviews clinical performance measures and designs quality improvement projects to improve these measures and hopefully downstream patient outcomes. The Centers for Medicare and Medicaid Services (CMS) publishes dialysis facility metrics on Medicare.gov—Dialysis Facility Compare (www.medicare.gov/dialysisfacilitycompare/) providing quality data for patients, providers, and the public to review. Facilities are rated up to 5 stars for such outcomes as hospitalizations, mortality, transfusions, dialysis adequacy, serum calcium, the use of arteriovenous fistulas, and length of time a dialysis catheter is in place. As discussed above, the ESRD Quality Incentive Program (QIP) is the first pay-for-performance program in a Medicare prospective payment system.

Improving treatment through interprofessional practice

Models of healthcare delivery are evolving from individual practitioner-patient interactions to team-based care. Health professional schools are working to incorporate principles of interprofessional education and practice into the curriculum. In fact the Liaison Committee on Medical Education (LCME) that sets the accreditation standards for medical schools in the US has implemented a standard for interprofessional education stating "the core curriculum of a medical education program must prepare medical students to function collaboratively on health care teams that include other health professionals. Members of the health care teams from other health professions may be either students or practitioners."

Nephrology is a model specialty to teach health professional students about team-based care; it has successfully applied interprofessional practice for many years. Care of the CKD patient requires a coordinated approach by multiple caregivers in addition to the nephrologist. Dieticians, pharmacists, nurses, advanced practice providers, social workers, dialysis technicians, psychologists, and others all actively participate in care of the CKD patient. In fact, an interdisciplinary team approach to care is required in the Conditions of Coverage for dialysis units that dictate the minimum health and safety rules that all Medicare and Medicaid participating dialysis facilities must meet.

The chronic care model: improving outcomes and putting patients at the center of care

The chronic care model integrates community, health system, self-management support, delivery system design, decision support, and clinical information systems to manage chronic disease. The approach incorporates patient, provider, and system level interventions with a major focus on the patient being at the center of care. This model has been applied in nephrology in the form of the CKD Clinic. Advanced Chronic Kidney Disease Certification process through the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) is available for recognizing CKD Clinics that have met JCAHO standards. Studies have demonstrated improved outcomes when CKD patients are in interdisciplinary clinics including better adherence to clinical practice guidelines, reduced hospitalizations, improved survival, decreased progression, and higher placement rate of arteriovenous fistula.

Integrating palliative care into clinical practice

ESRD is a life-limiting illness requiring an intentional and proactive approach to care decisions. For patients with CKD, advanced care planning can align treatment goals with patient preferences before there is a healthcare crisis in which the patient may be impaired and unable to make a decision. Critical issues, especially whether the patient wants dialysis, need to be addressed and are a model for shared decision making, emphasizing the need to inform patients about the risks and benefits of treatments taking into account the patient's values, preferences, and life goals.

Delivering care to remote locations

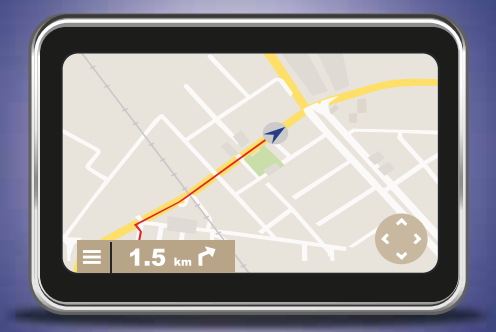
Strategies are needed to improve care of patients with chronic disease especially those in more remote locations. This care should reduce adverse health outcomes, provide a timely and convenient care experience for patients no matter their location, and be of high value with the potential to reduce overall health system costs. Telehealth is an example of such a strategy. It has been used, with or without case management, in various forms to manage patients with chronic illnesses including heart failure, chronic obstructive pulmonary disease, and diabetes mellitus. Despite its growing use, telehealth outcomes have been variable, and its expense is often considerable, emphasizing the need to carefully assess its effectiveness.

The use of telehealth in nephrology to manage patients with CKD was the subject of a recent randomized controlled trial performed at the Minneapolis VA Health Care System *(Am J Kid Dis* 2016, in press). In this trial, delivery of health care by an interprofessional team using telehealth could be effectively implemented for both rural and urban patients, but did not reduce the risk of death, hospitalization, emergency department visits, or admission to skilled nursing facilities compared with usual care. While the overall study was negative, rural patients may be a select subgroup in which the use of telehealth and interprofessional care may offer benefits, particularly in areas that are scarce in subspecialty care. Telehealth may be an effective strategy for following patients in rural dialysis units, as support for home dialysis therapies, and for routine follow-up of kidney transplant recipients.

Conclusions

Healthcare today is evolving rapidly, and medical education must keep pace and prepare students and trainees to enter today's healthcare environment and advance future care. Nephrology continues to stay ahead of the curve. The success nephrologists have had incorporating change can be applied to more effectively connect medical education to the delivery of high quality, patient-centered care.

Mark E. Rosenberg, MD, FASN, is Professor of Medicine and Vice Dean for Education at the University of Minnesota Medical School in Minneapolis, MN.



Drivers have GPS.

Get connected to patients on home peritoneal dialysis.

Amia Automated PD System with Sharesource

The **Amia** Automated PD System features touch-screen navigation with voice-guided directions and full-color animation.

The **Sharesource** Connectivity Platform features a two-way connection between a patient's **Amia** cycler and their clinic, on demand access to timely, accurate historical treatment data, and the ability for clinicians to adjust device programs remotely.

TOGETHER, the **Amia** Automated PD System with **Sharesource** Connectivity Platform helps you get connected to your patients on home peritoneal dialysis.

Rx Only. For safe and proper use of these devices mentioned herein, refer to the Instructions For Use or appropriate Operator's Manual.

Making possible personal.

Dialysis Patients have Amia

VOICE GUIDED

TOUCH SCREEN

REMOTE MONITORING

FULL-COLOR ANIMATION

For more information, please contact your local Baxter representative today.

USMP/MG91/15-0019 05/16

Baxter

Distinguished Conversations

It is a great pleasure to continue our series of "Distinguished Conversations" in recognition of ASN's 50th anniversary. In each conversation, a leader in nephrology invites a mentor or esteemed colleague for a discussion of nephrology, past and future. This month Sharon Moe, MD, FASN, interviews Sharon Anderson, MD, FASN.

Dr. Moe is Professor of Medicine and Director, Division of Nephrology, in the Department of Medicine, at the Indiana University School of Medicine. Dr. Moe has been actively involved in ASN for a number of years, including serving on the Communications, Postgraduate Education, Program, and Nominating Committees as well as the Media Relations Task Force. She served as ASN Councilor from 2009 to 2016 and as ASN President in 2014–2015. Dr. Moe's translational research involves the study of all aspects of chronic kidney disease–mineral bone disorder (CKD-MBD). The 150 publications in her name have contributed greatly to the advancement of knowledge and treatment of CKD-MBD.

Dr. Anderson is Professor of Medicine and Chair of the Department of Medicine at Oregon Health & Science University, where among many awards, she received the OHSU School of Medicine Dean's Award, one of the school's highest honors, in 2001 and again in 2014. Dr. Anderson received her bachelor's degree from the University of Maryland and her MD from Louisiana State University Medical Center. Dr. Anderson is a past Chair of the Nephrology Board, American Board of Internal Medicine; past Chair of the NIH General Medicine "B" Study Section; and presently serves on the highly influential NIH NIDDK Council as well as the NIH Council of Councils. She was elected to the ASN Council in 2004 following a decade of dedicated service to the Society. She served as ASN President in 2009–2010, and was the first woman in this role. She has authored or co-authored well more than 150 publications and received the David Hume Award from the National Kidney Foundation this year.

Richard Lafayette, MD, editor-in-chief, ASN Kidney News

Sharon Moe, MD, FASN

Sharon Anderson, MD, FASN

Dr. Moe: How did you decide to go into nephrology? What was your runner-up in terms of specialties?

Dr. Anderson: My decision to go into nephrology was serendipitous. I had vague thoughts of being a primary care doctor when I started medical school.

The nephrology training I received as a medical student wasn't very good, and I think this is an area we can improve on. So although I started my internship without a clear idea of what I wanted to do, I was lucky that my second rotation was on a renal ward. We had terrific patients on the ward—patients with glomerulonephritis, dialysis patients, and transplant recipients. I had an outstanding attending, Dr. Bill Bennett, a former ASN President. The combination of interesting patients and a dynamic attending made me fall in love with nephrology, and I never really considered anything else.

Dr. Moe: Many institutions now employ hospitalists and no longer have renal wards. How has the movement away from renal wards affected the practice of nephrology?

Dr. Anderson: I think we've lost a great opportunity for instilling interest in nephrology.

Many people, including me, were able to get medical students, interns, and residents excited about nephrology through the experiences on the renal ward. Hospitalists are now the role models on the wards, so we've lost this very important contact with our trainees.

The other issue that I think is of great concern is that fewer and fewer nephrologists attend on the general medicine wards. When I was a junior faculty member, everyone had to attend on the general medicine wards, whether they were good at it or not. With all the changes in the curriculum and training, nephrologists' exposure, even to residents, is much less than it used to be. Our residents, for example, do renal consult rotations, but sometimes they last just a week or two. By not being front and center and right there with trainees, we are losing a huge opportunity to get them excited about nephrology.

Dr. Moe: How has your career in nephrology changed during your lifetime? What other aspects of nephrology have changed?

Dr. Anderson: I think careers in nephrology and nephrology itself have changed in dramatic ways. Sometimes when I'm talking to young people, I tell them that when I was in training, if you were an academic, there was sort of a clear path to follow. You did a research fellowship—it was all bench research in those days—and you wandered up the academic path. Then maybe you became a division head later on.

Now there are so many different paths people can follow. The career of being a clinician educator has blossomed in recent years, and deservedly has become a very viable and vibrant career path.

Obviously, the practice of nephrology has changed in that we have more novel therapeutics. We still don't have a lot of great treatments for CKD, but at least for

some of the glomerular nephridities, there are exciting treatments. I think the practice of dialysis will always be a huge part of what we do, but that seems to be evolving and changing too, with a greater emphasis on quality and perhaps more scrutiny of how we do things.

And then of course there's everything beyond traditional nephrology. Many people have found successful careers in pharma, for example, or in other academic roles, such as my current role as chair of medicine.

Dr. Moe: As chair of medicine, how do you recruit top talent and balance academia, teaching, patient care, and your own research? How do you advise junior faculty to find their niche?

Dr. Anderson: I will start with my own career. I heard a great anecdote once: A young person went up to a senior academic and said, "You are a quadruple threat. You've done everything—you're a great teacher, a great researcher, a great administrator, and a great clinician. How in the world can you do everything so well?" The answer was, "Not all at the same time." I think that is the perfect answer.

Our careers have chapters. For much of my career, I was a basic scientist and spent much of my time in the lab, sometimes teaching and doing clinical work, sometimes a bit of administration. During the current chapter of my career as chair of medicine, I'm obviously spending a lot of time doing administration. So you can't do it all at one time, but you can certainly do it all over the course of a career. For me, that keeps it fresh—there are new challenges with each chapter of my career.

I tell young people that they need to be proactive in deciding on their career path. When I was younger there was basically one career path, and nobody knew there were others. Now there are many different career paths, and young people need to actively seek the mentors they need and focus on their chosen path. To be outstanding clinicians and educators, they need to get training in how to apply modern concepts of teaching and perhaps try to not get too distracted participating in clinical trials, for example.

There is a short period of time when young people can begin their junior faculty career and dabble in all kinds of things. Here is my advice: Figure out what you want; go out and get the additional training you need, whether it's an additional postdoc equivalent, educator training, or whatever; and keep your eye on where you're going.

Dr. Moe: ASN is celebrating its 50th anniversary this year. As you think back to what you remember about ASN, what was your first encounter with the society?

Dr. Anderson: I was fortunate to encounter ASN very early in my career. As a medical resident, I decided I wanted to pursue nephrology and got involved in some research projects with David McCarron doing rat studies, partially as an elective but mostly on nights and weekends, which is how research seems to work when you're a resident. I was fortunate to get a couple of projects done, and during my first year of fellowship I had a poster at the ASN meeting. I went to the ASN meeting early in my career and have gone every year since.

Most training programs are very proactive about getting their fellows involved with ASN, and as you know, ASN offers programs to bring residents and even medical students to the meeting. The earlier we can get young people to come to the meeting and see all the exciting things that are going on, the better.

Dr. Moe: How has the ASN meeting changed since your first meeting?

Dr. Anderson: In the good old days when it was held at the Omni Shoreham Hotel in Washington, DC, the ASN meeting was much smaller and more intimate, which was nice in its own way because you had a pretty good chance of running into everybody you knew. Now it has become much larger—as it should.

There was less clinical science at the early ASN meetings. Over time, it became clear that not only is clinical nephrology something we all continue to do, but we have a very large audience who are interested—perhaps more so than in the past—in clinical and translational science. Embracing clinical and translational science, by definition, helped to expand the society.

There are so many different things going on in nephrology now. All the efforts on quality and performance improvement, onco-nephrology, and many other subfields of nephrology did not exist 10 or 20 years ago.

The ASN meeting is the premier nephrology meeting in the world, and we are very fortunate to be able to attend.

Dr. Moe: What did it feel like to be the first woman president of ASN?

Dr. Anderson: I felt that it was about time, don't you think?

I believe my time as the 46th president of ASN mirrored what was going on in the larger society. When I gave my presidential talk, I showed a picture of the founders of ASN, who were eight white men—they were the ones doing nephrology back in 1966. Obviously the field has greatly expanded in terms of not just gender, but ethnicity as well. I felt it was really a step forward for our society to have a woman as president.

Men outnumber women in nephrology today, although not nearly to the extent as when I was in training and coming up the ranks. But I think that the more the leadership as well as the membership of ASN can reflect the diversity in our profession, the better. I was honored and pleased to be the first woman president of ASN. And then of course my colleague, Dr. Moe, was the second ASN woman president, so we're making progress.

There is a short period of time when young people can begin their junior faculty career and dabble in all kinds of things. Here is my advice: Figure out what you want; go out and get the additional training you need, whether it's an additional postdoc equivalent, educator training, or whatever; and keep your eye on where you're going.

Dr. Moe: Yes, and now we have our third and fourth Councilors (who will be president), Eleanor Lederer and Susan Quaggin, so things do change.

How did being ASN president help you look at the ASN in a different way, in terms of how we approach trainees and how we look at health care? Do you feel that being in that kind of position changed your view of ASN in general?

Dr. Anderson: I was pleased that I was able to be part of helping ASN move in the direction of greater diversity. As you know, increasing diversity was one of my crusades as ASN president. I felt it was extremely important that, for example, all of the committees and advisory groups not only have reasonable representation of women, but also that women be represented among the leadership of the groups.

The focus is not just gender diversity, but also experiential diversity. We need to get young people involved and active in leadership roles. The business world learned that diversity is good for business a long time ago, and it's good for us as well. We need to understand the interests and needs of our constituents and tailor our programs and offerings to fit.

Dr. Moe: What do you think we should be doing over the next 50 years—or perhaps the next 5 or 10 years?

Dr. Anderson: We need to be continually attentive to trends that will affect not just patient care, but how we practice. For example, we are moving rapidly into the era of value-based care. It's not going to be all relative value unit (RVU)–based, and I would love to see ASN take the lead in helping nephrologists figure out the best way to deliver that care.

Continued on page 16

Continued from page 15

You and I both work at the VA, so we know that the VA has advantages in this arena. We've been doing telemedicine and electronic consults at the VA for years. I can electronically answer the vast majority of the renal consults I receive without wasting the patient's or my time in a 20-minute visit that isn't needed. My university is just starting to pilot e-consults, so they're learning.

All of medicine is struggling to figure out how best to deliver value-based care. Perhaps ASN, for example, could explore some sort of best practices in health care delivery—not just clinical guidelines or the best way to treat diabetic nephropathy—but innovative ways to deliver health care. There are some great experiments out there, such as the SCAN Echo project, which involves telehealth for people who live in remote locations, as do many CKD patients. We should always aim to improve the efficiency, patient centeredness, and quality of the care we deliver.

I was a training program director for a long time, and although I am not one now, I think nephrology training will be a challenge for the next several years. We need to rethink it. This might sound heretical, but one of the reasons hospital medicine is so popular is because it is shift work. To those of us of a certain age, the concept of shift work and the resulting discontinuity in patient care is anathema, yet shift work is what seems to be selling these days. I would love to see nephrology training programs continue to innovate and look at different ways to fashion the training experience, because training programs need to be perpetually attentive to what is going on in the practice world.

Dr. Moe: Do you think long work hours have driven a move to this so-called shift-training? In terms of general medical education, we've made a lot of changes in the past 5 or 10 years. Do you foresee any additional changes down the road? Will the 80-hour work week continue?

Dr. Anderson: It is hard to know. There has been a bit of a backlash to duty hour restrictions now. It is difficult to prove that duty hour restrictions actually improve patient safety, which was the original goal. The tradeoff for residents who aren't so tired is endless handoffs of patients, so it is difficult to figure out who actually "owns" the patient or has been following the patient for more than a couple of days.

I do not think the concept of not wanting to work 100 hours a week is going away. Part of it is a generational thing. Millennials and younger people are better at demanding a better work–life balance than people ever were when I was their age. Whether or not you prescribe how many hours interns can work at a time, we will not again see the days when they were on every third night and stayed overnight in the hospital. We have to adapt as well. Maybe knowing that you are likely to be called in the middle of the night is distancing people from nephrology. I haven't seen much in the way of, for example, nephrology fellow nocturnists, so to speak. Perhaps we could do what hospitalists, cardiologists, and ICU doctors do, and have someone whose job it is to be there at night for a whole week, with a day team coming in fresh each morning.

Again, I am not a training program director currently so there may be more going on than I'm aware of. But I think we have to do something to stem the diminishing attractiveness of nephrology to people looking at careers.

Dr. Moe: I think we have to think outside the box. We've been stuck in a rut with the same types of programs for a long time, and a lot of work is going on at ASN to think outside the box. But it will take time for us to come to whatever might be the new norm.

Dr. Anderson: Yes. ASN will be at the forefront of these efforts. The society's very active Training Program Directors (TPD) group meets every year at the ASN meeting, and is also very active throughout the year. TPD is a great example of how ASN contributes to our profession by fostering and supporting an active group of very dedicated educators who want to figure out the right thing to do and how to do it.

Dr. Moe: Tell me about your professional accomplishments over the years. If you had to state the best three things you accomplished, what would they be?

Dr. Anderson: I was fortunate early in my research career as a fellow to be involved in some very important work. I was part of the group that originally looked at the use of ACE inhibitors in experimental progressive CKD. It worked very well in rats, and turned out to benefit patients as well. If I did not accomplish anything else in my career, I would be humbled and honored to be recognized for my involvement in this work that helped advance understanding and treatment of kidney disease. That work was exciting and will always remain with me.

Much of my career since then has been a bit accidental. So I am talking out of both sides of my mouth when I say that young people need to figure out exactly what they want to do very early on. I did not. I was moving along in my career and opportunities came my way. My first administrative role was a number of years ago. I was working at the Portland VA when my section chief walked into my office and said, "I'm leaving the VA, and I want you to be the interim section chief." I started crying and said, "You can't leave, I need you here. I can't be the acting section chief." But the opportunity was there and I took it, and really enjoyed it.

I think this makes an important point—that you need to keep your eyes open to opportunities that come your way. I'm a big fan of Sheryl Sandberg, COO of Facebook, and her book *Lean In* is an inspiration to me. She has a great anecdote: One of her friends wrote to her and said, "I was going to apply for this or that job with you, but then I realized everybody is asking you for a job, so let me do this. Let me ask you what you need." Sandberg replied, "I really need help with HR." Her friend said she would do it. Sandberg makes the point that your career may veer off in unexpected paths, but you need to be open and take the opportunities. I have done that too.

At one point, the Dean came to me and asked if I'd be the first ever Associate Dean for Faculty Affairs and Faculty Development. I said "Okay… what is that exactly?"

I've found my attention span, career wise, is about 6 or 7 years. By the time I've been in a job that long, I'm starting to think that maybe I should think about doing something else. I've been fortunate to be in places where those opportunities are there.

As you know, I did my training at the Beth Israel Hospital and Brigham and Women's Hospital and was there for several years. Then I started looking for jobs. One of the reasons I chose Oregon Health & Science University, which is where I am now, is that I sensed it would be a place where multiple opportunities might arise, including things that I wasn't even thinking about then. And that has happened. For me, career changes have been about keeping an open mind and taking a leap. As is often said, "Life begins when you step outside your comfort zone."

Dr. Moe: I basically had the same situation. One thing led to another entirely different position. Sometimes, things come your way and provide an opportunity that changes your career trajectory. I think if you worry too much about what the future holds and try to plan too much, sometimes it might just hold you back.

Dr. Anderson: Exactly.

Dr. Moe: What about balancing career and personal life? As ASN's first woman president, what would you tell the women in our profession who want to know how you managed and how it affected your personal life?

Dr. Anderson: Everyone needs to be able to prioritize, and everyone's priorities are going to be different. I find it very helpful to compartmentalize. When I'm in work mode, I'm working. When I'm not, I'm not. Compartmentalizing requires developing some personal skills, and you have to figure out how to do that for yourself. I really love my job and always have, so it's not a strain on me to put in the number of hours needed to do it well. But I have also realized that I need to carve out some time for myself. Some would argue I'm not as good at that as I should be, but I strive to do it.

You can think of your career in chapters. There are times when you will be able to put in more hours and energy into your work and other times when you cannot. And that's okay. You just have to do what seems right at the time. Whether you are taking part-time work for child care—or whatever—you will see what the world looks like when you return.

Dr. Moe: I think one of the advantages of a career in medicine is that there are so many different ways to make it work. You can work in many different environments and locations and it can be part-time or full-time. When I speak with people thinking about medicine as a career and all the years of planning needed, I tell them, "Yes, but when you're finished, you can do whatever you want to do and carve it out for yourself."

Dr. Anderson: Absolutely. One of the reasons I decided to go into medicine was that I sensed (with a lot less knowledge than I have now) that there would be multiple opportunities out there. Nephrology is a great field. I hope it continues to be as vibrant as it is and that we get a little better about recruiting people into it.

Policy Update

CMS Plans to Consolidate EHR, Value-Based Payments Under New MACRA Rule

By Bridget M. Kuehn

Physicians will have more flexibility to choose quality indicators and less restrictive electronic health record requirements under a streamlined value-based payment system proposed by the Centers for Medicare & Medicaid Services (CMS) in April.

The Medicare Access and CHIP Reauthorization Act of 2015 (MACRA) passed in spring 2015 repealed the Sustainable Growth Rate formula Congress had used to establish Medicare payments for physicians and accelerated CMS's shift toward value-based payments. Now, a proposed rule published in the Federal Register on April 27, 2016, gives physicians a first look at how these value-based payments could be structured. The rule outlines the agency's plans to consolidate the patchwork of programs currently used to reward physicians for efficient and high-quality care. It is the first step toward implementing the changes, and the agency will accept comments on the rule until June 27 (http://www.regulations.gov).

Under the proposed rule, the Physician Quality Reporting System, the Value Modifier Program, and the Medicare Electronic Health Record (EHR) Incentive Program and alternative payment models like Accountable Care Organizations (ACOs) would all be streamlined into the Quality Payment Program. Physicians could choose to participate via 2 tracks: the Merit-based Incentive Payment System (MIPS) or Advanced Alternative Payment Models (APM).

"By proposing a flexible, rather than a one-size-fits-all program, we are attempting to reflect how doctors and other clinicians deliver care and give them the opportunity to participate in a way that is best for them, their practice, and their patients, " said Patrick Conway, MD, MSc, CMS acting principal deputy administrator and chief medical officer.

Physicians who choose the MIPS track will receive a score that would help determine their reimbursements. Half the score would be based on 6 quality measures chosen by the physician. An additional 25% of the score will be based on the physician's use of technology. Again, physicians will be able to choose from a menu of options that are intended to boost information sharing. Practice improvements such as care coordination, patient engagement, or patient safety efforts will account for 15% of the score. Cost as judged by Medicare claims and adjusted by specialty will account for the final 10% of the score. The first scores will be assigned in 2017 and will influence 2019 CMS payments.

"Our initial review suggests that CMS has been listening to physicians' concerns," said Steven J. Stack, MD, president of the American Medical Association in a statement. "In particular, it appears that CMS has made significant improvements by recasting the EHR Meaningful Use program and by reducing quality reporting burdens."

For nephrologists, the "devil may be in the details" of the more than 900-page rule, which may take some time to fully understand, said John R. Sedor, MD, FASN, chair of the American Society of Nephrology's Public Policy Board and a nephrologist at MetroHealth in Cleveland, Ohio. Still, Sedor also sees the shift away from fee-for-service as an opportunity for nephrologists to help develop new care models that better meet their patients' needs.

"We're going to have to really use this to think about what we want to do as kidney doctors," Sedor said. "We've been very dialysis-centric because of the previous reimbursement models. We need to reconnect with our roots where we take care of patients with complex disease or multiple diseases and try and work them through various transitions in care."

Physicians who meet CMS's criteria for participation in APMs would be exempt from the MIPS reporting requirements and be eligible for bonus payments. But not all organizations participating in APMs would qualify as "advanced." Only models in which clinicians accept some financial risk would qualify. For example, the Comprehensive ESRD Care (CEC) Initiative track for large dialysis organizations would qualify as an advanced APM, because its participants do assume a sufficient level of financial risk based on their performance, according to Rachel Meyer, Associate Director of Policy and Government Affairs at ASN.

But the small dialysis organizations participating in the CEC Initiative would not qualify because they don't assume a large enough risk. These small CECs would have to participate in MIPS, but they would get a more favorable score than physicians who are not participating in any type of APM, Meyer noted.

"Clearly, CMS wants to drive physicians into risk-based models," said Sedor.

Still, Sedor sees an opportunity for nephrologists to play a bigger role in managing medically complicated kidney patients within these models.

"It gives us an opportunity to try and influence how APMs are implemented and what the role of specialists will be in them," Sedor said.

Industry Spotlight

Fresenius Kidney Care Launches

Fresenius Kidney Care is the new name of the dialysis division of Fresenius North America.

"We created this name to better communicate our approach to helping people with kidney disease thrive and continue doing the things that matter most to them," said Ron Kuerbitz, CEO of Fresenius Medical Care North America. "The Fresenius Kidney Care name underscores the focus and attention that our caregivers provide to our patients' unique health needs at more than 2200 dialysis centers across the nation."

Along with the name change, Fresenius Kidney Care has launched a consumer-friendly website, www.freseniuskidneycare.com. The site offers educational materials and patient stories, with information on treatment options, tips for better health while on dialysis, appropriate recipes, and more. Content is organized for patients in various stages of kidney dialysis. Fresenius Kidney Care has also launched new Facebook, Twitter, and YouTube pages.

Biosimilars Gain Traction

One year after the biosimilar version of Zarxio, manufactured by Novartis and a competitor of Amgen's drug Neupogen, landed on the market, the US Food and Drug Administration (FDA) has approved a second biosimilar drug. (Neupogen is used to treat neutropenia, lack of certain white blood cells caused by cancer, bone marrow transplant, or chemotherapy).

In early April, the FDA approved a biosimilar called Inflectra, by Celltrion (Incheon, South Korea, with marketing by Pfizer) that works in a way highly similar to that of Johnson & Johnson's Janssen Biotch drug Remicade or infliximab, which treats autoimmune diseases like Crohn's disease and rheumatoid arthritis, *Business Insider* reported. The drug is based on a monoclonal antibody and has a more complex biochemical structure than Zarxio.

Hospira Inc. (acquired by Pfizer last year) has an application before the FDA for a biosimilar that would compete with Amgen's Epogen and J&J's Procrit. These drugs are used to treat anemia in patients with chronic kidney disease who are on dialysis.

While Celltrion was pleased to announce the approval, Morningstar analyst Damien Conover said the branded Johnson & Johnson drug could lose half its sales by 2020, according to Reuters.

Biologic drugs are made from living cells and involve highly complex manufacturing processes. Biosimilar drugs are created to be similar to a biologic drug already approved by the FDA (the reference drug) and must be shown to be highly similar.

Congress has allowed biopharmaceutical innovators making the reference drugs 12 years of data protection to keep the market in balance, phrma.org reported, so that the market will not fill with a fleet of new, cheaper biosimilar medications that might discourage producers of reference drugs from pursuing innovation and creating original drugs through expensive development work.

In its first 4 months on the market, Zarxio was a factor in reducing Amgen's share of the market to 76 percent, wrote Biopharma-Reporter.com, a website that follows biopharmaceutical news. "Zarxio was launched at a 15% discount to its reference product," and was used by patients on dialysis as well as many others.

New Onco-Nephrology Curriculum Available Online

By Mark A. Perazella, MD, Chair of the ASN Onco-Nephrology Forum

On behalf of the ASN Onco-Nephrology Forum, it is a pleasure to announce the release of a new Onco-Nephrology Core Curriculum available online at www.asn-online.org/education/distancelearning/curricula/.

Developed in collaboration with other onco-nephrology experts, the ASN Onco-Nephrology Forum (ONF) series of 19 chapters covers most of the important onco-nephrology topics (Table 1). The chapters include Take Home Points and Board style questions to highlight important issues. The goal is to provide ASN members—including veteran nephrologists, newly minted nephro-clinicians, fellowship trainees, and other interested healthcare providers—the building blocks upon which further information can be added as the field advances. The ONF hopes the curriculum provides the initial framework to achieve this goal.

It should come as no surprise that cancer is associated with significant morbidity and mortality. Cancer is the second leading cause of death today (1). Both acute kidney injury (AKI) and chronic kidney disease (CKD) are highly prevalent in cancer patients, particularly those with renal cell cancer, liver cancer, multiple myeloma, leukemias, and lymphomas (4,5). Kidney disease frequently occurs in 5 major cancers: prostate, breast, gynecologic, lung, and colorectal (6).

In addition, mortality is higher in cancer patients with AKI/CKD. Possible explanations for this increased mortality include the association of AKI development with cessation of effective chemotherapeutic regimens, the presence of pre-existing CKD limiting the use of otherwise curative anti-cancer regimens, or both. The combination of cancer and kidney disease has led to the recognition that nephrology and oncology are intricately linked and require our full attention as a growing area of specialization (Figure 1). Thus, "onco-nephrology" was born and has steadily grown in many medical centers, hospitals, and clinics.

What exactly is onco-nephrology? It is a rapidly growing subspecialty area of nephrology that recognizes that kidney disease in cancer patients has become an important source of nephrology consultations over the past 10 to 15 years. Nephrologists have traditionally treated cancer patients with various forms of kidney disease. However, oncology patients now make up a significant number of the patients nephrologists see for kidney-related problems in the outpatient clinic, on the inpatient floors, and in the medical ICU.

The increase in cancer patients with kidney disease is in part related to the high incidence rates for many malignancies, as well as the overall reduction in cancer death rates owing to more effective chemotherapeutic agents that include biologics and stem cell therapies. These improved therapies have led to an increase in the number of cancer survivors who develop and survive with AKI and/or CKD due to their malignancy and/or its associated treatment.

Kidney injury from cancer occurs via several different mechanisms. Cancer can directly injure the kidneys through tumor infiltration or production of nephrotoxic (paraneoplastic) substances. Also, the growing number of therapeutic agents that extend patient lives can cause various types of AKI or CKD along with serious electrolyte and acid–base abnormalities.

Although typical AKI and electrolyte/acid–base disturbances can be handled by the practicing clinical nephrologist, it has become increasingly clear that many of the renal issues are more complex and highly specialized. For example, many nephrologists were not trained in the era of bone marrow/hematopoietic stem cell transplant, which can lead to a number of unusual and complicated forms of kidney injury.

In addition, the number of anti-cancer drugs with various types of nephrotoxicity has increased dramatically, and their entry into clinical practice continues at a fast pace. Patients may develop multi-organ illness requiring ICU-level care and renal replacement therapy. Certain malignancies are more likely to cause this severe form of multi-organ dysfunction and may be associated with higher mortality rates.

When this type of critical illness occurs in the setting of advanced malignancy, it also raises questions about the appropriateness of aggressive care and the role of palliation. Thus, care for oncology patients has become more specialized and complicated, requiring collaboration among nephrologists, oncologists, intensivists, and palliative care specialists.

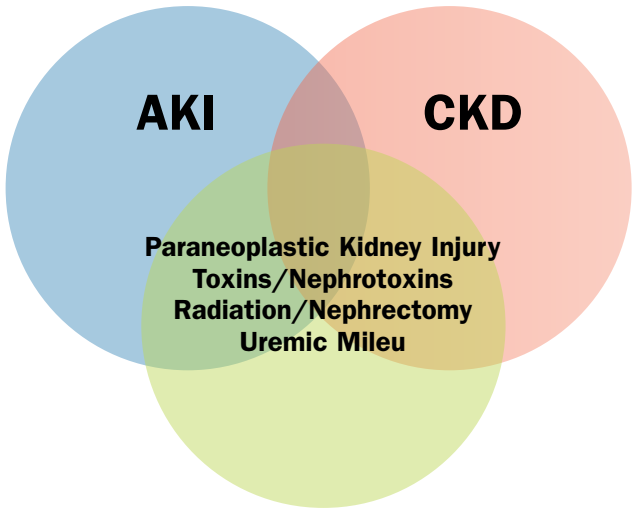
The remarkable advances made in cancer management present both new opportunities and complex challenges for the oncology and nephrology communities. It is essential for nephrologists to be informed and actively involved in certain facets of cancer care.

Nephrologists need a better understanding of the rapidly evolving field of cancer biology and its therapy in order to become valuable members of the cancer care team, and to provide the best nephrology care possible. Developing expertise in the practice of onco-nephrology will enable nephrologists to be well prepared to provide care for the unique renal complications that develop in patients with cancer.

Table 1
Onco-Nephrology Core Curriculum topics and authors

Topic	Author(s)
1. Onco-Nephrology: Growth of the Kidney–Cancer Connection	Mark Perazella, Mitchell Rosner
2. Why do we need an Onco-Nephrology Curriculum?	Mark Perazella, Mitchell Rosner
3. AKI associated with Malignancies	Amit Lahoti, Benjamin Humphreys
4. Tumor Lysis Syndrome	Amaka Edeani, Anushree Shirali
5. Electrolyte and Acid–Base Disorders and Cancer	Anushree Shirali
6. Glomerular Disease and Cancer	Divya Monga, Kenar Jhaveri
7. Hematologic Diseases and Kidney Disease	Ala Abudayyeh, Kevin Finkel
8. Clinical Tests for Monoclonal Proteins	Nelson Leung
9. Hematopoietic Stem Cell Transplant-related Kidney Disease	Sangeeta Hingorani, Joseph Angelo
10. Radiation-associated Kidney Injury	Amaka Edeani, Eric Cohen
11. Chemotherapy and Kidney injury	Ilya Glezerman, Edgar Jaimes
12. Pharmacokinetics of Chemotherapeutic Agents in Kidney Disease	Sheron Latcha
13. CKD as a Complication of Cancer	Maurizio Gallieni, Camillo Porta, and Laura Cosmai
14. Hereditary Renal Cancer Syndromes	Katherine Nathanson
15. Work-up and Management of Small Renal Masses	Susie Hu, Anthony Chang
16. Cancer in Solid Organ Transplantation	Mona Doshi
17. Cancer Screening in ESRD	Jean Holley
18. Ethics of RRT, Initiation, and Withdrawal, in Cancer Patients	Michael Germain
19. Palliative Care in Patients with Kidney Disease and Cancer	Alvin Moss

Figure 1. Cancer, AKI, and CKD are linked by various exposures and pathways



Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; ESRD, end stage renal disease

References

1. Hoybert DL, Xu J. Deaths: Preliminary data for 2011. National Vital Statistics Report 2012; 61:6. www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_06.pdf
2. Age-adjusted SEER Incidence Rates, 2007–2011 (Table 2.7). SEER Cancer Statistics Review (CSR) 1975–2011. Surveillance, Epidemiology, and End Results Program. National Cancer Institute. http://seer.cancer.gov/csr/1975_2011/browse_csr.php?sectionSEL= 2&pageSEL=sect_02_table.07.html
3. Percent of Medicare patients aged 66+, (a) with at least one AKI hospitalization, and (b) with an AKI hospitalization that had dialysis by year, 2003–2012 (Figure 5.1). Chapter 5: Acute Kidney Injury. USRDS 2012. www.usrds.org/2014/view/v1_05.aspx
4. Christiansen CF, et al. Incidence of acute kidney injury in cancer patients: a Danish population-based cohort study. *Eur J Intern Med* 2011; 22:399–406.
5. Schmid M, et al. Predictors of 30-day acute kidney injury following radical and partial nephrectomy for renal cell carcinoma. *Urol Cancer* 2014; 32:1285–91.
6. Janus N, et al. Cancer and renal insufficiency results of the BIRMA study. *Br J Cancer* 2010; 103:1815–21.

Youth Program Focuses on Kidneys for Healthier Outcomes

By Cheryl Neal, MD, and Susan Bagby, MD

The MIKE program (Multicultural Integrated Kidney Education) is working to change Oregon's burden of chronic metabolic diseases. The Portland-based nonprofit offers youth sequential, applied learning activities that connect health science education with leadership skills and community service. As youth develop the knowledge, tools, and motivation to make educated decisions to prevent chronic disease personally, they begin to influence their peers, families, and neighbors to create a healthy future.

MIKE was created in 2000 in memory of Mike Hartnett, MD, the first nephrologist trained at what is now Oregon Health & Science University (OHSU). The program's innovative focus on the kidney provides youth with a unique scaffold for learning human anatomy, organ functions, chronic disease prevention, and best practices for increasing healthy behaviors.

MIKE advisor Randall Jenkins, MD, a Portland pediatric nephrologist at OHSU, sees firsthand how chronic diseases increasingly impact greater numbers of younger children. "In the 1990s when I started in Oregon, only one child with hypertension related to weight was in my practice," Jenkins said. "Now I see one child every week or two." Dr. Jenkins' practice is also seeing more Latino and African American children devastated by chronic diseases earlier in life. "It's related to lifestyle, eating, and physical activity," he said.

MIKE embeds a focus on prevention of kidney failure and youth development into school settings that serve low-resource neighborhoods, engaging very-low to moderate income, racially and ethnically diverse youth to become their own best advocates for health. About 77% of the youth participating in MIKE identify within communities of color, populations more likely to experience kidney failure.

MIKE partners with multiple higher education and healthcare institutions in the area to recruit and train diverse mentors, many of whom are pursuing professions in healthcare. MIKE mentors—of whom more than 50% come from communities of color—include first and second year medical students at OHSU School of Medicine, nursing degree program students with the University of Portland and Linfield School of Nursing, graduate students from Pacific University's School of Professional Psychology, and public health students at Portland State University. MIKE staff meet each week in a teacher-managed classroom to deploy the mentors, who serve as positive role models for small teams of youth during at least one entire academic semester, introducing, applying, and reinforcing steps to inspire healthy behaviors.

One youth participating in MIKE's afterschool program at Liberty High School in Hillsboro, Oregon, discovered that more than half of his immediate family members have been diagnosed with diabetes, hypertension, cancer, high cholesterol and/or obesity. Engaging in this type of exercise is part of MIKE's introduction process and provides context for youth to understand the impact of chronic diseases.

"What I learned from interviewing my aunt is that we actually do have kidney problems in our family," said another youth. "We also have diabetes on both sides of the family."

MIKE youth and mentors gain far more than experiential training and service delivery skills from the program. MIKE's health science education program combines the six fundamental building blocks of project-based learning: authenticity, academic rigor, adult connections, active exploration, application, and assessment. As youth progress, they work in groups with their mentor to create a health leadership project; by presenting their new knowledge to peers, family, and community members, MIKE youth advance health literacy and health equity in communities at high risk of poor health outcomes.

"I never realized that death from kidney failure was more prevalent than death from breast cancer," said Scott Hillesheim after his first week mentoring with MIKE at the high school. Hillesheim, a program manager at Kaiser Westside Medical Center, volunteers as a mentor at Liberty High School. "Now my goal is to spread much more kidney education and to take preventive measures for not only myself, but for my family and the youth I mentor."

Health career options

As part of its vison for health, MIKE promotes health career options. MIKE mentors guide youth through a variety of hands-on, health-focused experiences, exposing them to professional content experts who lead hands-on blood pressure clinics, guide construction of a makeshift kidney from household materials, and prepare youth for a visit to a dialysis clinic.

Youth list the dialysis clinic visit as one of the most compelling experiences with MIKE. Participants tour the facility, then talk with individuals undergoing dialysis, providing a personal lens that helps illustrate the impact of kidney failure in society.

There is broad scientific agreement that two factors drive the epidemic of chronic metabolic diseases: Poor nutrition (undernutrition or high-calorie malnutrition) in early life (in the womb and during early childhood); and unhealthy lifestyles in postnatal life (inadequate nutrition, sedentary lifestyles, and risky behaviors). Because high-calorie malnutrition in the womb (maternal obesity/gestational diabetes) leads to childhood onset of obesity/diabetes, which then typically persists as young women enter reproductive years, the vulnerability of their offspring to chronic disease becomes self-perpetuating across generations.

Thus the health practices of youth today will determine the health of their future pregnancies and the resilience of their babies to postnatal environmental stressors. This resilience applies not only to physical and metabolic health, but also to the cognitive, mental, and behavioral health that determines societal success.

By equipping teens with the skills, knowledge, and motivation they need to advocate for health within their academic and social communities, MIKE begins to disrupt the intergenerational health outcomes that increasingly generate high healthcare costs, add to the burden of socio-economic disparities, and widen gaps in academic and workforce achievements.

By preparing youth with the means and motivation to resist these stressors, MIKE helps them move toward healthier outcomes for themselves and their future families. For ways to help and for more information about MIKE, visit www.mike-program.org.

Cheryl Neal, MD, is founder and volunteer executive director of the MIKE Program. Susan Bagby, MD, is a professor of medicine at Oregon Health & Science University (OHSU), and is chair of the Community Education and Outreach Committee of the OHSU Bob and Charlee Moore Institute for Nutrition and Wellness.

ABIM Releases MOC Survey Results

The American Board of Internal Medicine recently released results from its survey "Improving the MOC Assessment Experience."

Among the survey's findings, 69.6% of respondents said they were dissatisfied with ABIM's MOC program as a whole. About 38% answered "positive" when asked, "How well has ABIM done over the past several months at addressing the needs and concerns of the internal medicine community?"

In December 2015, ABIM invited board-certified physicians to complete an online survey. A representative sample was identified for follow-up reminders. More than 9000 ABIM diplomates responded; 360 responses were from the random representative sample of 1125 respondents.

ASN released results from its own survey, "Maintenance of Certification – ASN 2016," in April 2016.

In an announcement, ABIM said it conducted the survey to determine physicians' views on what they believe maintaining board certification says about them as physicians, as well their opinions about potential innovations in examinations and other assessments.

The majority of physicians surveyed said board certification means that they are staying current in the knowledge they need to practice or are engaged in improving the quality of their practice.

The survey asked physicians about 4 possible options for length and frequency of examinations and assessments. Fifty-six percent responded positively to the idea of taking a series of shorter examinations over the course of a few years, with the potential to skip the traditional MOC exam if they score high enough. Another 14% said they were "neutral" to the idea or needed more information.

Respondents varied widely in their preferences for how long and how frequent examinations should be: 55.5% preferred yearly exams that take less than 1 hour, and 47% preferred the option of taking assessments of 2 to 4 hours duration every few years. Only 21% preferred an 8-hour exam every 10 years. The least favorable option was "assessments that require a few minutes, every week," at 10.5%.

There was clear support (86.4%) for taking examinations at a location other than a testing center, such as at home, office, or elsewhere, and for allowing access to online reference material during an examination (76%).

"Alternative assessment models were favored in the survey of ABIM board-certified physicians (which included nephrologists, as well as other physicians). An assessment model that could be used by physicians to support lifelong learning would be an important change," said Mark E. Rosenberg, MD, FASN, ASN Education Committee Chair and Professor of Medicine and Vice Dean for Education at the University of Minnesota Medical School in Minneapolis, MN. "ASN looks forward to working through the important but controversial issue of MOC with the newly formed ASN Task Force on Recertification."

Gentzon Hall, MD, PhD, Receives First ASN-AMFDP Award

As the first recipient of the American Society of Nephrology–Amos Medical Faculty Development Program (ASN-AMFDP) Award, Gentzon Hall, MD, PhD, intends to build on his current work in renal genomics, with a primary focus on hereditary focal segmental glomerulosclerosis (FSGS). Dr. Hall is a medical instructor in the Duke University Division of Nephrology.

Through a partnership with the Harold Amos Faculty Development Program (Amos Scholars), the ASN-AMFDP Award was created in February 2015 to support the research and career development of a kidney research scholar and future health care leader.

"As a junior faculty member at Duke, Dr. Hall has already distinguished himself as a scholar, role model for other trainees, and health care leader," said Donald Wesson, MD, FASN, co-chair of the ASN Diversity and Inclusion Work Group. "We are pleased that he is being honored with the ASN-AMFDP award, which will help further his career and research goals."

Dr. Hall's research career started in high school during a National Heart, Lung, and Blood Institute–sponsored summer research internship. The experience ignited Dr. Hall's decision to pursue a career as an academic physician-scientist, a decision shaped further during his undergraduate years and as he pursued an MD-PhD degree at the University of Maryland at Baltimore.

During his MD-PhD program and upon starting an internal medicine residency, Dr. Hall became interested in a career in cardiology and cardiovascular research.

However, these early career objectives changed after a meeting with the late Michelle P. Winn, MD, during an inpatient renal rotation as an intern. Dr. Winn invited him into her lab, and after a year learning the fundamentals of human genetics, Dr. Gentzon decided to pursue subspecialty training in nephrology. He was particularly moved by the predicaments of young African American patients who often do not have many options after being diagnosed with FSGS.

After his clinical nephrology training at Duke University, he began a postdoctoral fellowship in human genetics research under the mentorship of Dr. Winn. During his fellowship, Dr. Hall's accomplishments included 9 or more peer-reviewed publications, 3 awards, and 9 national scientific presentations.

Currently under the mentorship of Douglas A. Marchuk, PhD, and Dr. Rasheed Gbadegesin, MD, Dr. Hall will use the award to help focus on developing his skills in renal genomics and human glomerular disease modeling, particularly studying the genetics of FSGS in at-risk populations using state-of-the art genetic and whole animal modeling strategies.

Dr. Hall is married to Rasheeda Hall, MD, who is also a nephrologist and clinical researcher at Duke University.

KIDNEY WEEK 2016

Chicago, IL • Nov 15 - 20

Call for Abstracts

Submit your abstract for ASN Kidney Week® 2016: The world's premier nephrology meeting

Kidney Week is the premier educational and scientific event in the nephrology community and offers you the opportunity to present your research to more than 13,000 nephrology professionals.

NEW FOR 2016

The Fellows Case Reports submission category has been changed to **Fellows and Residents Case Reports**.

The full list of abstract categories and their descriptions are available at www.asn-online.org/KidneyWeek.

Please note that ALL abstract authors (including co-authors) must have current disclosures on file with ASN at time of submission.

IMPORTANT DATES (2016)

ABSTRACTS:

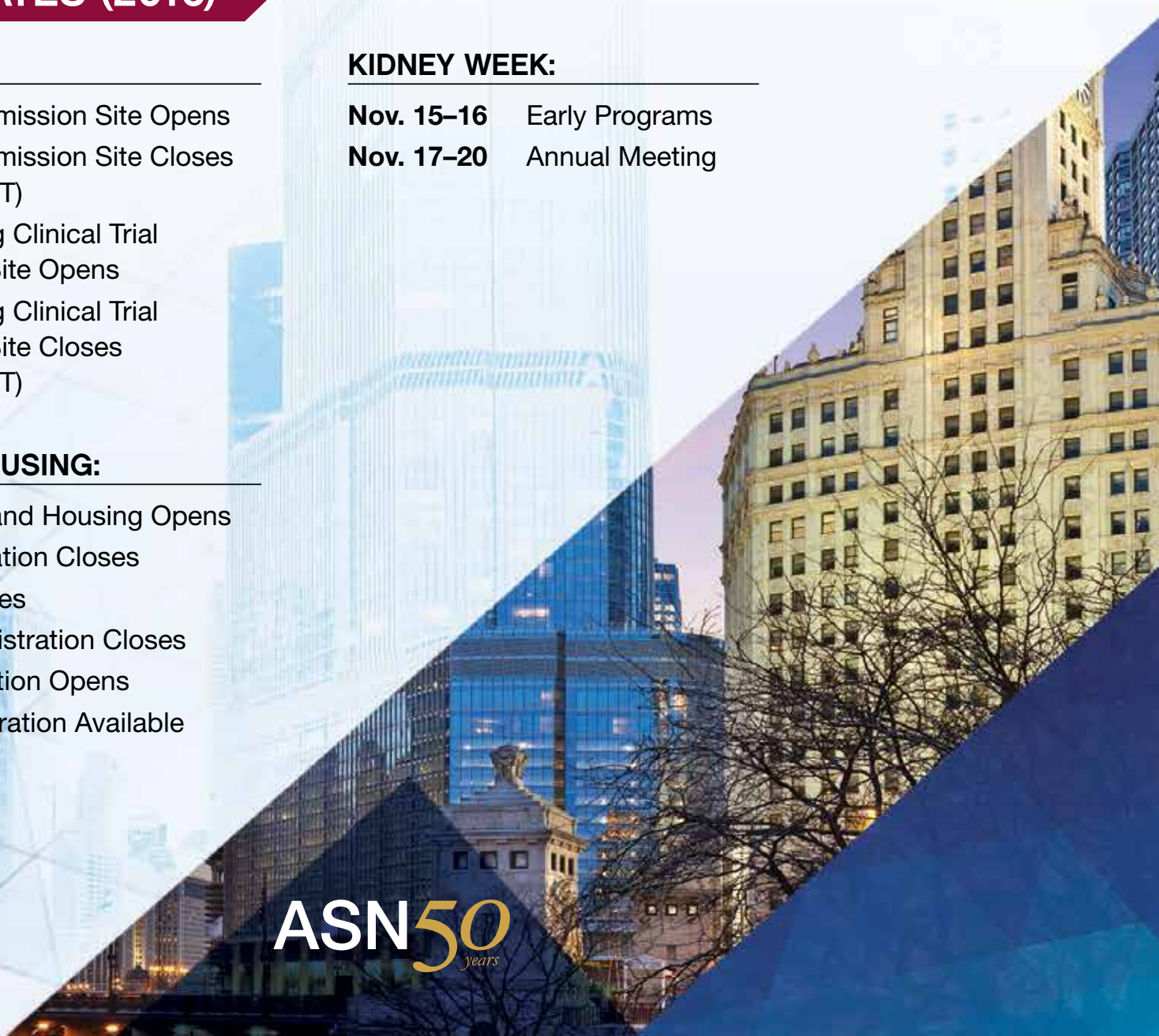
April 6	Abstract Submission Site Opens
June 8	Abstract Submission Site Closes (2:00 p.m. EDT)
July 13	Late-Breaking Clinical Trial Submission Site Opens
Sept. 7	Late-Breaking Clinical Trial Submission Site Closes (2:00 p.m. EDT)

REGISTRATION & HOUSING:

June 15	Registration and Housing Opens
Sept. 14	Early Registration Closes
Oct. 14	Housing Closes
Nov. 2	Advance Registration Closes
Nov. 3	Late Registration Opens
Nov. 15	Onsite Registration Available

KIDNEY WEEK:

Nov. 15–16	Early Programs
Nov. 17–20	Annual Meeting



ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Corporate Supporters

ASN gratefully acknowledges the Society's Diamond and Platinum Corporate Supporters for their contributions in 2015.

Diamond Level

AMGEN

FRESENIUS MEDICAL CARE
RENAL THERAPIES GROUP

Hospira
A Pfizer Company

Mallinckrodt Pharmaceuticals

relypsa

Platinum Level

KERYX BIOPHARMACEUTICALS, INC

OPKO Renal

SANOFI RENAL

Classified Ads

NEPHROLOGIST
COOPER UNIVERSITY HEALTH CARE
CAMDEN, NEW JERSEY

This is an outstanding opportunity to join the growing Nephrology division of a 180-member Department of Medicine multi-specialty faculty group of an academic medical center with an excellent reputation. The Department of Medicine of Cooper University Hospital is affiliated with the Cooper Medical School of Rowan University (CMSRU) in Camden, New Jersey. Cooper/CMSRU is experiencing exponential growth in its clinical practice, undergraduate and graduate teaching, and in its clinical research programs. We are seeking a **full time faculty physician** in the Division of Nephrology.

Cooper University Hospital is a 570-bed, tertiary care facility located one mile from Philadelphia, serving the population of southern New Jersey and the Delaware Valley. The nephrology division provides comprehensive inpatient consultation services at Cooper University Hospital, and cares for outpatients at offices on the hospital campus and in the near suburbs. The division provides care for a large population of patients with end-stage renal disease, using all contemporary dialysis modalities (ICHD, PD, HHD). The position includes patient care, teaching of medical students, residents and nephrology fellows. There is ample opportunity for collaboration in major clinical research.

The successful candidate will be a nephrologist with a demonstrated commitment to patient care and medical education. Candidates are eligible for faculty appointment at CMSRU. Starting salaries are very competitive and commensurate with qualifications and experience.

To apply in complete confidentiality, please forward CV, or requests for additional information via email to: **Weisberg-Lawrence@CooperHealth.edu**

Equal Opportunity Employer M/F/D/V.

Cooper University Health Care

Nephrologist

Spartanburg Nephrology Associates is seeking a full-time Nephrologist to join their medical practice in Spartanburg SC. Duties will include treating patients in the office, hospital and dialysis clinic settings. Competitive benefit package. Please mail or fax your CV to: Attn: Donna Lancaster, Spartanburg Nephrology Associates, 322 North Pine Street, Spartanburg, SC 29302, Phone: 864-582-5099, Fax: 864-597-1260, dlancaster@spneph.com.

Nephrologist – Part Time

East Meadow, LI, NY. Nassau University Hospital Medical Center seeking a part-time nephrologist to help cover its services. Please send your CV to lbalsam@numc.edu. An EOE.

Index to Advertisers

1966 50 years 2016

To our membership and leaders,
to our community and supporters,
and to the generations of nephrologists
who have advanced kidney care for 50 years,

Thank You.

ASN 50 years
www.asn50.org

ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE