

Kidney News

September 2016 | Vol. 8, Number 9

Urine Biomarkers May Indicate Presence of Kidney Injury in Preterm Infants

By Tracy Hampton



The field of neonatal acute kidney injury (AKI) is in its infancy, but some reports indicate that up to one-quarter of newborns in intensive care units may develop AKI, which puts them at increased risk of poor clinical outcomes and even premature death. Premature

newborns have an elevated risk of developing chronic kidney disease and end stage renal failure compared with term infants, and AKI may possibly contribute to this risk.

Although detecting AKI in newborns is critical for their current and future health, it can be challenging to achieve with current serum creatinine-based tests, in part because serum creatinine levels on postnatal day 1 reflect maternal levels, which decline over time depending on gestational age. Now, new research published in the *Clinical Journal of the American Society of Nephrology* indicates that several proteins are excreted differently in preterm infants with kidney injury compared with those with healthy kidneys. The biomarkers may be used to develop better diagnostics related to kidney health in newborns.

“Having better diagnostic tests to diagnose kidney injury can have an important impact on how we care for infants, how

we prognosticate outcomes, and how we design studies to prevent and/or mitigate AKI,” said David Askenazi MD, an associate professor in the University of Alabama at Birmingham’s Department of Pediatrics and director of the university’s Pediatric and Infant Center for Acute Nephrology.

Using single drops of urine from 113 preterm infants (birth weight ≤ 1200 g and/or ≤ 31 weeks gestational age), Askenazi and his colleagues prospectively examined the potential of 14 urine proteins for indicating the presence of kidney damage. Among the 113 infants included in the study, 28 (25%) were diagnosed with AKI. Death occurred in 13 (11.5%) infants. Babies with AKI had smaller birth length, were less likely to be born from mothers with preeclampsia [1/28 (4%) vs. 32/85 (38%)], and were more likely to have an umbilical artery catheter [18/28 (64%) vs. 29/85 (34%)].

The researchers found that several of the urine proteins measured during the

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After Years of Increase, CKD Prevalence Levels Off But Continued Rise in African Americans Poses Concerns

By Tim O’Brien

Data going back to the mid-1970s have suggested steady increases in the percentage of Americans with advanced chronic kidney disease (CKD). But that may be changing, as an updated data analysis finds no significant increase in CKD in the US adult population since the

early 2000s, according to an updated analysis of population-based data.

“In a reversal of prior trends, there has been no appreciable increase in the prevalence of stage 3 and 4 CKD in the US population during the most recent decade,” concludes the new report, published by the

Annals of Internal Medicine last month.

It’s a welcome finding that is consistent with recent evidence of stabilization in incidence of end stage renal disease (ESRD). While CKD prevalence has remained stable in most subgroups, the investigators strike a note of concern regarding continued increase in prevalence of CKD among African Americans.

Study updates nationwide data on CKD trends

The study by the Centers for Disease Con-

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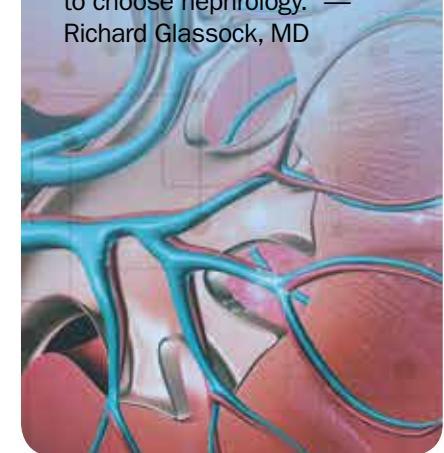
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“I hope my optimism will encourage at least one individual on the cusp of making a decision about where to go with their medical career to choose nephrology.” — Richard Glasscock, MD



Urine Biomarkers

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first 4 postnatal days were good candidates for further investigation. Compared with those without AKI, those with AKI had 2.0 times higher median levels for cystatin C, 1.8 times higher neutrophil gelatinase-associated lipocalin (NGAL), 1.7 times higher clusterin, 1.7 times higher osteopontin, and 3.7 times higher alpha glutathione S-transferase (α -GST). On the other hand, those with AKI had 1.4 times lower median epithelial growth factor (EGF) and 1.6 times lower median uromodulin than those without AKI.

Of the biomarkers that were significantly different between patients with and without AKI, all had fair discriminative capability, with the highest being uromodulin, followed by α -GST and EGF. The biomarkers with the lowest discriminative ability were clusterin and albumin.

Maximum biomarker values (or minimum for uromodulin and EGF) occurred

before the diagnosis of AKI by serum creatinine criteria in 44% to 66% of infants for any given biomarker. This percentage was elevated to 78% to 85% for any given biomarker when evaluating the timing of biomarker maximum/minimum on the day before or the day of AKI diagnosis.

Although other studies have suggested that urine kidney injury molecule-1 (KIM-1) can be an early marker of AKI in premature infants, the marker was not significantly associated with serum creatinine elevation in this study. "This could be due to differences in tubular development in premature infants, or it could be that the reasons for elevation of serum creatinine were different in our cohort compared to others," the authors wrote.

The researchers also noted that their work previously found a protective association between AKI and preeclampsia in premature infants, which was again present in this study. They explained that it is possible that preeclampsia alters the physiology of the premature kidney in a way that reduces its susceptibility to develop

AKI, for example by causing episodes of ischemia pre-conditioning. Studies with larger cohorts are underway to address some of the study's remaining questions and limitations.

"The burgeoning field of AKI urinary biomarkers has largely ignored one of the most vulnerable populations, namely very-low-birth-weight infants. This study has examined 14 multiplexed biomarkers in a relatively large cohort, confirming the results of previous smaller studies examining only a single biomarker," said Prasad Devarajan, MD, FAAP, who was not involved with the study and is the director of the Division of Nephrology and Hypertension at Cincinnati Children's Hospital Medical Center. "If validated in larger multicenter cohorts, these findings hold promise for the development of biomarker panels to predict neonatal AKI and its adverse outcomes, as well as to design clinical trials guided by biomarker changes."

Additional research is needed to determine whether the candidate biomarkers predict significant clinical outcomes, includ-

ing the development of chronic kidney disease, and whether interventions guided by the biomarkers can impact these outcomes.

Study co-authors include Rajesh Koralkar, MPH, Neha Patil, MD, Brian Halloran, MS, Namasivayam Ambalavanan, MD, and Russell Griffin, PhD.

Disclosures: All authors declare no real or perceived conflicts of interest that could affect the study design, collection, analysis and interpretation of data, writing of the report, or the decision to submit for publication. Askenazi is a speaker for the Acute Kidney Injury (AKI) foundation, Baxter, and BTG. He received a career development award from ASN. That support was critical to gathering of the data for this work.

The article, entitled "Acute Kidney Injury Urine Biomarkers in Very Low Birth Weight Infants," is available online at <http://cjasn.asnjournals.org/content/early/2016/07/27/CJN.13381215.abstract>.

CKD Prevalence

Continued from page 1

trol and Prevention's Chronic Kidney Disease Surveillance Team analyzed trends in CKD prevalence among US adults. The CKD Surveillance System provides a centralized source of data for use in tracking the full scope of kidney disease, including risk factors, impact on population health, and the healthcare system's capacity for managing CKD. In addition to the CDC, the CKD Surveillance System is supported by research teams at the University of California, San Francisco, led by Neil Powe, MD, MPH, MBA; and the University of Michigan, Ann Arbor, led by Rajiv Saran, MD.

The CKD Surveillance Team analyzed National Health and Nutrition Examination Survey (NHANES) data from 1988 to 1994, and every two years from 1999 to 2012. Stage 3 or 4 CKD was defined as an estimated glomerular filtration rate (eGFR) of 15 to 59 mL/min/1.73 m². The eGFR estimates were derived from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, using calibrated serum creatinine measurements.

The study was supported by the Centers for Disease Control and Prevention and the National Institutes of Health. In addition, lead author Daniel Murphy, MD—previously a UCSF medical student, now a resident at the University of Minnesota—received support from the American Society of Nephrology Foundation for Kidney Research Student Scholar Grant Program.

The results suggest a steady increase in the percentage of Americans with CKD from the late 1980s through the early 2000s. The crude prevalence of stage 3 or 4 CKD rose from 4.8% in 1988–94, to 5.3% in 1999–2000, to 6.4% in 2001–02, to 6.9% in 2003–04.

Since then, there has been no further change in CKD prevalence. From NHANES 2005–06 to 2011–12, the fig-

ures have remained in the range of 6.4% to 6.9%.

While prevalence leveled off across age groups, estimates were substantially higher in older Americans. In 2011–12, the figures were 3.8% in participants aged 40 to 64 years, 21.7% in those aged 65 to 79, and 51.1% in those aged 80 years and older. The pattern was similar for participants with and without diabetes—peak prevalences were about 19% and 5%, respectively.

In non-Hispanic white participants, the figures followed the overall population trend: peaking at about 8% in 2005–06 and remaining stable thereafter.

However, there was evidence of a continued increase in prevalence among non-Hispanic blacks: from 3.7% in 1988–94, to 4.9% in 2003–04, to 6.2% in 2011–12. All of these patterns—including the persistent rise in CKD among non-Hispanic blacks—persisted in adjusted analyses.

A secondary outcome evaluated the complete spectrum of CKD stages (1 to 5), including individuals with eGFR of 60 mL/min/1.73 m² or higher who had a marker of kidney damage (urine-to-creatinine ratio of 30 mg/g or higher). The results showed a similar pattern: starting in the early 2000s, overall crude prevalence remained stable at about 14%, while the adjusted prevalence decreased slightly.

As in the main analysis, the prevalence of CKD (all stages) continues to increase among the non-Hispanic black population, although there was no statistically significant interaction. Similar patterns also prevailed in a sensitivity analysis using the Modification of Diet in Renal Disease (MDRD) Study equation to calculate eGFR.

Stabilization is consistent with trends in ESRD

Because nearly all cases of ESRD are preceded by CKD, reducing the prevalence of CKD would seem to be a critical step

toward reducing the number of cases of ESRD. After decades of increases, the incidence of ESRD has decreased since the early 2000s. According to the 2015 US Renal Data System report, the adjusted incidence rate of ESRD decreased from 386 cases per million persons per year in 2003 to 351 per million in 2013. "There is no room for complacency however," added Saran, who is Director of the USRDS Coordinating Center. "Falling mortality rates in the general population could affect future prevalence of CKD in an aging population or in specific subgroups, and should continue to be monitored closely along with intensive efforts at prevention, earlier detection, and management."

Previous reports have suggested continued increases in the prevalence of CKD—by up to 5% per year. However, these studies have not incorporated data from more recent years.

Of course the analysis of NHANES data can't explain why CKD prevalence has flattened out—but recent improvements in medical management seem likely to play a role, according to an accompanying editorial by Linda F. Fried, MD, MPH, and Paul M. Palevsky, MD, of the University of Pittsburgh. "One can speculate that it is related to improvements in blood pressure and glycemic control among high-risk persons and increased use of medications blocking the renin-angiotensin system in patients with proteinuria," Drs. Fried and Palevsky write. "If so, this would support intensified efforts to increase awareness and treatment of persons with CKD."

"When you're trying to decrease ESRD, the first thing you want to do is decrease the prevalence of earlier stages of the disease in addition to slowing progression of disease," Powe commented. "This reversal of the trend of rising CKD rates should ultimately mean less end stage renal failure and its morbid consequences and excess mortality. The kidney disease community should be commended for this scientific

progress." The researchers note evidence of similar trends in CKD from other countries, notably including England.

"For nephrologists, it's exciting to have these data supporting the effectiveness of our interventions to prevent and slow the progression of CKD," commented Chi-yuan Hsu, MD, of UCSF—along with Powe, one of the study's senior authors. "Our efforts are paying off in terms of combating kidney disease in the population."

Meanwhile, the apparent continued increase in CKD prevalence among African Americans is a major concern. "This is the group with the highest risk of developing end stage kidney disease, and needing to have kidney replacement therapy," Powe said. "African Americans have two to three times the risk of developing end stage kidney failure than any other racial or ethnic group. Genetics, quality of care and environmental factors together probably play a role."

The new finding occurs against the backdrop of known racial differences in the progression from CKD to ESRD, as well as recent data on the genetic factors (i.e., APOL1 gene variants) contributing to racial differences in CKD risk. Ongoing research is needed—particularly in light of recent data showing that, while ESRD incidence remains higher in the black population, it has decreased much faster than in whites. The CKD Surveillance Team calls for "careful monitoring" of CKD in the African American population, as well as studies to understand the pathophysiology of advanced CKD in blacks.

"These findings highlight the importance of getting all eligible patients into proper treatment for their conditions," Hsu said. "As nephrologists, we have a real opportunity to promote better CKD awareness and care among internists and primary care physicians who really provide most of the care antecedent to development of CKD, as well as much of the care given to diagnosed CKD patients."

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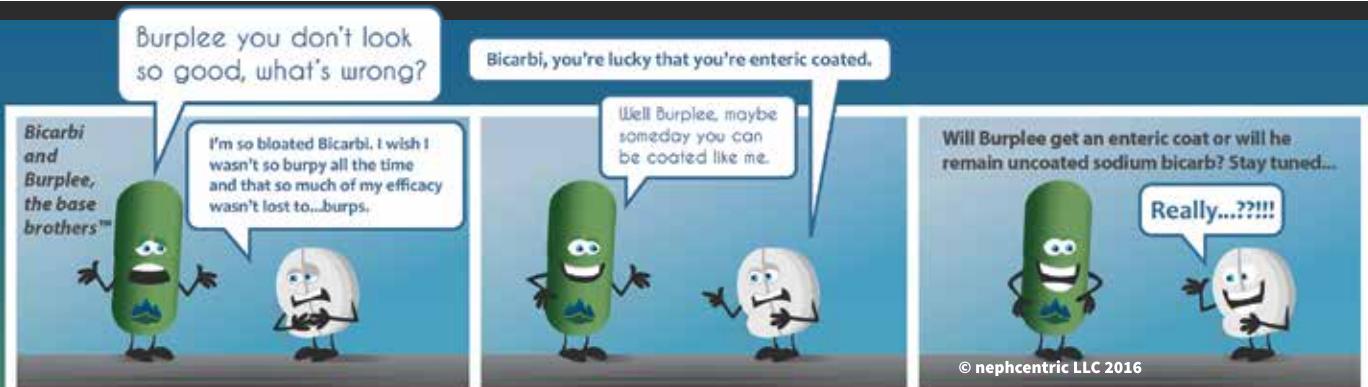
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Postmaster: Please send address changes to *ASN Kidney News*, c/o Customer Service, American Society of Nephrology 1510 H Street NW, Suite 800, Washington, DC 20005.

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.

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ASN President's Column

By Raymond C. Harris, MD, FASN



Raymond C. Harris, MD, FASN

also commit to training students—and ourselves—to lead. Some students are turned off by nephrology because they think it is “too hard and there is too much data.” We want the students who can appreciate the wonderful complexities of science and medicine in general, and the kidney specifically, but we must do a better job conveying to students that in learning to interpret this complex information, they will understand what energizes us as kidney professionals: the amazing gift of improving quality of life for our patients.

Unfortunately, we don’t tell that story well enough.

Are we enriching the training experience, advancing diversity, and educating trainees to lead? As Dr. Gibson and Dr. Wesson have noted, many of us are “accidental leaders.” We must reinvent training so that physicians and physician investigators are armed with the skills necessary to make the most of the leadership opportunities that will be offered them.

Finally, for those of us already working in kidney health, we must assure that in documenting our professional competence, we do not divert energy and time to efforts that do not actually promote professionalism or that impede our ability to make positive change in the lives of people with kidney diseases. We should take the lead in ensuring that lifelong learning appropriately reflects what we do, and we should make the most appropriate use of peer benchmarks, without taking valuable time from patient care or other leadership opportunities.

Administering health care in the future and mastering the data that will advance science and practice require the mindset of a nephrologist—someone who excels at understanding and applying knowledge that can promote positive change for the care of our patients. I challenge kidney professionals across the globe to take every opportunity offered to lead and to share the knowledge we have gained to improve science and medicine, health care, and policy. ●



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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.

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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 [see *Adverse Reactions*]. Monitor serum magnesium. Consider magnesium supplementation in patients who develop low serum magnesium levels on VELTASSA.

ADVERSE REACTIONS

The following adverse reaction is discussed in greater detail elsewhere in the label:

- Hypomagnesemia [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 VELTASSA cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice. In the safety and efficacy clinical trials, 666 adult patients received at least one dose of VELTASSA, including 219 exposed for at least 6 months and 149 exposed for at least one year. Table 1 provides a summary of the most common adverse reactions (occurring in ≥ 2% of patients) in patients treated with VELTASSA in these clinical trials. Most adverse reactions were mild to moderate. Constipation generally resolved during the course of treatment.

Table 1: Adverse Reactions Reported in ≥ 2% of Patients

Adverse Reactions	Patients treated with VELTASSA (N=666)
Constipation	7.2%
Hypomagnesemia	5.3%
Diarrhea	4.8%
Nausea	2.3%
Abdominal discomfort	2.0%
Flatulence	2.0%

During the clinical studies, the most commonly reported adverse reactions leading to discontinuation of VELTASSA were gastrointestinal adverse reactions (2.7%), including vomiting (0.8%), diarrhea (0.6%), constipation (0.5%) and flatulence (0.5%). Mild to moderate hypersensitivity reactions were reported in 0.3% of patients treated with VELTASSA in clinical trials. Reactions have included edema of the lips.

Laboratory Abnormalities Approximately 4.7% of patients in clinical trials developed hypokalemia with a serum potassium value < 3.5 mEq/L. Approximately 9% of patients in clinical trials developed hypomagnesemia with a serum magnesium value < 1.4 mg/dL.

DRUG INTERACTIONS

No formal drug interaction studies have been conducted in humans.

In *in vitro* binding studies, VELTASSA was shown to bind about half of the oral medications that were tested. Binding of VELTASSA to other oral medications could cause decreased gastrointestinal absorption and loss of efficacy when taken close to the time VELTASSA is administered. Administer other oral medications at least 6 hours before or 6 hours after VELTASSA. Monitor for clinical response and/or blood levels where possible.

USE IN SPECIFIC POPULATIONS**Pregnancy****Risk Summary**

VELTASSA is not absorbed systemically following oral administration and maternal use is not expected to result in fetal risk.

Lactation**Risk Summary**

VELTASSA is not absorbed systemically by the mother, so breastfeeding is not expected to result in risk to the infant.

Pediatric Use Safety and efficacy in pediatric patients have not been established.

Geriatric Use Of the 666 patients treated with VELTASSA in clinical studies, 59.8% were age 65 and over, and 19.8% were age 75 and over. No overall differences in effectiveness were observed between these patients and younger patients. Patients age 65 and older reported more gastrointestinal adverse reactions than younger patients.

Renal Impairment Of the 666 patients treated with VELTASSA in clinical studies, 93% had chronic kidney disease (CKD). No special dosing adjustments are needed for patients with renal impairment.

OVERDOSAGE

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Drug Interactions Advise patients who are taking other oral medication to separate the dosing of VELTASSA by at least 6 hours (before or after) [see *Drug Interactions*].

Dosing Recommendations Inform patients to take VELTASSA as directed with food and adhere to their prescribed diets. Instruct patients to prepare each dose separately using the preparation instructions provided in the FDA-approved patient labeling (Medication Guide). Inform patients that VELTASSA should not be heated (e.g., microwaved) or added to heated foods or liquids and should not be taken in its dry form.

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Maintenance of Certification: An Update from the ASN Recertification Task Force

By Mark Rosenberg, MD, FASN, and Phillip Kokemueller

Recertification is a significant and evolving issue for practicing nephrologists. In response to physician complaints, the American Board of Internal Medicine (ABIM) has proposed a number of recent modifications to its Maintenance of Certification (MOC) program. The latest change released in August 2016 was an update of the MOC examination blueprint in nephrology informed by input of over 400 nephrologists in order for questions to better reflect what is seen in practice (<http://goo.gl/f05DQX>).

Other recent developments include a decision to award MOC points to physicians who participate in Quality Assurance and Performance Improvement (QAPI) programs managed by the Centers for Medicare & Medicaid Services (CMS) and a proposal to award points to residency and fellowship program directors (and other educational faculty) for resident and fellowship quality improvement and patient safety activities.

Additionally, ABIM announced in May 2016 a plan to offer physicians alternative MOC assessment options (beginning January 2018) including shorter assessments that can be taken from personal or office computers more frequently than every 10 years, and a potential testing out option eliminating the need to take a high stakes examination every 10 years. Planning to offer this option initially to general internal medicine and two specialties, ABIM has not indicated when nephrologists would be eligible.

Despite these recent developments, ABIM and MOC remain controversial and the subject of much criticism. Concerns with the current MOC process include relevance to practice, redundancy with other required practice improvement activities, the time and cost required to complete MOC requirements, the lack of evidence to support the inherent benefit of current MOC activities, and the perception of accountability issues with ABIM.

ASN has been actively engaged in these MOC issues at every possible level. For example, ASN leaders and staff have met regularly with ABIM leadership to express the concerns of nephrologists. The society has communicated through letters to members and *Kidney News* articles about MOC developments (Table 1), and ASN has collaborated with other specialty societies to address MOC issues, including sending a letter to ABIM leadership asking for clarification of the vision and future strategy for MOC. ASN has also surveyed the society's membership about certification, recertification, and ABIM (<http://goo.gl/DApw0V>) with varied results on the importance of MOC and the activities that should count for MOC credit.

In light of the high stakes nature of MOC to nephrologists and the controversies surrounding both ABIM

and the MOC process, ASN formed a Recertification Task Force to define an ideal pathway to recertification (Tables 2 and 3). The task force met six times by conference call between May 10, and July 20, 2016. The purpose of this article is to inform ASN members and the broader kidney community about the deliberations of the task force, to outline principles and initial recommendations stemming from these deliberations to highlight areas where consensus has not been reached, and to encourage feedback from the society's members concerning the progress of the task force's (admittedly still evolving) recommendations.

The task force developed a set of principles to provide a foundation for its final recommendations:

I. ASN supports a commitment to lifelong learning for all nephrologists.

The goal of any recertification program should be to reinforce the commitment to continuously staying updated in relevant areas of knowledge related to the practice of nephrology to deliver the highest quality patient care throughout the career of the nephrologist. There was consensus among the task force with this principle.

II. A recertification credential should be a voluntary demonstration to all stakeholders of a nephrologist's commitment to lifelong learning.

The task force agreed that it was important to reconfirm that recertification is voluntary (not required for licensure, for example) but to recognize that recertification is required in many instances for hospital privileges and payer reimbursement.

III. The focus of any recertification activity should be on facilitating learning.

There was general agreement that the process for recertification should be user friendly and as simple as possible to ensure the majority of physician effort is spent on learning and not on trying to work through the logistics of how to accomplish recertification. Physicians should want to participate in recertification and not bear an undue burden in maintaining their status.

IV. Materials should use established adult learning theory in the design and execution of Continuing Medical Education (CME)/MOC activities and assessments.

An extensive evidence base exists on how to make learning more efficient and durable. There was general agreement that any recertification program should incorporate adult learning theory to enhance the quality and retention of information.

Table 2. Members of ASN Task Force on Recertification

Keith A. Bellovich, DO, FASN
David H. Ellison, MD, FASN
Lu Y. Huber, MD, PhD, FASN
Kenar Jhaveri, MD, FASN
Rakhi Khanna, DO, FASN
Katherine Westin Kwon, MD, FASN
Eleanor D. Lederer, MD, FASN (Council Liaison)
Lawrence S. Moffatt, MD
Britt B. Newsome, MD
Emily L. Petersen, MD
Mark E. Rosenberg, MD, FASN (Chair)
Amy W. Williams, MD

ASN Staff:
Gisela Deuter
Phillip Kokemueller
Lisa Netha

Table 3. Charge to ASN Recertification Task Force

- Identify pathways currently available for nephrologists to renew their subspecialty board certification.
- Analyze member survey data and report results and trends.
- Generate a decision matrix of pros/cons for Council deliberations on:
 - Supporting ABIM as the only recertification entity.
 - Supporting multiple entities, including ABIM and NBPAS.
 - Supporting ASN as the recertification entity for nephrologists.
- Draft a report of findings and recommendations for Council.
- Present report to Council no later than December 2016.

V. Financial transparency and accountability are a critical component of any recertification activity.

The task force agreed that it was important to have financial accountability as a core principle behind the recertification process. This belief includes identification and management of any real and perceived conflict(s) of interest.

VI. ASN should play a major role in the design of educational content for nephrologists.

ASN should continue to produce educational content that adds value to each nephrologist's practice. The task force agreed that the role of ASN and other professional societies should be focused on developing high-quality educational content.

Based on these principles, the task force has formulated initial recommendations. Some of the recommendations are straightforward, but others remain controversial and without complete consensus among task force members. At this time, the task force's rec-

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Table 1. Summary of previous ASN Kidney News communications about MOC since Kidney Week 2015

Date	Topic	Link
July 2016	Certification Concerns Persist	http://goo.gl/xqseYB
June 2016	ABIM Proposes New MOC Options	http://goo.gl/poQ1PN
May 2016	ABIM Releases MOC Survey Results	http://goo.gl/8aBi5a
April 2016	US Nephrologists Voice Opinions about Certification, Recertification, and ABIM	http://goo.gl/DApw0V
January 2016	Letter to the Editor (ABIM Response to December 2015 Editorial)	http://goo.gl/ZPlpQQ
December 2015	ASN's Options for Helping Nephrologists Maintain Career Excellence	http://goo.gl/5d9NFw

Maintenance of Certification

Continued from page 7

ommendations include:

1. Continue discussion with ASN members and other stakeholders regarding the pathway for remaining certified. This discussion involves two uncollected questions: 1) Should ASN support recertification? and 2) Should ASN support a single recertification entity or process with accountability to nephrologists and kidney professional organizations versus continue to support all options for recertification?

This recommendation was the most controversial topic among task force members with views ranging from continuing to work with ABIM as the single recertifying entity to establishing a separate recertification entity housed within a professional society, such as ASN. This lack of consensus was driven largely by a loss of confidence in ABIM as an organization that could effectively manage a recertification process. On the other hand, support for ABIM was based on an effort by ABIM to reach out to the community, admit mistakes, and make corrections, such as the suspension of the MOC Part 4 requirements and the recent MOC initiatives, including proposed alternatives to the 10-year examination.

The task force agreed that a need exists for independent research to establish an evidence base that MOC enhances patient outcomes and improves practice. Other considerations include conducting a feasibility study of ASN serving as or supporting an independent recertification entity. At this point, no consensus has been reached among task force members that is consistent with the ASN member survey data (<http://goo.gl/DApw0V>), particularly the question “Is ABIM the appropriate organization to recertify nephrologists?” to which only 42% of respondents answered yes.

2. Establish an independent recertification oversight committee comprised of nephrology professional organizations and other key stakeholders to advise and approve ABIM recertification policies and activities

if ASN were to accept ABIM as the single recertifying entity.

Given the controversies surrounding ABIM and MOC, and the past history of ABIM initiatives that have not been fully vetted by the physician community, the task force felt strongly that there should be an oversight committee comprised of nephrology professional organizations and other stakeholders to advise, and also to approve, any changes in recertification requirements. This oversight committee would be independent of ABIM and the newly established ABIM Nephrology Specialty Board. Oversight would primarily be around process and financial implications of any changes in MOC.

3. **Permanently eliminate Practice Assessment, Patient Voice, and Patient Safety requirements for MOC (Part 4).**

ABIM has suspended the requirement for Practice Assessment, Patient Voice, and Patient Safety in its MOC program through December 31, 2018. Physicians may still choose to earn MOC points for these areas but they are not mandatory. It was the recommendation of the task force that these areas should not be part of the ABIM MOC requirements to avoid redundancy. Quality improvement and patient safety (QI/PS) activities occur within practices, dialysis units, and health systems and will be a component of the clinical practice improvement component of the CMS Merit-Based Incentive Payment System (MIPS) that is part of the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA).

4. **High-quality, relevant educational activities (approved CME and MOC) should be the foundation for obtaining recertification credentials.**

There was general agreement within the task force that recertification should be based on completing accredited CME programs, many of which can now be registered for MOC medical knowledge self-assessment points, if certain conditions are met, including a comprehensive evaluation component. These activities could be combined with low-stakes examinations that could be used as part of self-assessment of knowledge gaps allowing the physician to

target CME activities to their practice needs.

5. **Eliminate the high stakes examination and move to more frequent low-stakes assessments (assessment for learning, not of learning).**

In general, the task force agreed with this recommendation. This position is consistent with the ABIM Assessment 2020 report (<http://transforming.abim.org/assessment-2020-report/>) informing ongoing design of the ABIM MOC program. The ABIM announcement in May 2016 discussed above is also moving in this direction, proposing low-stakes exams and a potential test-out option. The task force felt that the timeline for elimination of the every 10-year examination should be accelerated.

6. **Simplify any web-based information concerning CME/MOC activities for lifelong learning available to nephrologists with more complete information (requirements, cost, other) and transparency.**

The task force agreed, in general, that this recommendation was important to make needed information more accessible to physicians.

7. **Have the task force present at a Recertification Forum at ASN Kidney Week 2016 on Thursday, November 17, 2016, from 10:30 am to 12:30 pm.**

The task force looks forward to discussing MOC, recertification, and the principles and recommendations discussed in this article with Kidney Week participants at this session. Each member of the task force is very interested in more immediate feedback after members have read this article. Together, we will start a conversation about recertification issues on ASN Communities (<http://community asn-online.org/home>). While ASN continues in these discussions, please forward your comments or concerns related to certification, recertification, ABIM, and related issues to the main ASN email address (email@asn-online.org) and use the subject line “MOC.”

Mark Rosenberg, MD, FASN, is affiliated with the University of Minnesota Medical School in Minneapolis and is Chair of the ASN Recertification Task Force. Phillip Kokemueller is Special Advisor to the ASN Executive Vice President.

Findings

Poor Outcomes of Carotid Endarterectomy in Dialysis Patients

For patients on hemodialysis—particularly those with neurologic symptoms—the high risks of carotid endarterectomy (CEA) may outweigh the benefits, according to a study in *JAMA Surg*.

The retrospective analysis included data on 5142 dialysis-dependent patients undergoing CEA from 2006 to 2011 drawn from the US Renal Data System. Perioperative and long-term outcomes were assessed at a median follow-up of 2.5 years.

Eighty-three percent of patients were

asymptomatic, with no stroke or transient ischemic attack within the previous 6 months. Stroke occurred within 30 days after CEA in 2.7% of the asymptomatic group and 5.2% of the symptomatic group. The myocardial infarction rate was 4.6% versus 5.0%, respectively; mortality was 2.6% versus 2.9%, respectively. Factors associated with a higher perioperative stroke risk were symptomatic status (OR of 2.01), black race (OR of 2.30), and Hispanic ethnicity (OR of 2.28).

From 1 to 5 years, symptomatic patients had higher rates of stroke and death. Five-year overall survival was 33% in asymptomatic patients and 29% in symptomatic patients. Factors associated with higher long-term stroke risk were symptomatic status (HR of 1.67), women (HR of 1.34), and nonambulatory status (HR of 1.81). Risk factors for long-term mortality were older age (OR of 1.02), active smoking (OR of 1.22), history of congestive heart failure (OR of 1.25), and chronic obstructive pul-

monary disease (OR of 1.26).

This large analysis suggests “relatively poor” perioperative and long-term outcomes of CEA in dialysis patients. The authors recommend “optimizing medical management and avoiding CEA” in symptomatic patients and considering CEA only in a “small and carefully selected” group of asymptomatic patients [Cooper M, et al. Perioperative and long-term outcomes after carotid endarterectomy in hemodialysis patients. *JAMA Surg* 2016, in press].

Findings

Kidney Function May interact with Oral Anticoagulants

For patients with atrial fibrillation (AF), baseline renal function may influence the risks and benefits of oral anticoagulation with dabigatran versus warfarin, according to a research letter in the *Journal of the American College of Cardiology*.

The retrospective analysis included propensity-matched groups of adults with AF who were taking warfarin (11,546 patients) or dabigatran (5469 patients). Baseline eGFR showed normal kidney function in about 20% of patients, mild kidney disease in 50%, and moderate kidney disease in 30%. Only 2% had severe

kidney disease (eGFR of 30 mL/min per 1.73 m² or lower). Interactions between treatment and baseline eGFR for thromboembolic events and major bleeding were assessed.

For patients with normal kidney function, dabigatran was associated with a higher risk of thromboembolism (incidence rate ratio [IRR], 3.14) but a lower risk of major bleeding (IRR, 0.28). For those with mild kidney disease, thromboembolism risk was similar between treatment groups, but major bleeding risk remained lower with dabigatran (IRR, 0.39).

Among patients with severe kidney disease, there were no thromboembolic events in the dabigatran group versus 2.95 events per 100 person-years in the warfarin group. However, major bleeding risk was higher with dabigatran (IRR, 3.58). The interaction between kidney function and treatment was significant for gastrointestinal but not intracranial bleeding.

Studies have found dabigatran to be superior to warfarin in reducing AF-associated thromboembolism, with similar rates of major bleeding. Kidney disease increases the risk of both thromboembo-

lism and bleeding, whereas dabigatran has significant renal clearance.

This cohort study suggests that dabigatran has a more favorable risk-to-benefit ratio for AF patients with mild to moderate kidney disease but may be associated with a higher risk of thromboembolism in those with normal renal function. The study is limited by the small number of patients with severe kidney disease [Del-Carpio Munoz F, et al. Dabigatran versus warfarin in relation to renal function in patients with atrial fibrillation. *J Am Coll Cardiol* 2016; 68:129–131].

High BMI Increases Risk of Diabetes, Not MI or Premature Mortality

Independent of genetic factors, higher body mass index (BMI) is associated with a higher risk of type 2 diabetes, but not of myocardial infarction (MI) or death, suggests a twin study in *JAMA Internal Medicine*.

Using the Swedish national twin registry, the researchers identified 4046 monozygotic twin pairs discordant for BMI. Mean BMI was 25.9 in the heavier twins versus 23.9 in the leaner twins; because the twins were genetically identical, the difference in BMI was lifestyle-related. Twelve-year follow-up data were used to estimate

the effects of higher BMI on mortality and MI risk (composite primary outcome) and incident diabetes (secondary outcome).

During follow-up, MI occurred in 5.0 percent of the heavier twins and 5.6 percent of the leaner twins; mortality was 13.6 and 15.6 percent, respectively. On multivariable analysis, risk of the composite outcome was significantly lower in the heavier twins: adjusted odds ratio (OR) 0.75. On analysis of 65 twin pairs with at least a seven-unit discrepancy in BMI and where the heavier twin had a BMI of 30 or higher, the difference in MI risk or mortal-

ity was not significant.

However, incident diabetes risk was twice as high in the heavier versus leaner twins: OR 2.14. This risk increased with widening BMI discordance between pairs. Changes in BMI occurring about three decades before baseline were also unrelated to MI or mortality, but were significantly related to diabetes risk: OR 1.13.

Genetic factors may help to explain why population rates of MI and mortality are decreasing even as the prevalence of obesity increases. This study shows that lifestyle-related increases in BMI are asso-

ciated with the incidence of diabetes, but not with MI or death.

Obesity appears to have a causal association with type 2 diabetes, with no confounding influence of genetics. “Lifestyle interventions to reduce obesity may be more effective in reducing the risk of diabetes than the risk of cardiovascular disease or death,” the researchers conclude. [Nordström P, et al. Risk of myocardial infarction, death, and diabetes in identical twin pairs with different body mass indexes. *JAMA Intern Med* 2016; doi:10.1001/jamainternmed.2016.4104].

Abrupt Decline in Kidney Function Predicts Early ESRD Mortality

A sudden drop in kidney function in the few months before starting hemodialysis is associated with a threefold increase in the risk of death within the first year on dialysis, reports a study in *The American Journal of Kidney Diseases*.

The prospective study included 661 patients with mild to moderate chronic kidney disease who developed chronic kidney failure requiring hemodialysis. Patients were drawn from the Chronic Renal Insufficiency Cohort (CRIC) Study. Using data on annual estimated

glomerular filtration rate (eGFR), the researchers identified patients with an abrupt decline in kidney function, defined as an extrapolated eGFR of 30 mL/min/1.73 m² at 3 months before the start of hemodialysis.

Abrupt decline in kidney function was evaluated as a predictor of death during the first year on dialysis. Multivariable analysis included adjustment for demographic factors, cardiovascular disease, diabetes, and cancer.

Fifty-six patients met the study

definition of abrupt decline in kidney function—a rate of 8.5%. Sixty-nine patients died in the first year after starting hemodialysis. On adjusted analysis, patients with abrupt decline in kidney function were at increased risk of early death: hazard ratio 3.09. Patients with abrupt decline were more likely to have initial dialysis catheter access, but less likely to have nephrologist care before dialysis.

About 1 in 12 patients starting hemodialysis have an abrupt decline in

kidney function during the preceding three months. The new analysis of CRIC data suggests that this pattern is associated with an increased risk of early death. The authors call for further study to evaluate the causes of such sudden drops in eGFR, and whether interventions can improve survival after starting dialysis [Hsu RK, et al. Abrupt decline in kidney function before initiating hemodialysis and all-cause mortality: the Chronic Renal Insufficiency Cohort (CRIC) Study. *Am J Kidney Dis* 2016; 68:193–202].

After Bariatric Surgery, a Reduced Risk of Kidney Function Decline

Severely obese patients undergoing bariatric surgery are at lower risk of declining kidney function, independent of other factors, reports a study in *Kidney International*.

The study included a cohort of 985 patients with severe obesity—mean body mass index of 46.6—who underwent bariatric surgery between 2004 and 2013. They were matched to the same number of obese patients who did not have bariatric surgery. Propensity score matching included demographic factors, body mass index,

estimated GFR (eGFR), comorbid conditions, and previous nutrition clinic visits.

With a mean age of 45, 80% of patients were women, and 97% were white. One-third had a baseline eGFR of less than 90 mL/min per 1.73 m². At 1 year, patients in the bariatric surgery group had lost a mean of 40.4 kg body weight compared to 1.4 kg for controls.

At median follow-up of about 4 years, 8.6% of bariatric surgery patients had a 30% or greater decline in eGFR compared with 17.9% of controls. Bariatric surgery

was also associated with a lower rate of ESRD or doubling of serum creatinine: 2.2% versus 5.0%.

On adjusted analysis, bariatric surgery patients were at lower risk of both adverse kidney outcomes: hazard ratios of 0.42 for 30% or greater decline in eGFR and 0.43 for ESRD or doubling of serum creatinine. Subgroup analyses showed similar patterns in patients with eGFR less than 90 mL/min per 1.73 m², hypertension, or diabetes.

Bariatric surgery improves numerous

health outcomes for patients with severe obesity, but less is known about how it affects their very high risk of kidney disease. This matched cohort study finds a lower risk of declining kidney function and ESRD after bariatric surgery. The researchers conclude, “Bariatric surgery may be a possible treatment option to prevent and slow the progression of chronic kidney disease in severely obese patients” [Chang AR, et al. Bariatric surgery is associated with improvement in kidney outcomes. *Kidney Int* 2016; 90:164–171].

Policy Update

On Health Reform, Presidential Candidates Propose Divergent Paths

By Bridget Kuehn

With Republican Presidential candidate Donald Trump proposing to repeal the Affordable Care Act (ACA) and Democratic candidate Hillary Clinton promising to strengthen and expand it, this year's presidential race offers stark choices on health care reform.

Health care reform has played a prominent role since the start of the 2016 presidential campaign season, with candidates and even Speaker of the House Paul Ryan (R-WI) proposing everything from a repeal of the Affordable Care Act to Medicare for all. As voters prepare to head to the polls, health policy experts say there are still many unanswered questions about how the health system would be affected by the 2 remaining major party candidates' proposals or Speaker Ryan's proposal.

"These issues are necessarily complex, because the American system of delivering and paying for health care is extraordinarily complex," wrote Brookings Institution Senior Fellow Alice M. Rivlin, PhD, and Urban Institute Distinguished Fellow Robert D. Reischauer, PhD, in a report the pair issued at the outset of the presidential campaign in November 2015 (<http://brook.gs/2b4hJDX>). "Hence, proposed policy changes are inevitably complicated and hard to make clear to most voters."

The report cited 3 key challenges the candidates must address, including resolving the future of the ACA, slowing unsustainable health spending growth, and reforming Medicare to ensure its long-term viability. Rivlin and Reischauer urged the candidates to rise above the current hyper-partisanship surrounding health reform to tackle these enormous challenges.

"Health care has to be a bipartisan program. It is too important not to be," Rivlin said in an interview. "Unfortunately, we've gotten ourselves in this very polarized situation where the parties have very different approaches and there is gridlock."

So far, however, the candidates' and Ryan's proposals have broken down along party lines.

Expanding ACA

Hillary Clinton's health care proposals focus on expanding and strengthening the ACA.

"I want to build on the progress we've made," states Clinton on her website. "I'll do more to bring down health costs for families, ease burdens on small businesses, and make sure consumers have the choices they deserve."

Clinton proposes making health care premiums more affordable, providing more generous federal subsidies, reducing out-of-pocket expenses, and capping prescription drug costs. As a compromise with her former rival Sen. Bernie Sanders (D-VT), Clinton also proposes adding a public option to the existing ACA health insurance

exchanges. All of these proposals would require legislation and Clinton would have to negotiate with Congress, Rivlin noted.

Adding the public option is intended to increase options in markets where so far there has been less competition among insurers and fewer choices for consumers, explained Stephen Parente, MPH, PhD, Endowed Chair of Health Finance and Director of the Medical Industry Leadership Institute at the University of Minnesota.

But its effects on costs and competition depend on how it is structured.

We don't know what a public option would look like or whether it would save money," Rivlin said.

Prior to the enactment of the ACA, proponents of the public option worried that premiums in the insurance exchanges would be too high and argued a public option would bring premiums down, Rivlin explained. But 3 years into the exchanges, those assumptions have proven to be incorrect.

"Premiums came down in the individual insurance market quite dramatically, though they have crept up since," Rivlin said. "[Insurance company] profits have been variable, but it hasn't been a bonanza for insurance companies and many are losing money. It is not clear a public option would be a money saver."

Clinton also proposes allowing those over age 55 to buy into Medicare. Again, Rivlin said a lot depends on how this plan would be enacted.

"If they set the premium at a level that would cover the cost, it wouldn't affect the Medicare Trust Fund," said Rivlin.

Boosting Medicaid access is another goal of the Clinton plan, including passing legislation that would extend the ACA's Medicaid expansion to the 19 holdout states. If they are successful, about 10 million people would gain coverage through Medicaid, said Parente, "but it's a major cost."

Those who are still not covered by insurance could receive care at a community health center, noted Parente. Clinton proposed doubling the funding for federally qualified community health centers. Again, however, there are costs associated with such increased access, he noted.

While some of the proposals are associated with increased costs, Rivlin said that Clinton's plan stresses the continuation of health spending reforms created as part of the ACA. For example, Rivlin noted that Clinton has talked about moving alternative payment models and bundled payments from demonstration programs into wider use.

"I think she is very conscious of the problem of rising costs," Rivlin said.

While none of Clinton's proposals are specific to patients with chronic disease, if she succeeds in expanding coverage it

might result in more insurance coverage for individuals with CKD.

"Anything that improves access is helpful," said nephrologist John R. Sedor, MD, chair of the American Society of Nephrology's Public Policy Board.

Sedor, who works at MetroHealth in Cleveland, Ohio, said it might be particularly helpful for the population of low-income patients with CKD at his hospital.

Scraping ACA

On the other side of the aisle, Donald Trump promises to fully repeal the ACA, including the mandate that individuals buy insurance, and replace it.

"We will work with Congress to make sure we have a series of reforms ready for implementation that follow free market principles and that will restore economic freedom and certainty to everyone in the country," he states on his website.

The Trump plan would allow sale of health insurance across state lines, allow more individuals to deduct the cost of insurance purchased on the individual market, boost use of health savings accounts, and require price transparency from health care providers.

Trump's plan would change Medicaid into a block grant program, where states receive a set amount from the federal government to do with as they wish. Currently, the federal government has certain base requirements for state Medicaid programs and shares the costs with the states. States may offer more generous benefits.

An analysis of the Trump health reform plan by Parente and his colleagues at the Center for Health and the Economy found that the proposal would lead to an estimated 18 million fewer insured individuals, but is also projected to reduce premiums and health care spending (<http://bit.ly/2b8MV59>).

"It's considerably cheaper than the status quo with the ACA," Parente noted.

But there are trade-offs to the reduced costs associated with repealing the ACA.

"I think we'd go back to where we were with people having poor access to care," said Sedor. "They would appear on our doorstep extremely ill and often require emergent care."

Patients covered by Medicaid would be hardest hit.

"It's mostly the Medicaid population who is losing their coverage," explained Parente.

This loss of Medicaid coverage may be particularly detrimental to patients with CKD at the public hospital where Sedor works. He explained many of his patients have part-time jobs or jobs without benefits.

"Our patient population tends to be less highly employed; a lot of them don't necessarily get coverage through work," said

Sedor. "Without Medicaid, they may not have an option."

Patients with end stage renal disease (ESRD) wouldn't be affected, noted Parente, because Medicare covers them regardless of age. But for those with less severe kidney disease, coverage would be contingent on whether they have access to employer-sponsored health coverage, are eligible for their state's Medicaid program, and what they can afford, he noted.

"It really depends on disease severity, what state they are in, and how they want to try get their coverage," he said.

Parente and his colleagues projected that premiums would decrease under the plan because it would roll back the ACA insurance requirements, such as that plans cover certain essential benefits or that companies issue insurance regardless of an individual's health, explained Parente. Guaranteeing access to coverage regardless of health alone drives up premiums by 20%–25%, he noted.

"It reverts you back to what state regulations were in 2010," said Parente.

Lower premiums and the return of "catastrophic plans" that provide very limited coverage at low cost might somewhat counteract the increase in the number of uninsured, Parente said. But, "it by no means compensates for the loss of coverage you get from eliminating ACA's Medicaid expansion."

Some patients with CKD, however, may prefer high-deductible, consumer-driven plans because they often place fewer restrictions on which clinicians are covered, Parente said. He explained that lower deductible plans might contain costs by excluding physicians who appear to be providing expensive care. Clinicians who specialize in providing care for those with severe disease may fall into this category.

"I've known a few people who are on dialysis or on kidney care and they are some of the most astute shoppers I know, whether they are clerical workers or academics," Parente said. "They are not just shopping for a cheaper price but for more effective care."

But Rivlin said the effect of the Trump plan on premiums really depends on whether it would repeal all the insurance market reforms implemented as part of the ACA. If it does, the individual insurance market would revert to the "chaotic" pre-ACA state, where individuals with chronic diseases, like CKD, pay more—if they can get insurance at all, she said.

"Premiums would go down for healthy people and up for the unhealthy," Rivlin said. "We've been there."

"People forget what a huge advance the insurance reforms were," she said. "They've created a market in which insurance plans are competing on price and coverage rather

Continued on page 13

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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 ($\geq 3\%$ 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.



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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.

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Version: 09/2015

Policy Update

Continued from page 10

than just competing to insure the lowest cost group of people."

The Trump plan might also increase health spending, if it eliminates the cost-containment experiments like alternative payment models in the ACA, Rivlin noted.

The Ryan alternative

The Ryan proposal (<http://bit.ly/28MOcdF>) also draws on some Republican mainstays, including making Medicaid a block grant program. However, Parente and his colleagues at press time hadn't yet analyzed the plan's effects and were still gathering details about it.

"The Trump plan has ideas [Republicans] have talked about for 10 years, but is not stitched together very well," Parente said. "As a consequence, it leaves a lot of people without insurance. The Ryan plan tries to get some of the efficiency that is in the Trump plan but still covers as many as possible."

For example, the Ryan plan preserves a modified version of the ACA's prohibition on insurance denials based solely on pre-existing conditions, Parente noted. Individuals would at least receive a quote, he said. The Ryan plan also preserves a modified version of the ACA's community rating system. Under the ACA, companies are not allowed to set premiums based on health status, only age, geographic area, and smoking. The ACA also limits how much more insurers can charge based on these factors. Under the ACA, insurers can charge older customers up to 3 times more than younger ones for an identical insurance plan. Ryan's plan would allow them to charge older customers up to 5 times more than younger ones.

The Ryan plan proposes making high-risk pools available for patients who can't access coverage elsewhere.

The effects of Ryan's Medicaid block grant plan on coverage are uncertain.

"It would depend on how it would be structured," Rivlin said. "The fear is that

ungenerous states would cut back."

The official Republican National Committee platform also proposes shifting Medicare toward a premium support program rather than a defined benefit and increasing the eligibility age (<http://bit.ly/24W6Ipw>). Under such a plan, seniors would purchase competing commercial insurance plans using a federal subsidy, similar to the way ACA works, Rivlin noted.

"I'm on the record as thinking a gradual shift to premium support, if well designed, is a good thing," said Rivlin. "The federal government can define the subsidy and not increase it any faster than Congress wants to."

But it has to be done carefully and gradually, she emphasized. She noted earlier health reform proposals suggested by Ryan would be very gradual, but the subsidies over time would become much less generous than Medicare in its current form.

"It doesn't have to be that way," Rivlin said. "In fact, Ryan himself moved to a more moderate plan."

One possible scenario if Trump wins and Ryan remains Speaker of the House is that the Ryan plan will move forward, said Parente.

"The Ryan plan has probably greater traction to move," said Parente.

The chances that either parties' plans will be enacted as is, is "zero," said Rivlin. She predicts that most likely ACA and Medicare will be preserved and improved upon. Medicare might move in the direction of premium support, building on Medicare Advantage plans, which already cover about one-third of Medicare beneficiaries.

Regardless of who is elected, the health reform changes that are made during their presidency could well be a mash-up of the two parties' proposals. Parente, who advised Sen. John McCain (R-AZ) during the 2008 presidential campaign, noted that the ACA has ideas from both Hillary Clinton's and Sen. McCain's 2008 campaign health proposals.

"It more or less became a fusion of McCain's and Clinton's plans," he said. "That could happen here, too."

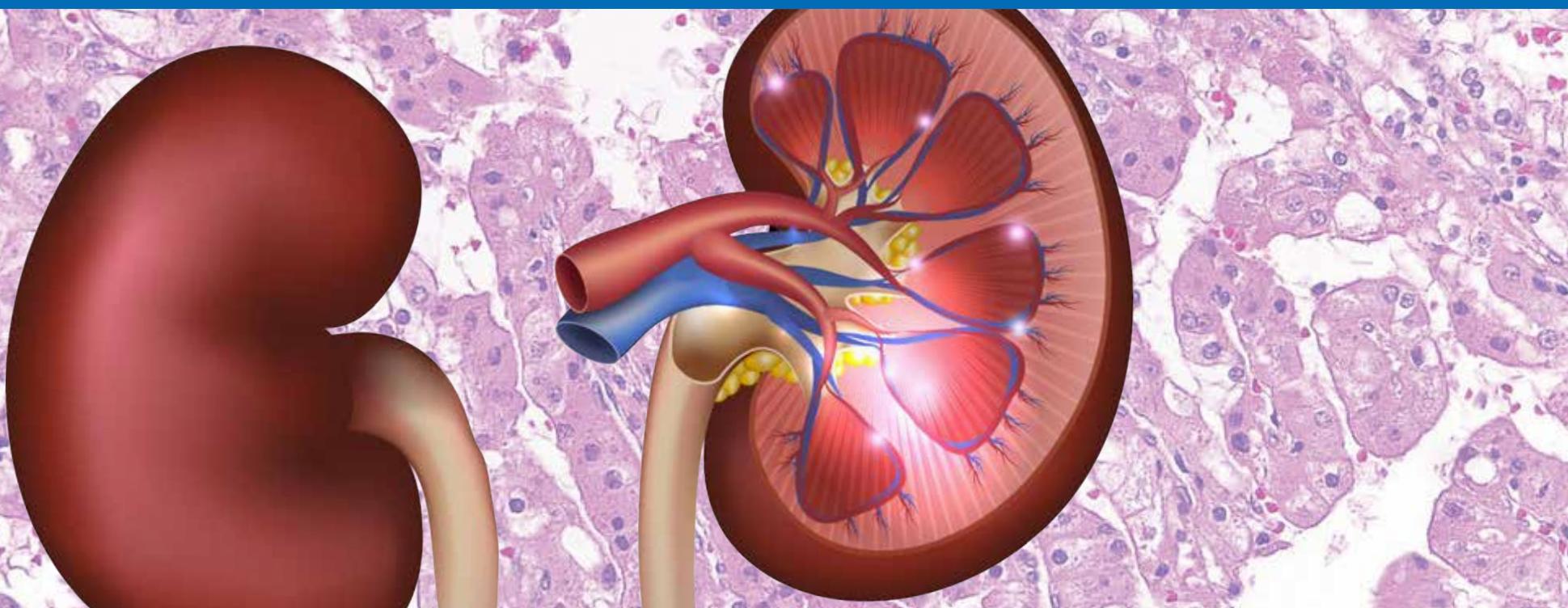
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Distinguished Conversations

Once again, *Kidney News* brings together two outstanding clinicians, scientists, teachers, and leaders in nephrology and medicine in a "Distinguished Conversation." Each has transformed the practice of nephrology with excellent examples of bed-to-bench problem-solving, bringing innovative care back to their own as well as to our patients.

Joel Kopple, MD, is currently Professor at the David Geffen UCLA School of Medicine and the UCLA Fielding School of Public Health. He served from 1981 to 2007 as Chief of the Division of Nephrology at Harbor-UCLA Medical Center. Known as the father of renal nutrition, Dr. Kopple has contributed greatly to our understanding of the impact of kidney disease on nutritional status and on the influence of nutrition on kidney function and health. Toward this end, he has published more than 500 papers, books, and chapters, including the authoritative "Nutritional Management of Renal Disease." He has garnered many prestigious awards, including the National Kidney Foundation (NKF) David M. Hume Memorial Award, the ASN Belding H. Scribner Award, and the Louis Pasteur Award of the University of Strasbourg, France.

Dr. Kopple served as President of NKF and the International Federation of Kidney Foundations. He played a seminal role in founding the International Society for Renal Nutrition and Metabolism, the International Federation of Kidney Foundations, and World Kidney Day, and he served a central role in founding the Rhoads Research Foundation of ASPEN and the National Kidney Disease Education Program (NKDEP) of the National Institutes of Health. The NKF Council on Renal Nutrition established the annual Joel D. Kopple Lectureship and Award in his honor, and the International Federation of Kidney Foundations also established an annual Joel D. Kopple Award.

Richard Glasscock, MD, is Professor Emeritus at the David Geffen School of Medicine, UCLA. He is an internationally known expert in nephrology, especially glomerular disease, the aging kidney, and kidney function.

A native Californian, Dr. Glasscock attended Duke University School of Medicine, graduated from UCLA Medical School, and trained in nephrology at the Brigham and Women's Hospital and in immunopathology at the Scripps Research Institute. He has held innumerable leadership positions, including Chair of Medicine at UCLA Harbor Hospital and at the University of Kentucky School of Medicine. He also served as Chairman of the American Board of Internal Medicine, President of NKF, President of ASN, and founding Editor-in-Chief of ASN NephSAP. Among his many honors are the NKF David M. Hume Memorial Award, the UCLA School of Medicine Distinguished Achievement Award, the NKF Distinguished Service and President's Award, the American Kidney Fund Torchbearer Award, the Medal of Excellence of the American Association of Kidney Patients, and the ASN Robert G. Narins Award for educational excellence. He has published over 600 papers, books, book chapters, and monographs. He continues to actively teach internationally and is widely sought for his academic and clinical insights.

Please enjoy this discussion and let us know what you think of the series.

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



Joel Kopple, MD



Richard Glasscock, MD

Dr. Kopple: Why did you become a nephrologist? Were there other fields you considered as alternatives?

Dr. Glasscock: Thank you, and the ASN, for this opportunity to tell you how proud I am to be part of the discipline of nephrology, especially since I believe it has done so much to provide relief from suffering and extend lives over the past 50 or 60 years. I hope I've been able to do a few things to help nephrology move along during my career.

I did not immediately start out to be a nephrologist, and I had very few role models to help steer me careerwise, other than a primary care physician during my high school days. I also didn't have any doctors in my family, so my initial exposure to nephrology was a chance event—a little bit of serendipity and good luck.

During my first year of residency at UCLA in 1960, patients were assigned to residents on a rotational basis, and a 17-year-old girl with end stage renal disease (ESRD) came under my care. I never knew exactly what she had, but in retrospect, her symptoms were certainly suggestive of some form of hereditary disease, perhaps medullary cystic disease. Her physician of record was Morton Maxwell, who had just joined the Department of Medicine at UCLA as a young faculty member doing clinical nephrology (although the term "nephrology" wasn't widespread at the time) and was trained by Homer Smith. It became apparent there wasn't anything we could do for the patient other than intermittent peritoneal dialysis, so it was decided that maybe she would be a good candidate for a kidney transplant. Transplantation of kidneys from related and unrelated persons had started in Boston under Murray and Merrill and colleagues in the '50s and early '60s, but was not yet a procedure that was widely applied to treatment of ESRD.

After being tissue-typed using leuko-agglutinin techniques, she received a kidney from her mother in the late fall of 1960. It turned out that they were reasonably compatible on the basis of leukocyte antigens. She was treated with cyclophosphamide, actinomycin, and steroids, as azathioprine was still an experimental drug at that time.

The surgery itself was reasonably successful, although she did develop a ureteral leak. Two weeks after transplant, she experienced a severe rejection, which was surprisingly reversed by high-dose steroids. To my knowledge, it was the first time an acute allograft rejection had ever actually been reversed by a drug. However, due to multiple rejection episodes, eventually she succumbed to the usual complications of excessive immunosuppression, probably a cytomegalovirus pneumonia.

The case transformed my professional career. I became very interested in and committed to pursuing nephrology, specifically transplantation. I participated in the care of several additional cases of renal transplantation at UCLA. Fortunately, the urologist leading the renal transplantation effort at UCLA, Willard Goodwin, happened to know Joseph Murray and John Merrill at the Peter Bent Brigham Hospital in Boston (Now Brigham and Women's Hospital; BWH) very well, and with a telephone call, he managed to get me a fellowship position in Merrill's lab, which I started in July 1963.

My co-fellow at the time was Bernie Carpenter. Bernie has unfortunately since passed away, but he and I were the first two medical transplant fellows at BWH, and our careers were intertwined for many years subsequently. Bernie was a great

friend who made numerous seminal contributions to the field of Transplantation, and remained at BWH for his entire professional career.

The BWH experience from 1963 to 1965 solidified my career choice. Under the influence of John Merrill, George Thorn, Joseph Murray, and Gustav Dammi (the Chairman of Pathology), my career took another twist when I was asked to go to Scripps Clinic and Research Foundation and undertake training in immunopathology, under Frank Dixon, and bring it back to the BWH. At the same time, Bernie Carpenter was sent away to develop a transplantation immunology expertise and would return a few years later.

This “outsourcing” was a common approach in those days: taking ambitious young fellows, encouraging them to pursue a career, giving them an opportunity for outstanding training in a basic laboratory of international reputation, and then having them return to the institution with a commitment to develop a program. I fell into that mold almost serendipitously, but it had a profound effect on my future. By the time I finished my year-and-a-half training with Frank Dixon in La Jolla, I was well on my way to a lifelong commitment to immunology, glomerulonephritis, transplantation, and clinical nephrology. That is really how my nephrology career began.

Dr. Kopple: I became a nephrologist several years after you, and I remember that during the treatment of people undergoing chronic dialysis or who had received a kidney transplant, we encountered many disorders that had never or only rarely been described before. It was like travelling through space to another planet. As you pointed out, it was thrilling to save people who otherwise would have died. It is hard to describe to someone who wasn't around during that era of medicine just how thrilling successes were and often how bitterly disappointing failures could be.

Dr. Glassock: I agree completely. The combination of curiosity and powerful new tools can be intoxicating.

Dr. Kopple: You stayed in academic medicine—obviously to everybody's benefit—but when did you first consider the possibility of becoming an academician? Did you want to do that before you started medical school or did that begin later in your career? What prompted your decision?

Dr. Glassock: My professional career goals during my last year of medical school were to become a solo practitioner in general internal medicine. That mindset continued during my first few months of internship. I had no particular preference for one discipline over another. I certainly had plenty of exposure and opportunities to look at fields like cardiology or hematology, which were very strong programs at UCLA at the time.

The singular experience described above, with the patient who was dying of a disease that no one could cure, and the transformation that occurred after she received a kidney transplant (compared to her miserable existence on weekly peritoneal dialysis with a temporary catheter) had a powerful influence on my career choice. This young woman was extremely brave, and my experience with her resulted in my abrupt change in focus.

I never intended to pursue a career in a research laboratory exclusively, and I didn't view myself as a laboratory scientist. I always wanted to be involved in patient care in some capacity and looked upon research as an opportunity to explain the problems of real patients.

Dr. Kopple: Would you ascribe any of the inspiration that led you to these decisions to your interactions with Dr. Maxwell, Dr. Merrill, Dr. Goodwin, or to other mentors or role models?

Dr. Glassock: I have had three principal mentors in my professional life who, looking back, had key effects on my career. One was David Solomon, a young UCLA faculty member (an Endocrinologist trained at Harvard) who offered me

an opportunity to work part time in his lab when I was a first year resident. David was inspirational from day one and he stimulated my curiosity in research. (He later recruited me to a Faculty position at Harbor-UCLA Medical Center).

Dr. Merrill, my first nephrology mentor at the BWH, was a charismatic person deeply involved in both transplantation and dialysis. He was a world leader in those fields, and everyone looked up to him. I learned a lot about patient care under Dr. Merrill, and without him, I would never have gotten the job with Frank Dixon, who propelled my interest in immunology to a much higher level. The rigors and demands of research as a career really came out in my day-to-day exposure with Dr. Dixon and the trainees he attracted. I still regard him as a brilliant and creative investigator of the highest magnitude.

Dr. Kopple: What events in your career have given you the greatest satisfaction?

Dr. Glassock: Other than the ability to see, analyze, and hopefully help patients, which continues to this day, I think my experience in the discovery of anti-glomerular basement membrane (anti-GBM) disease has to rank at or near the top. In 1964, we had only limited knowledge of autoimmune diseases of the kidney. We suspected they were real, and a lot of experimental evidence in animals had shown the way. So the seminal group of experiments that Richard Lerner, Frank Dixon, and I started in 1965 gave me a great deal of satisfaction. Not only was the work a first, but it helped bring this disorder to light in the minds of many other investigators who went on to make very significant contributions. In the past 50 years, we have gone from the discovery of anti-GBM disease to a cure for many patients—the whole cosmos of discovery to cure encapsulated in a single disease entity. I am very proud of what I was able to contribute to the field in that early experience.

Dr. Kopple: What other achievements gave you great satisfaction?

Dr. Glassock: I had one experience . . . and I wouldn't necessarily say it gave me great satisfaction, but I learned much from it. I studied the pathogenesis of membranous nephropathy (MN), which as you know, has turned out to be another autoimmune disease of the kidney. I worked pretty diligently on that problem—using experimental models. Trying to understand how the disease develops was one of the subjects of my first NIH grants. We carried out a series of well-designed experiments that led us in *one* direction, but it turned out it was not exactly the *right* direction.

Others, such as Bill Couser, actually discovered the true answer to the question of the pathogenesis of this disease. However, if you carefully examine the thread of ideas over 15 or 20 years, they all cumulatively fostered and eventually contributed to the landmark discovery by Laurence Beck, David Salant, and their colleagues in Boston of the anti-phospholipase A2 receptor and its role in human MN.

More recently, in my post-retirement career, I have become very interested in chronic kidney disease (CKD) and the aging kidney. This work has given me a lot of satisfaction, particularly because it has allowed me to write and publish when I might have been spending time tending the roses or walking on the beach. Instead I've been spending time thinking and writing, which is fun and enjoyable for me.

Dr. Kopple: As someone who has not only followed your career, but also watched the evolution of nephrology, your writings in the field of CKD have added a number of dimensions to the way most of us consider this disorder. Over the years, you have added an enormous amount of perspective and wisdom to the way we approach disease.

Dr. Glassock: Thank you, Joel. For those reading this interview who find writing challenging, I want to tell you that I found writing scientific papers incredibly difficult—painful even—in the beginning. But as I gained more knowl-

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Distinguished Conversations

Continued from page 15

edge and familiarity with the literature and read the work of others who were truly great writers, I found it became easier and more enjoyable.

I now relish the opportunity to sit down at a computer and write an analysis, a review, or an original manuscript, which would have been anathema to me when I was in my 20s and 30s. So do not give up hope if you think you can't write. It is an acquired talent that isn't easy, and it does take a lot of practice.

I have done a lot of writing in the hope that it will help people better understand various diseases. Although I may not have always contributed original ideas, I have tried to translate the writings of others into content that is perhaps more digestible and practical to clinicians facing the day-to-day problems of patients with CKD, particularly those with glomerular disease.

Anti-GBM disease and the excitement of the experiments we did in the late '60s still remain among my most treasured memories in the field of glomerular disease research. We utilized knowledge available at the time in experimental laboratories and translated it in a way that led to new diagnostic tests, novel classifications, and innovative therapies that had an immediate and lasting impact on patient care. I am very proud of that.

Dr. Kopple: It may not be well-known, but you recruited me when you were Chairman of Medicine at Harbor-UCLA Medical Center to replace you as Chief of the Division of Nephrology and Hypertension. From time to time, you graciously agreed to speak at our Renal Grand Rounds. I was always impressed that when word got around that you would be giving the lecture, the number of attendees would at least double and many private practitioners in nephrology from the surrounding area would come specifically to hear you. Your talks were extremely informative and scholarly, integrated diverse pieces of information, and invariably provided practical information that could be translated directly into patient practice.

Dr. Glasscock: Your point about recruitment speaks to how one becomes a successful leader in academic medicine. One of the fantastic talents of Donald Seldin, one of the great icons of Nephrology, was his ability to find extremely bright and gifted individuals and nurture their careers successfully. I think he has 4 Nobel Prize winners in his Department. I can now claim with some degree of humility that selecting you as my successor was one of the best decisions I ever made.

Dr. Kopple: I am deeply honored by your statement. Along this line, what advice would you give young physicians making decisions about which path to pursue in their professional careers?

Dr. Glasscock: I think the most important thing is to find something you love to do. Don't ever choose a path that you feel uncomfortable or unhappy with. There will also inevitably be periods of unhappiness in any career, so don't give up too early. I certainly had doubts about my own career path. My very first independent research activity didn't pan out as successfully as I'd hoped it would and there were many periods of discouragement, but in the end, it's a matter of being happy and satisfied with your choice.

If you want to pursue a career in research and clinical scholarship, you have to maintain a high level of curiosity; be persistent, patient, and resilient; and surround yourself with talented, passionate people and powerful tools. These ingredients for a successful career in nephrology haven't changed. Another ingredient is money in the form of grants or gifts to nurture career development, support investigator-initiated studies and trials, and to promote collaborative engagements. Funding for research and training has been an up-and-down affair over the years, but I don't think that money alone is the key to success in research. You've got to have the curiosity, the persistence, and the tools, and eventually things will come your way.

As far as clinical care is concerned, you have to love being around sick people and have confidence that somehow you can transform their lives for the better. Nephrology provides this in a big way. There are enormous opportunities to do good: transplantation, successful dialysis, diagnosis and treatment of glomerular disease, management of fluid and electrolyte disorders, treatment of hypertension, and so forth. This has been a characteristic of our discipline ever since it was founded, and I think it's just as attractive a discipline today as it was then.

Dr. Kopple: It is said that one attraction of a nephrology career is that nephrologists are often among the best all-around clinicians owing to the demands of the nephrology practice. Nephrologists must not only be specialists in their field, but their patients develop so many different complex, interrelated illnesses that they must have a strong background in other areas of medicine. Do you see it this way too?

Dr. Glasscock: I agree with you completely. Nephrologists are great internists and have a perspective in medicine that few other disciplines have. I was Chairman of the American Board of Internal Medicine in the early 1990s, and at that time there was a strong movement to balkanize medicine, to divide it up among its subspecialties and, in a sense, sever the link between the core of internal medicine to allow these subspecialty disciplines to pursue their own development without any firm linkage to the mother discipline. I would be very unhappy if nephrology ever became divorced from internal medicine and I hope that some of my efforts to prevent this were successful.

The knowledge I've gleaned from nephrology is often very applicable to common problems seen in internal medicine. Even today when I see patients without nephrology-related problems (and I do see such patients from time to time), my knowledge of nephrology is very useful.

Dr. Kopple: How can we best make nephrology more attractive to potential trainees or fellows?

Dr. Glasscock: We can communicate the fact that opportunities for the pursuit of knowledge have never been greater. Gene technologies and bioengineering—which were unimaginable a few years ago—are on the cusp of being applied to patient care. Such technologies can lead to excitement, and excitement leads to interest. So communicating the opportunities in clinical scholarship to the next generation of nephrologists is key.

We need to focus on the origins of some practitioners' dissatisfaction with nephrology and see whether the factors that are controllable can be modified. I don't think dissatisfaction with nephrology as a career stems from its lack of intellectual challenges. There are many intellectual challenges and opportunities in nephrology.

Money, I think, unfortunately, is one of the main reasons for dissatisfaction. One obstacle that didn't exist 30 or 40 years ago is the burden of debt. Medical students and residents come out of medical schools and training programs deeply in debt, and this can't help but influence their career choices to an extent. Inheriting so much debt and then having to struggle to resolve it in the face of reduced reimbursement places additional demands on practices that make for dissatisfying careers.

Medicine has become a business and that tends to divorce you from the day-to-day care of your patients. The patients have also changed. In dialysis units, we deal a lot with older patients with multiple comorbidities and often depression. Oncologists also deal with older patients with diseases that lead to desperation—yet they have among the highest career satisfaction. I believe this is partly because they now can really do something to take care of their patients and see results. I think we can too. I just don't think we are communicating and showing it as well.

Dr. Kopple: I remember when we could not treat people dying of chronic kidney failure with dialysis, and of course transplants could only be done occasionally during the early '60s. To this day, every time I start a patient with ESRD on dialysis, I feel it is a miracle that I can do something now that could not be done when I was a student. It is like giving life to someone who otherwise would not have a future. Having said that, as you pointed out, chronic dialysis patients are often very depressed and anxious. I wonder whether the experience of many medical students and young doctors with depressed or anxious chronic dialysis patients discourages the former from going into nephrology.

Dr. Glasscock: Training of young residents has been very hospital-centric for many years. That's beginning to improve with more mandatory outpatient assignments, but can you imagine the viewpoint of a young internal medicine resident looking at nephrology as a career but seeing only those patients who are

too sick to be managed as an outpatient? They may not always get to see that many patients on renal replacement modalities have very reasonable lives.

You've referred to me patients who did magnificently on dialysis, but they were never in the hospital, so no residents ever saw them. If we want to encourage the next generation of nephrologists, we must find a way for these young people to see the discipline practiced in its broadest sense, not just a snapshot within the artificial environment of a hospital.

Dr. Kopple: You are saying that we need to rethink the way we organize training programs, not just for nephrology fellows, but also for residents who are still considering which specialty they may want to pursue.

Dr. Glasscock: Peer interaction also has not gotten as much attention as it should. My peers—people like Barry Brenner, Alan Hull, Tom Parker, Claudio Ponticelli, Bernie Carpenter, and yourself, as well as the numerous trainees that I supervised over my career—had a huge influence on my professional development. Opportunities for discussion arose whenever I was among these people, and we all inspired each other. The interactions I had and continue to have with my peers provide reassurance and confirmation that within the discipline of nephrology, the sum is greater than the parts.

So isolation from the broader sphere of nephrology can be a great detriment to professional development. Physicians considering nephrology as a career should take advantage of every opportunity to develop mutually constructive relationships with their peers. This is possible now, much more than in the past, because of new technologies like the internet and social media that encourage these kinds of relationships.

Dr. Kopple: Where do you see nephrology going in the future? If you were to look ahead 50 or 75 years from now, what do you think nephrology will be like?

Dr. Glasscock: I think we are going through a transitional period in which the primacy of dialysis as a major part of nephrology will diminish. You can see this vividly in evaluations of the global burden of dialysis—at least for developed countries like the US, not for underdeveloped countries, which may be decades behind. In America, I think the future of nephrology will see dialysis occupying a less major role in patient care.

Transplantation, on the other hand, will become a much more dominant part of the renal replacement portfolio because of changes in management and the fact that the ability to produce permanent tolerance is likely to occur in the next few decades.

So if I were to look at what nephrology will be like 50 years from now, dialysis will not be as common, transplantation will still be very important, and the variety of tools available for clinical nephrologists to prevent and treat diseases before they get to the end stages will be enormous. I also do not think diabetes or diabetic nephropathy will be a major problem 50 years from now.

You might ask, "What's going to happen to nephrology if we don't have any diseases to treat?" Isn't that our goal anyway? There will always be disorders that arise that we don't even know about, like Mesoamerican nephropathy or a Zika-like virus that causes kidney disease, for example. These are inevitable, but going forward, we will do a better job of taking care of patients and preventing end stage renal disease.

Also, of course, we are learning that some patients have nothing to benefit from beginning dialysis. For the frail elderly, dialysis may not be the best option. Palliative or conservative care may be as good or better.

Dr. Kopple: Do you think there will be new sources of kidneys for transplantation?

Dr. Glasscock: The hope is that we can bioengineer a fully compatible kidney on a decellularized non-human kidney scaffold by implantation of embryonic stem cells directed to differentiate into the nephron segments. For the moment, I think that's a bit of magical thinking. No one to my knowledge has yet achieved anything close to a functional kidney via a bioengineering approach. But the principles are reasonable, and if we can overcome some of the present seemingly insurmountable obstacles, I think it's theoretically possible that we will eventually do away with the need for living donor and deceased donor transplants.

Dr. Kopple: What about preventive nephrology and public health measures?

Dr. Glasscock: We have a very promising arena for preventing acute kidney injury (AKI) in underdeveloped countries. AKI is often related to diarrhea, infectious diseases, and community-based toxic exposures. If we can improve the water supply and early treatment of diarrhea and infectious diseases like malaria and leptospirosis, if we can eliminate snake bites and the like, then yes, we could make major inroads in AKI in underdeveloped countries.

As for CKD, yes, we can do a great job with prevention. But I'm not convinced that large-scale screening is the approach we should take. I'm more inclined to believe our approach to prevention will become more nuanced and targeted to specific diseases recognized by molecular techniques or other forms of genetic analysis rather than screening a seemingly healthy population for markers of disease. Essentially, I think prevention is going to be a dominant part of our discipline as we learn more about the genetic and immunologic origins of the diseases we are now treating. The better we get at identifying the pathogenesis of disease, the better equipped we will be to prevent it.

Dr. Kopple: It has been pointed out that about 70–72% of people with end stage kidney failure have diabetes, hypertension, or other, obesity-related kidney diseases as the cause of their kidney failure. Do you think there could be a major role for public health measures to reduce the contribution of these disorders to end stage kidney disease, particularly because one should be able to prevent many of these conditions?

Dr. Glasscock: In principle, your concepts are quite defensible. In practice though, I think we have overestimated the ability of physicians to alter behavior in a manner that will prevent diseases. You're talking about a fundamental change at a societal level of the factors that are believed to have contributed to these common diseases, such as overeating, lack of exercise, consuming too much salt and the wrong kind of calories, too much smoking . . . that all involves a behavioral change in the patient starting when they appear healthy.

I have kids who believe they're immortal. I believed I was immortal when I was their age too. Convincing them to change their behavioral habits in order to glean a benefit at the end of their life is very difficult. Although you are right about obesity, overeating, and under-exercise, translating that knowledge into an effective tool to prevent disease is an extraordinarily difficult and often unsuccessful effort. There is a 90% recurrence rate after treatment for obesity. Unless we eventually learn to better understand exactly what causes obesity (and it is a very heterogeneous disease, like so many, that will have to be dissected into its various components), some treatments will work for some but not necessarily for others. So I agree with you in principle, but in a pragmatic way, I'm less fully convinced.

Dr. Kopple: I might make a minor dissenting point. Obesity was much less prevalent in the United States and other countries until sometime around the 1970s—the pandemic of obesity is quite recent. When I watch old movies made before the mid- or late 1960s, it's fascinating how much thinner people generally were. It's my hope that we might be able to change our eating patterns and in some ways revert back to the way we used to be.

I completely agree that the treatment of obesity, other than perhaps by bariatric surgery, gives poor results. Perhaps we can develop educational programs and other societal tools for preventing people from becoming obese in the first place. This is my hope.

Dr. Glasscock: Let me use a personal example. When I started out in nephrology and dialysis, a major cause of end stage renal failure was glomerulonephritis. Most patients considered as candidates for renal replacement therapy, and young patients in particular, had glomerulonephritis. Back then, we didn't dialyze any diabetics. But look at today—glomerulonephritis as a cause of end stage renal failure is decreasing in many parts of the world.

Continued on page 18

Distinguished Conversations

Continued from page 17

So if you understand the mechanisms of the disease processes that lead to end stage renal failure, you can eventually deliver effective tools to manage it. Glomerulonephritis, which is my field of expertise rather than obesity, is a prime example of that precept. Better tools for detection, classification, and management of glomerulonephritis will logically form a better understanding of the disease processes and lead to better outcomes.

Anti-GBM disease is now often curable, as patients can go into long-term remission if the disease is detected early enough and treated appropriately. That accomplishment happened over the past 50 years. It took the efforts of many investigators and brave patients, but this, I think, is the paradigm of how one needs to pursue the diseases that cause end stage renal disease today. That's why I'm so optimistic about the future of nephrology, because the great achievements that have occurred in glomerulonephritis have and are occurring in hypertension, diabetes, and obesity.

Dr. Kopple: There is another cause of progressive kidney failure: as people age, they usually lose a large proportion of their glomerular filtration rate. This is associated with histological changes within the kidney. Do you see advances occurring in this area as well?

Dr. Glasscock: That's a good question, and I've spent a lot of time thinking about it. Organ senescence, as it occurs in the kidney, is a loss of nephrons over time. We've documented that from measurements of the number of nephrons remaining in peoples' kidneys as they get older. The origin of renal senescence is very complicated, and I think we're only beginning to understand it.

The rate of renal senescence may begin in utero. You're born with a certain number of nephrons. Barry Brenner has been the leading force in demonstrating the relevance of this to human biology. However, no two individuals are alike with respect to the number of nephrons they have at birth. Some have

very few and some have too many. This is all conditioned on the fact that intra-uterine nutrition modifies nephrogenesis, and it is manifested by low birth weight. Low birth weight and low nephron endowment predict, in my opinion, the eventual impact of renal senescence and loss of nephrons later in life. If this hypothesis is true, and you happen to be born with a weight <2.5 kilograms, my prediction is that the effect of renal senescence will be greater because you started out with fewer nephrons.

If this idea translates into reality—and it hasn't yet—it may offer an opportunity to alter the rate of renal senescence going forward by eliminating a treatable disease—*intrauterine fetal malnutrition*. We're not always going to have the greatest tools to do that, but we can help prevent fetal malnutrition by improving maternal nutrition. I think you can grasp the significance of this hypothetical framework about what it means to lose nephrons over one's lifespan and how important it is, in my opinion, to ensure that you're born with the most nephrons possible and to protect those nephrons to the maximum extent throughout life. I believe attention to this approach will have an impact on the rate of CKD as it appears in populations studied by epidemiologists.

Dr. Kopple: That's a very interesting perspective. Before we close, are there any final comments you would like to make?

Dr. Glasscock: I want to congratulate ASN and the leaders who decided to allow us old-timers to tell our stories. I hope my optimism will encourage at least one individual on the cusp of making a decision about where to go with their medical career to choose nephrology. I can assure them that if they take this choice seriously, they will not be disappointed and that the future of nephrology is golden and bright. If they just put themselves in the right place at the right time with a heavy dose of curiosity, they will have a wonderful lifelong experience with this magnificent and noble profession we call nephrology. ●

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Practice Pointers

Viral Glomerulonephritides

By Cynthia C. Nast

Which viruses cause glomerular disease?

A number of viral infections can result in glomerular damage, inducing a spectrum of lesions with differing pathogenetic mechanisms (Table 1, Figure 1). The most common of these include hepatitis B, which typically causes glomerulopathies when there is a chronic carrier state, often owing to childhood infection in endemic areas. Glomerular lesions occur in long-term hepatitis C infection, and are found in acute or chronic infection with human immunodeficiency virus (HIV). Less often, parvovirus B19 and cytomegalovirus (CMV) induce glomerular injury. Detailed specific lesions associated with these viruses are provided below. Nonspecific entities, such as postinfectious glomerulonephritis and AA amyloidosis secondary to chronic disease, are not discussed.

What types of glomerular disease are caused by hepatitis B and C?

Hepatitis B and C produce similar types of immune complex glomerulonephritides, although with differing incidences. Secondary membranous nephropathy, often with mesangial hypercellularity and mesangial or subendothelial deposits, is the most common hepatitis B-associated lesion and occurs less frequently with hepatitis C. Contrarily, immune complex membranoproliferative glomerulonephritis (MPGN), often with endocapillary mixed cryoglobulin deposition, typically is found with hepatitis C and much less often with hepatitis B, the latter usually without cryoglobulins. In fact, hepatitis C is the most often identified cause of secondary MPGN. Nonspecific mesangial proliferative glomerulonephritis may result from immune complex deposition in patients infected with either form of hepatitis. Rarely, patients infected with hepatitis C have immune deposits with a fibrillary substructure diagnostic for fibrillary or immunotactoid glomerulonephritis, the latter with very few reported cases.

How does HIV manifest as renal disease?

There are varied glomerular lesions associated with HIV infection that may owe, in part, to differing HIV subtypes and host genetic heterogeneity. The most well-known renal complication is collapsing glomerulopathy (HIV-associated nephropathy or HIVAN), characterized by glomerular capillary obliteration with hypertrophy and hyperplasia of epithelial cells, and tubulointerstitial injury with microcystic tubular dilatation. This lesion occurs predominantly in black patients, particularly in those with two APOL1 risk alleles and not receiving highly active antiretroviral therapy (HAART).

HIV also is associated with more typical forms of focal and segmental glomerulosclerosis (FSGS), although it is uncertain if this is due to the virus, reflects the incidence of FSGS in the non-HIV infected patient population, or is a nonspecific result of chronic kidney injury due to hypertension, diabetes, or other factors related to aging. A number of immune complex glomerulonephritides have been attributed to HIV infection. In Caucasian patients, the most prevalent is IgA nephropathy, which has the usual morphologic and clinical features of this disease with the exception of endothelial tubuloreticular inclusions in untreated patients, a hallmark of HIV infection. A lupus-like immune complex lesion has been described in children and adults, sometimes with positive lupus serologies, and has been associated with lower viral loads compared to patients with HIVAN.

What types of disease are associated with other viral infections?

Parvovirus B19 has been reported in association with collapsing glomerulopathy with a predilection for black patients, similar to HIVAN and also possibly augmented by APOL1 risk alleles. Typical FSGS also has been described in chronic infection, but more likely indicates secondary scarring. Proliferative glomerulonephritis has been identified infrequently and occurs soon after viral infection, with IgG or IgA dominant immune complexes identified in glomeruli; the latter may clinically simulate Henoch-Schonlein purpura.

There are few reported cases of CMV-related glomerulopathies in humans; these include mesangial proliferation with or without necrosis, MPGN and membranous nephropathy typically described in infected infants or immunosuppressed renal transplant recipients, and collapsing glomerulopathy in immunocompetent and transplanted patients.

How do viral infections cause glomerulonephritis?

There are common mechanisms of virally induced glomerular injury including direct infection of glomerular cells, damage due to upregulated cytokines and pro-inflammatory factors, and deposition of immune complexes. Additionally, for all glomerular lesions secondary to viral infections, host genetic factors likely play an important role. HIV and parvovirus B19 directly infect glomerular epithelial, and possibly endothelial, cells as evidenced by detection of intracellular viral genome, with expression of viral proteins resulting in cytokine production, cell injury, proliferation, apoptosis, and dysregulation or dedifferentiation. Virally induced immune complex glomerulonephritis occurs following deposition of circulating immune complexes containing viral antigens, *in situ* immune complex formation after a planted viral antigen, or autoantibody formation against intrinsic antigens due to molecular mimicry.

A number of HIV antigens, such as p24 and gp41, have been found in circulating immune

complexes or as circulating antibody targets, while p24 also has been found in eluted glomerular immune deposits. Hepatitis B and C generally are considered not to directly infect renal cells, but to cause immune complex disease. Increased circulating immune complexes have been found in hepatitis B-infected patients with glomerulonephritis. All major hepatitis B antigens (core, surface, and e) have been identified in immune complex deposits, with e antigens associating with subepithelial, and core and surface antigens with mesangial and subendothelial, immune deposits. Hepatitis C envelope protein E2 can induce rheumatoid factor production and cryoglobulins, in association with a high prevalence of circulating anti-hepatitis C antibodies and immune complex formation. It has been suggested that parvovirus B19 also can stimulate antibody production and immune complexes. Data regarding CMV-associated glomerulopathies are scant and contradictory with mechanisms for disease not yet established.

In what way do treatments directed toward these viral infections affect glomeruli?

In the era of HAART, the incidence of HIV-associated glomerular disease has decreased owing to drug efficacy in preventing and treating HIVAN. HIV thus often behaves as a chronic illness in these patients, who may develop other disease processes with resulting glomerular lesions such as diabetic glomerulosclerosis, arteriosclerosis with glomerular ischemia, and secondary FSGS due to aging and nephron loss.

Treatments for active hepatitis B include nucleotide and nucleoside reverse transcriptase inhibitors and interferon alpha, the latter also used for hepatitis C typically with ribavirin with or without a protease inhibitor. The newest treatments for hepatitis C include sofosbuvir

Table 1. Glomerular lesions associated with viral infections

Hepatitis B

- Membranous nephropathy (common)
- Immune complex-mediated membranoproliferative glomerulonephritis (MPGN)
 - With a crescentic pattern (rare)
- Mesangial proliferative glomerulonephritis, including IgA nephropathy
- Focal and segmental glomerulosclerosis (very rare)

Hepatitis C

- Immune complex-mediated MPGN (common)
 - Usually with cryoglobulins
- Membranous nephropathy
- Fibrillary glomerulonephritis
- Mesangial proliferative glomerulonephritis (rare)
- Collapsing glomerulopathy (rare)

Human Immunodeficiency Virus (HIV)

- HIV-associated nephropathy (collapsing glomerulopathy)
- Immune complex-mediated glomerulonephritides
 - IgA nephropathy
 - Lupus-like immune complex glomerulonephritis
 - IgM nephropathy
 - Nonspecific immune complex glomerulonephritis
- Focal and segmental glomerulosclerosis (not collapsing variant)
- Minimal change disease (usually children)
- Thrombotic microangiopathy

Parvovirus B19

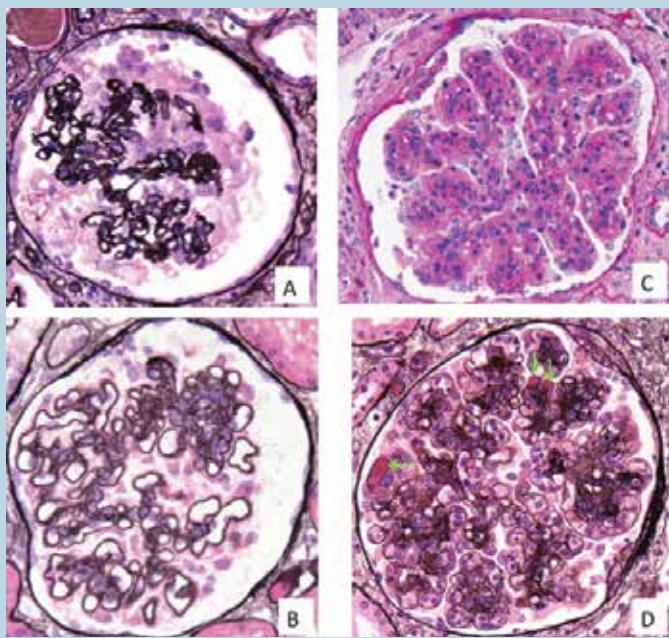
- Collapsing glomerulopathy
- Proliferative (endocapillary and mesangial) glomerulonephritis
 - IgG dominant (rare)
 - IgA dominant (very rare)
- Focal and segmental glomerulosclerosis

CMV

- Collapsing glomerulopathy (rare)
- Immune complex-mediated glomerulonephritis (rare)
 - Membranoproliferative glomerulonephritis
 - Mesangial proliferative glomerulonephritis
 - Membranous nephropathy
- Necrotizing and crescentic glomerulonephritis (rare)



Figure 1. Common glomerular lesions associated with viral infections



- A.** Collapsing glomerulopathy (HIV, parvovirus B19, and rarely CMV and hepatitis C). Hyperplasia and hypertrophy of glomerular epithelial cells with capillary wrinkling and collapse are present, Jones stain.
- B.** Secondary membranous nephropathy (hepatitis B and C, rarely CMV). Capillary walls have subepithelial deposits and basement membrane spikes with segmental mesangial hypercellularity, Jones stain.
- C.** Membranoproliferative glomerulonephritis (MPGN) (hepatitis B and C, rarely CMV). Lobular glomerulus with mesangial hypercellularity and capillary wall double contours, PAS stain. **D.** MPGN with cryoglobulins (hepatitis C, less often B). Lobular hypercellular glomerulus with capillary double contours, endocapillary hypercellularity and cryoglobulin thrombi (arrows), Jones stain. (All x 240)

with ledipasvir, grazoprevir with elbasvir for those with eGFR <30 mL/min, and other direct-acting antivirals. These treatments typically are effective in viral eradication, with glomerular improvement reflected by reductions in proteinuria and progression to renal failure; however, there may be persistence of glomerular injury and cryoglobulins. Additionally, interferon therapy is associated with development of podocytopathies including minimal change disease and FSGS, including the collapsing variant. Other treatments such as steroids, rituximab, and plasma exchange may be employed with the caveat that careful monitoring is needed to detect possible worsening viral symptoms. There are no specific therapies for treatment of parvovirus B19-associated glomerulopathies, and the immune complex lesions largely resolve spontaneously. Based on data from transplant recipients with parvovirus B19-associated glomerulopathies, including collapsing glomerulopathy, intravenous immunoglobulin may provide some clinical benefit. ●

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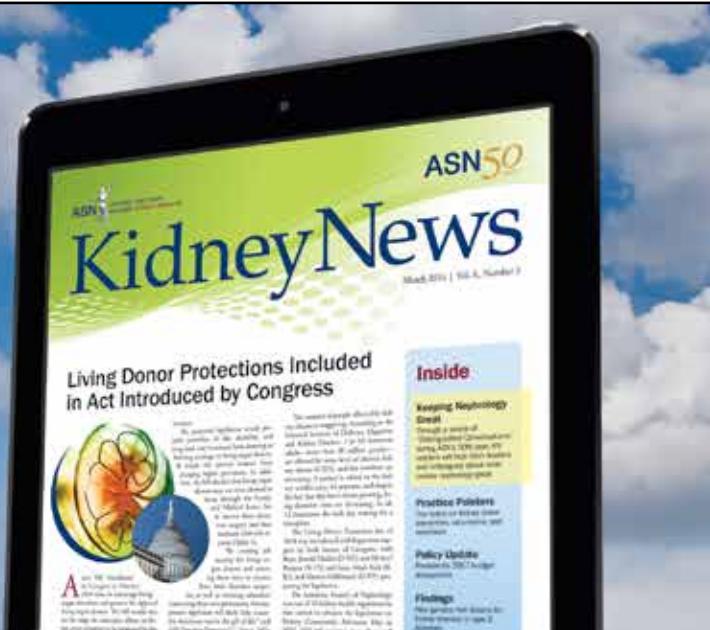
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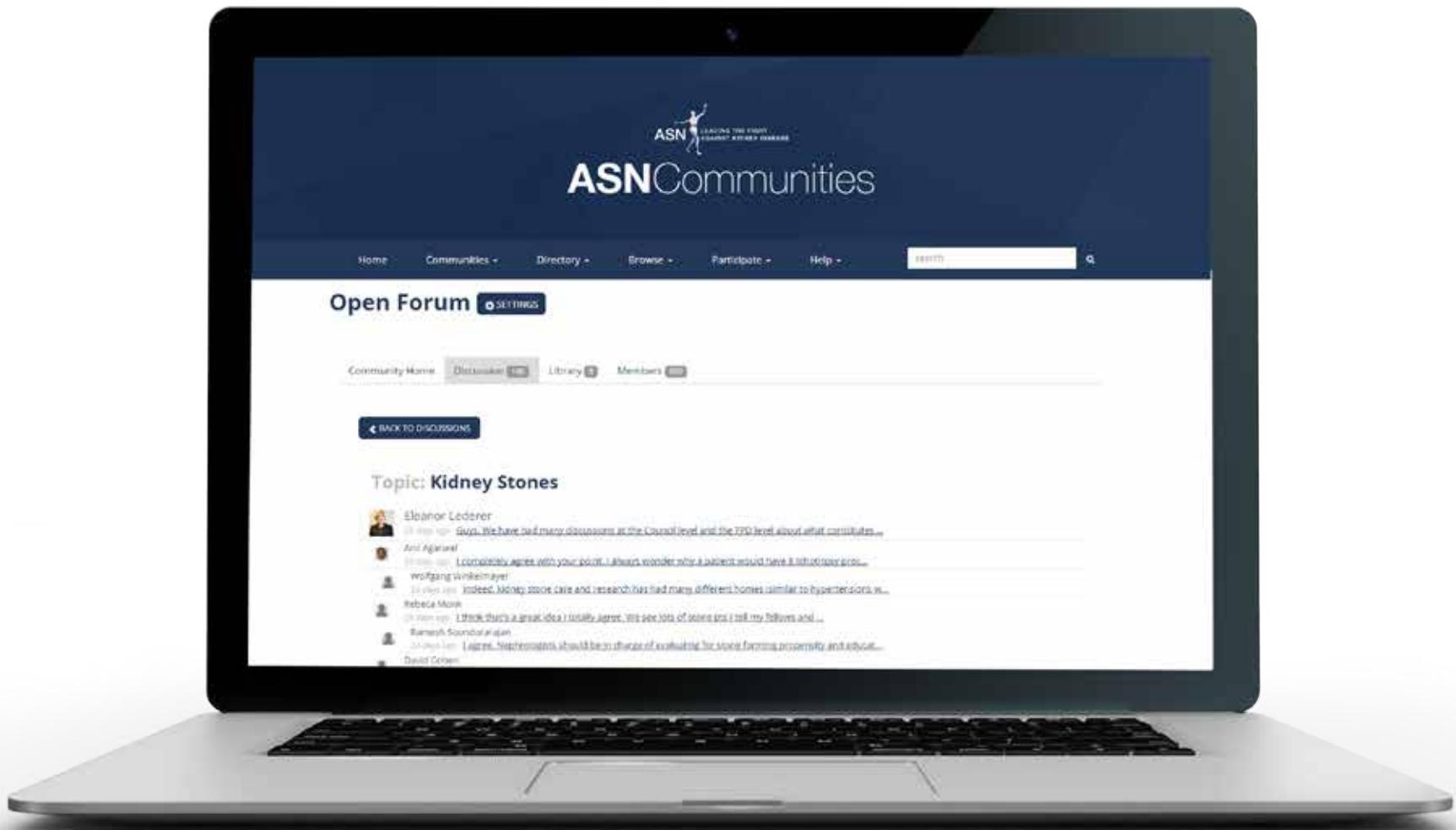


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