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ASN 50 years

Kidney News

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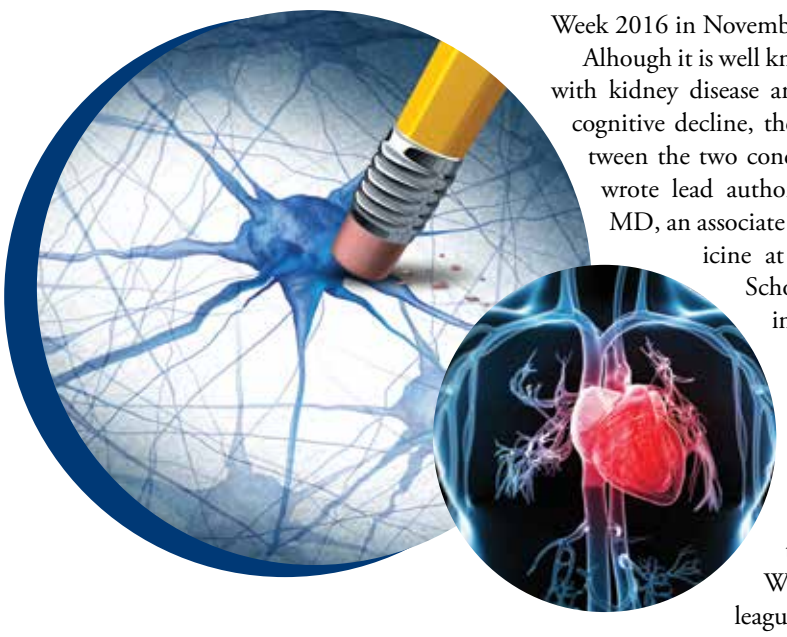
Vascular Disease Contributes to Cognitive Decline in Patients with Kidney Disease

By Bridget M. Kuehn



Chicago—Underlying vascular disease likely explains the high risk of cognitive impairment in patients with kidney disease, according to study results presented at Kidney Week 2016 in November.

Although it is well known that patients with kidney disease are at high risk of cognitive decline, the relationship between the two conditions is unclear, wrote lead author Daniel Weiner, MD, an associate professor of medicine at Tufts University School of Medicine in Boston. To better understand this connection and probe the potential role of vascular disease in these conditions, Weiner and his colleagues analyzed baseline data from a substudy of the Systolic Blood Pressure Intervention (SPRINT) study called SPRINT-MIND.

The SPRINT-MIND study enrolled 9361 participants, including more than 2700 who in addition to kidney disease-related testing completed an extensive battery of cognitive tests and 637 who underwent brain imaging. When Weiner and his colleagues adjusted baseline study data for certain demographic and clinical characteristics, they found that having a higher albumin-to-creatine ratio (ACR) in the urine was associated with worse performance on tests of overall cognitive function, executive function, memory, and attention. In fact, the cognitive effect of each doubling of ACR was comparable to the effect of 6 to 14 months of aging.

Lower estimated glomular filtration rates (eGFR) also were associated with worse performance on tests of overall cognition and memory. Among patients who underwent brain imaging, higher ACRs were associated with abnormalities in the brain's white matter, but lower eGFRs were not linked to such brain changes.

"The findings cement the association between kidney damage and cognitive

Continued on page 2

Basic Science Helps Decode the AKI to CKD Transition

Until recently, nephrologists may have underappreciated the risks that acute kidney injury (AKI) poses to long-term kidney health. But a raft of clinical and epidemiological studies has shown that AKI greatly increases the risk of chronic kidney disease (CKD), end stage renal disease, and death (Coca SG, et al. *Kidney Int* 2012; 81:442–448).

"There has been a dramatic shift in our understanding of potential patient outcomes following AKI," said David P. Basile, PhD, associate professor of medicine at Indiana University in Indianapolis, during a symposium at Kidney Week 2016.

A growing understanding of the molecular mechanisms underlying the continuum between AKI and CKD is helping nephrologists better understand why some patients with AKI never fully recover. The discoveries may one day help identify patients with AKI at risk of CKD and lead to kidney-protective AKI interventions.

Capillary loss

A rat model of what was thought to be "reversible AKI" first led Basile and his colleagues to discover permanent vascular damage that could lead to CKD. The rats undergo an ischemia reperfusion injury, and closer study revealed that not all the rats return to normal (Basile D, et al. *Am J Physiol* 2001; 281:F887–899).

Continued on page 2

Inside

Vascular Disease

Continued from page 1

functioning, suggesting that albumin in the urine and changes in brain structure are likely both representations of the same vascular process, just in different organs," said Weiner in a press release. "This manifests with worse brain function, particularly in domains linked to cerebrovascular disease."

The fact that the results came from a large study of a nationally representative population of patients with kidney disease suggests the results may be relevant to "tens of millions of US adults," said Weiner.

"It's a great study to take advantage of to look at these relationships," said Anne Murray, MD, MSc, professor of medicine and geriatrics at the Hennepin County Medical Center's Berman Center for Clinical Research in Minneapolis.

The results confirm previous studies that show vascular disease contributes to cognitive decline in patients with chronic kidney disease, Murray said. She noted evidence that the brain and kidneys share many common anatomic and vasoregulatory features; they are low resistance end organs exposed to high-volume blood flow, which may make them especially vulnerable to microvascular damage (Bugnicourt JM, et al. *J Am Soc Nephrol* 2013; 24:353–363).

"The results also highlight that memory is impaired to a greater extent than executive function, in contrast to some other studies," said Murray. She noted, however, that this result is consistent with results from the Brain in Kidney Disease Study (BRINK) (Murray AM, et al. *Am J Kidney Dis* 2016; 67:593–600).

One of the study's strengths is that it looked at both ACR and eGFR, which showed that multiple mechanisms are likely involved, Murray said. One limitation is that the mean eGFR was high and the mean ACR was low in this patient population. Only a small percentage of patients had eGFRs below 30, a point at which the risk of cognitive impairment is high, and memory loss becomes more predominant, Murray explained.

"So, it's difficult to interpret the 'dosage' effect of lower ranges of eGFR and higher ACR on each outcome," she said.

In the meantime, it is important for clinicians to be aware that patients with eGFRs below 45, especially those with eGFRs below 30, and even somewhat elevated ACRs may be experiencing cognitive decline, Murray said.

"Clinicians should suspect significant cognitive impairment and manage their care accordingly," she said. For example, the patient may not be able to be compliant with their medications so physicians might suggest having a caregiver or family member supervise medication administration. If there are decisions that need to be made regarding access, placement, dialysis initiation, or being placed on the transplant list those discussions should be held with family members present in case the patient's judgment is impaired," she stressed. This is particularly important for patients starting dialysis who are likely to experience further cognitive declines after 3-6 months of dialysis, she noted.

"Cognitive Function and Kidney Disease: Baseline Data from the SPRINT Trial" (Abstract 744)

Basic Science

Continued from page 1

"Renal blood vessels are permanently reduced following recovery," he explained. "The vascular network is significantly compromised."

Now, many investigators are studying vascular loss in AKI. Studies of tissue samples from patients with AKI have also revealed decreased peritubular vascular density and the development of fibrosis, Basile noted.

"We knew very little about what was going on with vessel loss," Basile noted. But recent studies have shown that ischemia leads to the loss of endothelial cells then a gradual reduction of capillaries during the period after AKI when the kidney usually recovers (Ehling J, et al. *J Am Soc Nephrol* 2016; 27:520–532).

"While the rest of the kidney is putting itself back together, the vessels decline," he said.

Animal studies now reveal that vascular damage contributes to the development of fibrosis, he said. This suggests there may be a window to intervene before permanent damage sets in.

"Intervention in early AKI might mitigate vascular loss," he suggested.

Failed repair

Now, a growing body of evidence suggests that the kidney's normal repair mechanisms may go awry and lead to an accelerated-aging like condition (Ferenbach DA and Bonventre JV. *Nat Rev Nephrol* 2015; 11:264–276).

Benjamin D. Humphreys, MD, PhD, chief of the division of nephrology at the Washington University School of Medicine, is one of the researchers at the cutting edge of this research. As part of the symposium, Humphreys delivered The Barry M. Brenner, MD, endowed lectureship, which recognizes the contributions of investigators like Brenner and Humphreys who have helped to nurture the careers of young nephrology investigators.

"We are interested in studying failed repair," explained Humphreys, whose collaborator Monica Chang-Panesso, MD, presented an abstract (OR130) at Kidney Week tracing genetic factors that may inhibit kidney repair. She found that cells in the proximal tubule dedifferentiate to facilitate repair rather than relying on a population of progenitor cells.

Another collaborator, Rafael Kramann, MD, has developed a mouse model of AKI progressing to CKD. Like Basile's rat model, Kramann's model undergoes a loss of capillaries. The group has found that ablating kidney pericytes expressing Gli 1+, which help to regulate vascular structure and stability in the kidneys, leads to capillary loss (Kramann R. *J Am Soc Neprol* [published Sept. 13, 2016] pii:ASN.2016030297).

"The capillary dropout is permanent," Humphreys said.

Already, Humphreys and his colleagues are studying experimental therapies that might prevent fibrosis. For example, they demonstrated that a small molecule that inhibits Gli2 reduces fibrosis by 60% in the AKI mouse model (Kramann R, et al. *J Clin Invest* 2015; 125:2935–2951).

"It is proof of principle that targeting pericytes might be a viable strategy," said Humphreys.

Another gene of interest identified by the group is an enzyme that synthesizes retinoic acid that is up-regulated in the kidney during development. The retinoic acid may help kidney cells redifferentiate during the repair process, suggested Humphreys, and a lack of retinoic acid might contribute to failed kidney repair.

They are now studying the role of retinoic acid in human kidney organoids, which are created by coaxing stem cells into forming kidney-like structures in the laboratory. Treating the organoids with retinoic acid boosts markers of repair, but when it is absent there is capillary loss and fibrosis.

"Our data suggest that after AKI, about 80% of epithelia are able to undergo what we call successful repair, but about 20% of cells fail to repair," said Humphreys.

In addition to highlighting his own laboratory's research, Humphreys acknowledged the enormous contributions Brenner made to the field and urged others to follow in his footsteps as a mentor. He noted that many future department heads, division chiefs, and deans trained in Brenner's lab. These "bright minds" were attracted there by scientific innovations made in Brenner's lab, he said.

"It behooves all of us to support our young people to make those scientific discoveries that will improve patient care and serve to reinvigorate the field," Humphreys said.

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ASN President's Column

By Raymond C. Harris, MD, FASN

Raymond C. Harris, MD, FASN

In my last column I looked back at nephrology in 1966, the year ASN was founded, and marveled at the advances made in the past 50 years. In this column I've described my thoughts of what will be roles and activities of the nephrologist of the future, and the way in which kidney professionals will transform that future.

A Look into the Future

There will be an increasing reliance on "big data" to inform our understanding of underlying mechanisms of kidney pathophysiology, and we will have new and more precise tools to analyze the data so that we can break down barriers between basic and clinical research and between disciplines.

- Precision medicine initiatives will provide a better understanding of the interactions of genetic and environmental factors in kidney diseases and will help in the design of more focused clinical trials and more targeted therapies.
- "Telehealth" will no longer be separated from "health."
- Transplant waiting lists will shrink as the range, type, and usability of artificial organs grows.
- EHR documentation will transform continuing education as it has the patient record, allowing providers to spend time learning about new advances, or areas new to their practices.

Nephrologists Transforming the Landscape

Nephrologists are uniquely suited to apply their skills, talents, and interests to propel transformative change to assure that the profession will remain vibrant.

- Nephrologists may be uniquely suited to bring credibility to big data:
  - As data explodes, so do the opportunities for misinterpretation across a variety of "borders."
  - Nephrologists have always excelled at data interpretation.
- Having access to large datasets about human kidney disease will allow more focused preclinical studies by MDs and PhDs and better integration with, and design of, meaningful clinical studies.
- It is imperative that nephrologists work in concert with all health care agencies, providers, and governmental agencies to decrease disparities in access to care for our kidney patients both in this country and around the world. One concrete step that we can take is to continue to advocate strongly for increased funding for, and utilization of, telehealth, which can help to provide access to health care for patients in remote or under-resourced areas.
- We must work to overcome the current problem of insufficient organs for our potential transplant patients. Although improved allocation strategies may incrementally increase the number of suitable kidneys for transplant, ultimately transplant medicine will be transformed by technology, and in the future new technologies, either xenotransplantation or stem cell based technologies, will give all potential kidney transplant patients the chance to receive a functioning organ.
- Nephrology, with its focus on the holistic care of our patients and mastery of the complex data involved in their care, is well suited to lead advances in care that alter the lives of all patients, not just those with kidney diseases. We must ensure that all kidney professionals are trained and ready to take on this challenge to shape dramatic and positive changes in the future of medicine and science.

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Findings

Dialysis Outcomes Unchanged after 'Bundling' and ESA Label Changes

Five years after the shift to a "bundled" reimbursement system and revised drug labeling for erythrocyte-stimulating agents (ESAs), overall outcomes are no worse—and some outcomes have improved—for hemodialysis patients covered by fee-for-service Medicare, reports a study in *JAMA Internal Medicine*.

The retrospective analysis included data on nearly 70,000 incident hemodialysis patients, 66 years or older, who were enrolled in Medicare parts A, B, or D for at least 12 months before starting dialysis. One cohort initiated hemodialysis before the transition to a bundled comprehensive payment system and ESA labeling changes (2008–09); the other cohort started dialysis after these changes (2011–13). Differences in outcomes were compared between groups, including major adverse cardiovascular events (MACEs), hospitalization for congestive heart failure, venous thromboembolism, and red blood cell transfusions.

The two cohorts had similar baseline characteristics. There was no difference in the overall risk of MACEs, death, congestive heart failure hospitalizations, or venous thromboembolism. The postpolicy cohort had a significant reduction in stroke, hazard ratio (HR) 0.77.

Use of ESAs decreased after the policy and labeling changes, while the rate of blood transfusions increased: HR 1.09. Subgroup analyses showed significant reductions in MACEs and all-cause mortal-

ity for black patients: HR 0.82 for both outcomes.

The findings help to answer concerns that the change to bundled payments and the ESA drug labeling changes might adversely affect clinical outcomes for hemodialysis patients. The results show no overall change in MACEs after these changes, but a significant reduction in stroke.The changes are associated with a decrease in monthly ESA dose and a modest increase in blood transfusions. Black patients show significant reductions in MACEs and overall mortality [Wang C, et al. Association between changes in CMS reimbursement policy and drug labels for erythrocyte-stimulating agents with outcomes for older patients undergoing hemodialysis covered by fee-for-service Medicare. *JAMA Intern Med* Published online October 24, 2016. doi:10.1001/jamainternmed.2016.6520].

Adjuvant Sunitinib Improves Survival in High-Risk RCC

Adjuvant treatment with the oral antiangiogenic drug sunitinib increases disease-free survival but increases toxicity in patients with metastatic renal cell carcinoma (RCC) at high risk of recurrence, reports a trial in *The New England Journal of Medicine*.

The randomized, international, phase 3 trial included 615 patients with locoregional, high-risk clear-cell RCC who had undergone nephrectomy. Intervention patients received sunitinib, 50 mg/d, on a 4-weeks-on, 2-weeks-off schedule. Treatment continued for up to 1 year; controls received placebo. Disease-free survival was compared between groups, along with secondary outcomes.

Sunitinib was associated with significant improvement in disease-free survival: 6.8

Continued on page 8

Findings

High-Risk RCC

Continued from page 7

versus 5.6 years, hazard ratio 0.76. Overall survival could not be assessed at the time of data cutoff; about 20% of patients had died in each group.

Sunitinib was associated with increased toxicity, including higher rates of grade 3 and 4 adverse events and adverse events requiring dose reductions, interruptions, or discontinuation. The overall rate of serious adverse events was 21.9% with sunitinib and 17.1% with placebo, with no toxicity-related deaths.

Previous studies have established that sunitinib, a vascular endothelial growth factor pathway inhibitor, is an effective treatment for metastatic RCC. The new trial shows that adjuvant sunitinib can increase survival in patients with locoregional, high-risk clear-cell RCC. Sunitinib is associated with increased toxicity, leading to moderate declines in quality of life during active treatment [Ravaud A, et al. Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy. *N Engl J Med* October 10, 2016 DOI: 10.1056/NEJMoa1611406].

Angioplasty and Stenting for Renal Stenosis: Evidence Still Limited

Available evidence shows no consistent benefit of percutaneous angioplasty with stent replacement over medical therapy for patients with atherosclerotic renal artery stenosis (ARAS), concludes an updated systematic review in the *Annals of Internal Medicine*.

A comprehensive literature review identified 83 studies providing evidence on the benefits and harms of PTRAS versus medical therapy for ARAS. Thirty-three studies were newly identified since a 2007 review. The review was funded and followed a standard protocol by the Agency for Healthcare Research and Quality.

The review identified 15 comparative studies including a total of 4006 patients. Of these, 7 were randomized controlled trials (RCTs) including 2178 patients, most enrolled in two large trials (ASTRAL and CORAL). Five of the RCTs reported similar blood pressure control with ARAS versus medical therapy. None found significant differences in kidney function, mortality, need for renal replacement therapy (RRT), cardiovascular events, or pulmonary edema.

There were 8 nonrandomized comparative studies including 1828 patients. The findings were variable, especially in terms of kidney function and blood pressure. Most of the studies reported no differences in mortality, RRT, or cardiovascular events.

There were few procedure-related adverse events, and no medication-related adverse events. Two RCTs reported no patient factors affecting clinical outcomes with either PTRAS or medical treatment. Some relevant patient characteristics were reported in single-group studies, but these were inconsistent. Some case reports suggested clinical benefits of PTRAS in patients with acute decompensation.

The updated review does not find strong evidence that PTRAS is superior to medical therapy alone for most patients with ARAS. Some observational studies suggest improvements in kidney function or blood pressure for certain groups of "high-risk" patients. The researchers write, "Future studies should focus on patients who are putatively most likely to benefit from PTRAS, namely those with proven hemodynamically significant ARAS or those who have signs of decompensation" [Raman G, et al. Comparative effectiveness of management strategies for renal artery stenosis: an updated systematic review. *Ann Intern Med* 2016; 165:635–649].

Continued on page 14

ASN News

ASN Aligns Bylaws with New Strategic Plan

Endorsing a more diverse, inclusive, and global society, 93% of ASN Active Members recently approved the first revision of the society's bylaws since 2006.

In addition to making several "technical corrections" to ensure that the bylaws comply with the new Washington, DC, business organizations code § 29 401.02(24), the revised bylaws help ASN move toward accomplishing its new strategic plan. The new ASN Strategic Plan required two additional changes to the bylaws.

The revised bylaws (available on ASN's website) change the structure of the ASN Council (the society's governing body). The new Council structure offers several different opportunities for service. This change is intended to encourage members who are interested in contributing to the Council (but who are not interested in serving as president) to participate. Importantly, the term of service has been reduced from a seven-year to a four-year commitment.

The first change to the bylaws increases the number of ASN Councilors from eight to nine. Four of the nine councilors are elected at-large members who serve staggered four-year terms. At-large councilors are limited to one term, although they are eligible to run for and, if elected, serve one term as an officer or appointed treasurer.

Four of the nine councilors will serve as elected officers. The progression of those elected to Council as officers is Year 1 (secretary), Year 2 (president-elect), Year 3 (president), and Year 4 (past president). Elected officers cannot serve a second term, and are not eligible to serve as at-large councilors or treasurer after completing their term as officers.

Following tradition, the Council will appoint a ninth member as treasurer, who serves one non-renewable four-year term, is eligible to serve as an at-large councilor or officer, and could have previously served as an at-large councilor but not as an officer.

As of result of these changes, active members now have three pathways to become ASN Councilors:

- Serve as an at-large councilor for four years.
- Serve as an officer for four years.
- Be appointed by the ASN Council to serve as ASN Treasurer for four years.

Voting rights

The second change to the ASN bylaws concerns voting rights. Previously, only ASN Active Members (MDs, PhDs, or equivalent who live in North or Central America) had the right to vote. Based on ASN membership data for 2015, less than 50% of the society's members had the right to vote. As a result of the recent election, ASN Corresponding Members (MDs, PhDs, or equivalent who live outside North or Central America) now have the right to vote (Table 1).

Many societies that are similar to ASN in mission, focus, and culture have already extended the right to vote to physicians and scientists across the world. ASN now joins these organizations in expanding voting rights.

ASN continues to work with its leadership, contributors from the ASN Communities, as well as kidney health professionals throughout the world, to collect feedback, continue to improve, and maintain its status as a dynamic organization that provides a structure and services to help its members lead the fight against kidney diseases. In 2017, ASN will continue to focus on accomplishing its new strategic plan (http://www.asn-online. org/about/).

Table 1

2016 Membership	Number	Percentage of total membership	Right to vote?
Active members	7612	45.2%	Yes
Corresponding members	2705	16.1%	Yes
Other	6507	38.7%	No
Total ASN members	16,824	100%	

Policy Update

Quality Payment Program: What You Need to Know

By David White

With Kidney Week 2016 in review and the end of the year rapidly approaching, one New Year's treat is already waiting for everyone. It arrived January 1, 2017, as scheduled. The New Year heralds the beginning of the new Quality Payment Program (QPP) that was created by the Medicare Access and CHIP Reauthorization Act (MACRA).

Congress passed MACRA in 2015 with large bipartisan vote margins in both the Senate and House of Representatives. There is widespread consensus that while parts of the program may have to be adjusted if the Affordable Care Act is repealed or modified, the new Medicare reimbursement program will proceed largely intact.

American Society of Nephrology (ASN) President Raymond C. Harris, MD, FASN, spoke eloquently about the future of nephrology in his Kidney Week President's Address as ASN marked its 50th anniversary. With the future in mind, Dr. Harris emphasizes that "the move to a quality-driven health care system is real and a part of the future for the nephrology care team and everyone else in medicine. As such, we all need to familiarize ourselves with this new Medicare payment system and get started."

Responding to concerns raised by ASN and other peer societies regarding the short timeline to prepare for the new program, Medicare determined that 2017 will be a transition year. As such, the Quality Payment Program in 2017 will have reduced reporting requirements and lower scoring thresholds to allow clinicians the opportunity to adjust to the new reimbursement system. Here's what everyone needs to know.

Who participates in the Quality Payment Program?

You participate in the Quality Payment Program if you bill Medicare Part B more than $30,000 per year and provide care for more than 100 Medicare patients per year, and are one of the following clinicians:

- Physician
- Physician assistant
- Nurse practitioner
- Clinical nurse specialist
- Certified registered nurse anesthetist

However, if 2017 is your first year participating in Medicare, you will not be required to participate in MIPS.

There are two paths to participation in the Quality Payment Program.

- Merit-Based Incentive Program (MIPS)
- Advanced Alternative Payment Models (APMs)

What is MIPS?

This program replaces three Medicare reporting programs: Meaningful Use (MU), the Physician Quality Reporting System (PQRS), and the Value-Based Payment Modifier (VM). Physicians and practices that participated in the old reporting programs will find that much of MIPS is familiar.

MIPS has four performance categories:

- Quality—Replaces Physician Quality Reporting System (PQRS)
- Improvement Activity—New category
- Advancing Care Information—Replaces Meaningful Use
- Cost—Replaces Value Modifier; will not be counted until the 2018 performance year

CMS anticipates that most physicians and practices will participate in MIPS for the 2017 calendar year. Per CMS' Quality Payment Programs Fact Sheet, approximately 500,000 clinicians will be eligible to participate in MIPS in 2017.

What are Advanced APMs?

A smaller number of clinicians participating in the Quality Payment Program will do so via the APM pathway instead of the MIPS pathway. An advanced APM is an APM that must meet these specific requirements:

- Be CMS Innovation Center models, Shared Savings Program tracks, or certain federal demonstration programs,
- Require participants to use certified EHR technology,
- Base payments for services on quality measures comparable to those in MIPS, and
- Be a Medical Home Model expanded under Innovation Center authority, or require participants to bear more than nominal financial risk for losses.

CMS anticipates that the following models will quality as Advanced APMs in 2017:

- Comprehensive End State Renal Disease Care Model (Two-Sided Risk Arrangements including non-LDOs as advocated for by ASN)
- Comprehensive Primary Care Plus
- Medicare Shared Savings Program Tracks 2 and 3
- Next Generation ACO Model

CMS is making additions to the list. A final list will be published before Jan 1, 2017.

What does "Pick Your Own Pace" mean?

Since 2017 is a transition year, you have flexibility in reporting and may select the number of measures and timeframe you report. These four options will enable you to avoid a negative payment adjustment, and in certain cases offer the potential for a positive adjustment, in 2019:

- Test the Quality Payment Program by submitting some data,
- Participate for part of the 2017 calendar year,
- Participate for the full 2017 calendar year, or
- Participate in an Advanced APM in 2017.

Physicians and practices that do not participate at all in 2017 will receive a 4% negative payment adjustment in 2019.

For more information, visit ASN's Quality Payment Program resource page and CMS' updated Quality Payment Program website.

New CMS Payment Changes Boost AKI Care, Telehealth

By Bridget M. Kuehn

Telehealth services for home dialysis patients and care for patients with acute kidney injury (AKI) will get a boost from changes to the Physician Fee Schedule and the End-Stage Renal Disease (ERSD) Prospective Payment System (PPS) announced by the Centers for Medicare & Medicaid Services (CMS) in October and November.

The changes, which go into effect in 2017, are part of an ongoing effort by the agency to improve care quality while lowering costs by changing the way care is delivered and clinicians are paid, according to the agency. The changes expand access to outpatient dialysis for patients with acute kidney injury (AKI), encourage telehealth consultations for home dialysis education and advanced care planning, and will allow patients to choose having their nephrologist lead their care.

The new Physicians Fee Schedule will let patients designate their nephrologist as their primary care provider. This allows them to avoid additional visits to a primary care physician on top of coming to a dialysis center three times a week or doing daily home dialysis, said Rajnish Mehrotra, MD, MS, a professor at the University of Washington and nephrology section chief at Harborview Medical Center in Seattle.

"It will be better for patients," Mehrotra said. "Even nephrologists sometimes lose sight of the enormous burden that the treatment of ERSD places on patients."

It may also allow nephrologists more time to provide high quality care. For example, Mehrotra noted managing high blood pressure or diabetes requires time for patient education and a good relationship between the patient and the health care team.

It also lays the groundwork for the development of new payment models that will reward nephrologists for coordinating the care of their patients.

"Clearly, this is an area that needs further exploration in demonstration projects, but it seems to be a reasonable first step in recognizing the care that many nephrology practices are already providing," said Daniel Weiner, MD, MS, associate professor of medicine at Tufts University in Boston.

Acute kidney injury

Perhaps the biggest change for nephrologists is that patients with AKI will now be able to receive dialysis from outpatient centers that serve patients with ERSD. Previously, patients with AKI had to receive dialysis through a hospital, which could be far from home, explained Mehrotra.

"Now, they can go to the dialysis unit in their community," Mehrotra said.

They also will no longer miss out on the specialized chronic disease care, including social work and dietary advice, that ERSD centers provide, Weiner said.

Services that are needed for patients with AKI, including drugs and lab tests, that are not currently covered as part of the ERSD bundle will be reimbursed by CMS. Weiner stated, however, that there are still some questions about how tests and interventions included in the bundle will be reimbursed. For example, he noted that he would more frequently check kidney function labs, urine clearance, and electrolytes in patients with AKI than in patients with ERSD. There are also questions about when patients who don't recover from AKI should be designated as having ERSD.

Overall, the changes are an improvement, Weiner said.

"There remains a lot of work to be done here, including review of payment adequacy, clinical monitoring, and clinical outcomes," he said. "Hopefully, this year's PPS rule will be the first step in an iterative process that will mature over time."

Telemedicine

The rules also boost reimbursement for telehealth services for patients with chronic kidney disease.

Payments for home dialysis training were doubled to $95.60 under the ERSD program. The Physician Fee Schedule also extended coverage for telehealth services for patients receiving dialysis at home and for advanced care planning. Such services avoid unnecessary patient trips to a facility and may increase the likelihood of patients getting care, Methrotra noted. They also afford patients more privacy than might be possible at a dialysis center for delicate discussions about sensitive issues like end-of-life care, he said.

"Many patients select home dialysis due to logistic considerations that make visiting centers challenging," said Weiner. "A lot more work is needed to explore how to best incorporate telehealth into dialysis and other nephrology care, but this expanded coverage is a necessary first step."

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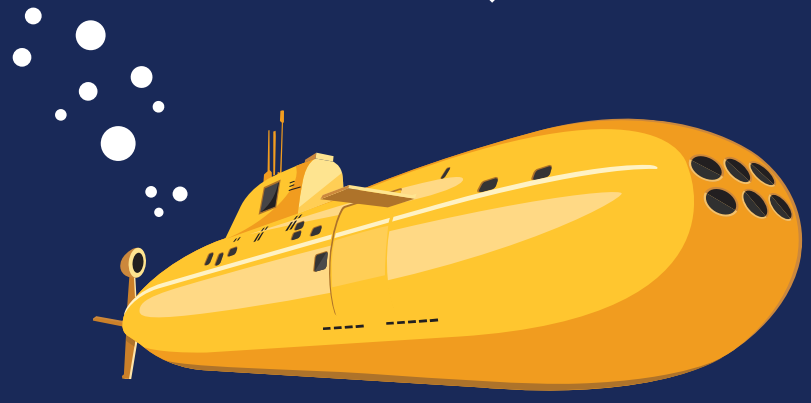

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Findings

Continued from page 8

Increased CKD Risk after Community-Acquired AKI

Patients with acute kidney injury (AKI) seen in the emergency department are at increased risk of chronic kidney disease (CKD) and death within 5 years, reports a study in *Kidney International*.

The prospective cohort study included 616 patients admitted to the emergency department of a Portuguese tertiary hospital and followed up for a median of 5 years. Of these, 130 met criteria for AKI. Another 159 had transient azotemia and 15 had stable CKD; the remaining 312 had normal kidney function. Risks of CKD and mortality associated with community-acquired AKI were assessed, along with the added predictive value of plasma biomarkers measured in the emergency department.

With adjustment for clinical factors, patients with AKI were at significantly increased risk of stage 3 CKD, hazard ratio (HR) 5.7; and death, HR 1.9. In a model including biomarkers, serum cystatin C increased predictive ability for both markers: HR 1.5 for stage 3 CKD and 1.6 for death.

Plasma neutrophil gelatinase-associated lipocalin had no predictive value in addition to AKI. Patients with transient azotemia were also at increased risk of CKD: HR 2.4.

Critically ill hospitalized patients who survive an episode of AKI have a known increase in risk of progression to CKD. Less is known about the risk of CKD or death associated with community-acquired AKI, a less severe but more common condition.

The new study shows a fivefold increase in the risk of stage 3 CKD among patients with community-acquired AKI, compared to emergency department patients with normal renal function. The AKI patients also show a modest but significant increase in mortality risk. The researchers conclude: "Our findings highlight the importance of follow-up of patients with community-acquired acute kidney injury, for potential early initiation of renal protective strategies" [Soto K, et al. The risk of chronic kidney disease and mortality are increased after community-acquired acute kidney injury. *Kidney Int* 2016; 90:1090–1099].

Belatacept Improves Long-Term Renal Function after EDC Kidney Transplant

Compared to cyclosporine, belatacept-based immunosuppression improves long-term outcomes in extended criteria donor (ECD) kidney recipients, reports a study in the *American Journal of Transplantation.*

The researchers present 7-year follow-up data on 543 kidney recipients from the "Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial–Extended Criteria Donors" (BENEFIT-EXT) study. Patients were assigned to primary immunosuppression with a more-intensive or less-intensive belatacept regimen, or to a cyclosporine regimen. Patient and graft survival and estimated glomerular filtration rate (eGFR) were assessed at 7 years' follow-up.

With both the more- and less-intensive belatacept regimens, time to death or graft loss was similar to that with cyclosporine. At 7 years, mean estimated eGFR was 53.9 mL/min/1.73 m^2 with more-intensive belatacept and 54.2 with less-intensive belatacept, compared to 35.3 with cyclosporine. Patients receiving less-intensive belatacept were less likely to meet a composite endpoint of death, graft loss, or eGFR of 20 mL/min/1.73 m^2 or less: hazard ratio 0.706.

Acute rejection rates and safety outcomes were similar across regimens. The belatacept groups had lower rates of de novo donor-specific antibodies.

Belatacept might have advantages for ECD transplant recipients, who may be more vulnerable to nephrotoxicity from calcineurin inhibitors. As in the 5-year results, ECD kidney recipients receiving belatacept show improvement in eGFR through 7 years' follow-up. Risks of death and graft loss are similar with belatacept versus cyclosporine, as are safety outcomes [Durrbach A, et al. Long-term outcomes in belatacept-versus cyclosporine-treated recipients of extended criteria donor kidneys: final results from BENEFIT-EXT, a phase III randomized study. *Am J Transpl* 2016; 16:3192–3201].

Wider Use of Intensive Blood Pressure Control Could Save Lives

Chicago—Wider use of intensive control of systolic blood pressure could save the lives of as many as 32,145 individuals with chronic kidney disease each year, estimated a study presented at Kidney Week 2016.

Lowering systolic blood pressure to 120 mm Hg or less was found to reduce deaths by 27% compared to standard blood pressure control after an average follow-up of 3.26 years in the Systolic Blood Pressure Intervention Trial (SPRINT). The SPRINT trial enrolled 9361 adults age 50 or older at high risk of cardiovascular disease. Participants were randomized to either intensive blood pressure control (≤ 120 mm Hg) or standard blood pressure control (≤140 mm Hg). The trial excluded individuals with diabetes, stroke, polycystic kidney disease, and several other characteristics (SPRINT Research Group. *N Engl J Med* 2015; 373:2103–2116).

Now, Tisha Joerla Tan, MD, of Loyola University Medical Center, and her colleagues have used data from the National Health and Nutrition Examination Survey (NHANES), an annual nationally representative survey of the US population, to estimate how many US individuals would benefit if the tight blood pressure control were applied to those who meet the criteria used in the SPRINT trial. The analysis included adults age 50 or older with a systolic blood pressure between 130 and 180 mm Hg depending on how many antihypertensives they were taking, and one or more risk factors for cardiovascular disease. Individuals with diabetes, a history of stroke, proteinuria greater than 1g/day, heart failure, or an estimated glomular filtration rate (eGFR) <20 mL/min/1.73 m^2 were excluded from the analysis.

About 18 million US adults met SPRINT criteria and Dr. Tan and her colleagues estimated that applying intensive blood pressure control to these individuals would prevent about 100,000 deaths each year. The researchers also estimated the number of deaths that could be prevented among adults with eGFRs between 20 and 59 mL/min/1.73 m^2.

"Our analyses also showed that more than 4 million adults with stage 3–4 chronic kidney disease meet SPRINT criteria, and intensive systolic blood pressure lowering was projected to prevent 32,800 deaths per year in this group," said Dr. Tan in a press release.

The SPRINT trial has demonstrated that intensive lowering of blood pressure can provide cardiovascular benefits and reduce deaths, said George Thomas, MD, director of the Center for Blood Pressure Disorders at the Cleveland Clinic in Ohio. But he also noted it is important to remember that patients with uncontrolled hypertension on multiple medications, diabetes, past strokes, or with severe kidney disease were excluded. And NHANES doesn't provide all the information needed to determine all SPRINT exclusion criteria, he said.

"Additionally, the risks of intensive therapy need to be kept in mind," he said. "It is not possible to predict who would experience a benefit and who would experience harm."

Patients who were intensively treated in the SPRINT trial had higher rates of hypotension, syncopal events, electrolyte abnormalities, and acute kidney injury compared with the standard group, explained Dr. Thomas. Additionally, it may be more difficult to monitor for potential adverse events in practice than in the trial.

"Patients in the trial were very closely followed and blood pressure measurements were done with an automated device following a very strict protocol for measurement," Dr. Thomas said. "In real-world practice, this

may not happen and the adverse events may potentially be higher."

Longer-term data from the SPRINT trial on quality of life, neurologic effects, and long-term kidney outcomes in intensively treated patients may help clinicians decide who might benefit from tighter blood pressure control, Dr. Thomas said.

In the meantime, he recommended that clinicians carefully measure patients' blood pressure, and closely monitor patients whose blood pressure is being tightly controlled. This monitoring should include kidney function and electrolyte levels. "Pros and cons of intensive therapy need to be discussed with patients, and blood pressures goals should be individualized rather than taking a one size fits all approach," Dr. Thomas said.

"Intensive Blood Pressure Lowering Will Prevent Over 100,000 Deaths Annually" (Abstract 2229)

Smoking Counteracts the Benefit of Medications for Kidney Disease

Smoking may partly counteract the benefits of treatment with angiotensin converting enzyme inhibitors (ACE inhibitors) for patients with chronic kidney disease (CKD), according to a study presented at Kidney Week 2016.

Smoking has been linked to worsening kidney decline, but the exact mechanisms are unclear, according to lead author Bethany Roehm, MD, of Tufts Medical Center in Boston.

"The importance of smoking as a renal risk factor is highlighted by the fact that its negative effects have been shown in subjects of the general population and in patients with primary or secondary renal disease," said Stephan R. Orth, MD, PhD, FASN, of the Dialysis Center in Bad Aibling, Germany (Hallan SI and Orth SR. *Kidney Int* 2011; 80:516–523).

One of the reasons it is difficult to pinpoint how smoking contributes to kidney disease exacerbation is that cigarette smoke is made up of more than 4000 chemicals, Orth said, but it is "sensible to assume that several of these components act as nephrotoxic potpourri."

To further study smoking's effects, Roehm and her colleagues enrolled 216 patients with early CKD who were taking ACE inhibitors; 108 were smokers and 108 were nonsmokers. All of the smokers were given a smoking cessation intervention, but 83 continued to smoke and 25 quit. All of the patients were followed for 5 years after starting ACE inhibitors. At enrollment, patients in all groups had comparable estimated glomerular filtration rate (eGFR) and systolic and diastolic blood pressures. But urinary 8-Iso/cr was higher in the continuing smokers and those who later quit.

Those who never smoked and those who quit had slower worsening of their kidney function, according to Dr. Roehm and her colleagues. After 1 year of taking ACE inhibitors, the nonsmokers had lowered their alb/cr to 395 ± 143 compared with 420 ± 148 ($p<0.01$) at initiation. In quitters these levels didn't change significantly from their entry levels, (356 ± 178 vs. 367 ± 160, $p=0.15$). But continuing smokers saw increases in alb/cr (453 ± 152 vs 426 ±138, $p<0.01$). Continuing smokers also had higher urinary 8-iso/cr (3.6 ± 0.8) than nonsmokers (1.6 ± 0.3, $p<0.01$) and quitters (1.6 ± 0.3, $p<0.01$). At 5 years, eGFRs were also lower in the continued smokers (54.9 ± 5.6 mL/min) than in the nonsmokers (66.8 ± 5.8 mL/min) and quitters (64.1 ± 5.6 mL/min) with a p value <0.01.

Dr. Roehm and her colleagues concluded that ongoing smoking was counteracting the typical decrease in protein excretion seen in patients treated with ACE inhibitors likely owing to oxidative stress.

"It has practically become dogma that if you have a patient with high blood pressure and CKD that you start them on an ACE inhibitor, and we are often comforted as clinicians that we are doing something to help slow progression of their kidney disease in doing this," said Dr. Roehm. "But our data suggest that in smokers this may not be the case, and our study underscores the importance of doing all we can as clinicians to encourage our patients to stop smoking."

The study shows ACE inhibitors alone are not enough to counteract smoking's affects, said Orth.

"The results are absolutely in line with what we know about the renal effects of smoking in patients with nephrosclerosis and other renal diseases," he said. "The newest aspect is that ACE inhibition is not able to fully protect from the adverse renal effects of smoking."

But cessation strategies can make a big difference. "The benefit of quitting smoking was particularly impressive due to the fact that eGFR at the end of the study [for quitters] did not differ from never-smokers," Orth said.

Studies that show how nephrologists can boost cessation rates would be useful, said Orth.

"Nephrologists should be aware that smoking cessation strategies in smokers with a diseased kidney are part of their therapeutic armamentarium," he said.

"Cigarette Smoking Partially Negates the Kidney Protective Effect of ACE Inhibition in Stage 2, Non-Diabetic, Hypertension-Associated CKD" (Abstract 2784)

Use of Palliative Care Lags Among Minority Patients at the End of Life

Use of palliative care among patients with end stage renal disease (ESRD) has increased steadily since 2004, but use among minority patients lags behind whites, according to a study presented at Kidney Week 2016.

Palliative care, which focuses on comfort measures and may include discontinuing dialysis, may ease the burden for patients with ESRD who are nearing the end of life. To help ensure that patients are advised about the option of palliative care, the Centers for Medicare & Medicaid Services included voluntary end-of-life counseling in the 2016 physician fee schedule, wrote lead author Haytham Alkhaimy, MD, of Augusta (Georgia) University and his colleagues in their abstract.

"In medicine, unfortunately we sometimes prolong suffering," said Alkhaimy. "We shouldn't be shy about talking about palliative care at some point."

Alkhaimy and his colleagues analyzed all deaths of patients receiving dialysis between 2004 and 2011 in the United States Renal Data System (USRDS) to see how many received palliative care or discontinued dialysis at least 4 days before death. Among the 874,777 patients who initiated dialysis during that period, 52% had died by the end of 2012.

Use of palliative care increased from 4% to 20% of dialysis patients in the database between 2004 and 2011, according to the analysis. "This is good news," Alkhaimy said. "We have been using palliative care more."

Patients who received palliative care were significantly more likely to be older at the start of dialysis (72±12 vs. 67±14 years). Women made up 47% of the palliative care patients vs. 44% of nonpalliative care patients.

Patients who had more hospitalizations were also more likely to receive palliative care (RR 1.04), likely because these patients had exposure to more physicians or to hospitals with palliative care units, suggested Alkhaimy.

Palliative care did not appear to hasten death, as there was no significant difference in the time to death between the two groups.

"If you go into palliative care you may think your life will be shorter, but this shows it will be the same," Alkhaimy said. The analysis included all patients who had a palliative care code under ICD9, he said. Some may have continued dialysis while receiving palliative care, which may have prolonged life.

Patients whose causes of death were coded as cardiac, gastrointestinal, metabolic, vascular, or infection-related were less likely to receive palliative care. "If you have a heart attack or something immediate there may not be time to go into palliative care," Alkhaimy explained.

There were also significant differences between the use of palliative care by minority patients and white patients. About 80% of the patients receiving palliative care were white, 17% were black, and only 3% were from other minority groups.

The study could not explain the reasons behind the differences in palliative care utilization between groups, noted Alkhaimy. He said there is a need for more studies, including prospective studies, about the use of palliative care to help understand its use in patients with ESRD.

There are likely multiple factors that might contribute to disparities in the use of palliative care, said L. Ebony Boulware, MD, MPH, chief of the division of general internal medicine at Duke University School of Medicine.

"Evidence shows that there are differences in patient preferences, patient-provider communication, education, and lack of trust among minorities, all of which could influence receipt and use of palliative care," Boulware said.

Studies aimed at understanding patient, provider, and system level factors that influence use of palliative care in dialysis patients are warranted, she said. In particular, identifying barriers to palliative care, especially for minorities, might help explain the patterns identified in the study.

"Efforts to educate patients as well as providers and to make both aware of the role of palliative care in the context of dialysis may be critically needed," Boulware said.

In the meantime, Alkhaimy suggested that clinicians educate themselves about palliative care so they can discuss the option with patients who might benefit. He acknowledged that end-of-life care options are a difficult topic to discuss, which may cause physicians to hesitate.

"You don't want to be uncomfortable," he said. "You don't want the patient to be uncomfortable."

But he noted that if a patient is nearing the end of life and has a poor quality of life as a result of dialysis or other treatments, failing to discuss palliative care may prolong their suffering.

"Palliative care is sometimes needed for comfort measures and to improve a patient's quality of life," he said.

"Racial Disparities in the Utilization of Palliative Care in Dialysis Patients from the United States Renal Data System" (Abstract 4963)

Poor Sleep Increases Kidney Failure Risk

Chicago—Too little and poor quality sleep are associated with a greater risk of kidney failure, according to results from the Chronic Renal Insufficiency Cohort Study (CRIC) presented at Kidney Week 2016.

While sleep disorders are common in patients with chronic kidney disease (CKD), how poor sleep may affect disease progression is not clear, according to the study's lead author Ana C. Ricardo, MD, MPH, an assistant professor in the division of nephrology at the University of Illinois College of Medicine at Chicago.

So Ricardo and her colleagues conducted a prospective study of 432 adults enrolled in the CRIC study at 2 centers. The CRIC study is a longitudinal, multicenter study that has followed nearly 4000 people with CKD for several years. Participants in the sleep study wore a wrist activity monitor for 5–7 days to record their sleep duration and sleep quality. They also filled out questionnaires about their sleep quality, daytime sleepiness, and risk of sleep apnea. The participants were then followed for an average of 5 years during which 70 developed end stage renal disease (ESRD) and 48 died.

An average night of sleep for participants in the study was 6.5 hours, and about 1 in 5 participants experienced sleep interruptions. For every extra hour of sleep, the researchers found a 19% lower risk of developing ESRD when they controlled for several factors, including body mass index, blood pressure, baseline kidney function and cardiovascular disease (HR 0.81, 95% CI 0.67–0.99 per hour increased sleep length). Patients who had more interrupted sleep also had increased risk of developing ESRD with a 4% increase in risk for every 1% increase in sleep fragmentation (HR 1.04, 95% CI 1.01–1.07 per 1% increase in sleep fragmentation). More fragmented sleep was also linked to declines in eGFR (-0.17 mL/min/1.73 m^2/year, p=0.016).

"Short sleep and fragmented sleep are significant, yet unappreciated risk factors for CKD progression," Ricardo said. "Our research adds to the accumulating knowledge regarding the importance of sleep on kidney function, and underscores the need to design and test clinical interventions to improve sleep habits in individuals with CKD."

Earlier this year, another study that followed 4238 participants in the Nurses' Health Study for 11 years found that nurses who reported sleeping less were at higher risk for more rapid declines in their estimated glomerular filtration rate (McMullan CJ, et al. *Kidney Int* 2016; 89:1324–1330).

While the previous study suggested a link between shorter sleep duration and earlier stages of CKD, the Ricardo study strengthens the evidence by linking sleep duration to ESRD, said Mark J. Sarnak, MD, MS, Director of Research in the Division of Nephrology at Tufts Medical Center. The CRIC Study also used more objective measures of sleep duration and quality than the previous study.

How reduced or poor quality sleep might contribute to declining kidney function is less clear, Sarnak noted.

"A valid question is whether quantity or quality of sleep is a causal risk factor for kidney function decline or have we not sufficiently adjusted for covariates that may be associated with both poor sleep and kidney function decline," Sarnak said.

Larger studies that adjust for such factors as well as additional mechanistic studies may help answer these questions and lay the groundwork for studies of potential interventions that improve sleep quality and slow progression of kidney disease, he said.

Although there is not yet enough evidence to definitively say that sleeping better will reduce the progression of kidney disease, there is sufficient evidence to show that sleep is important for overall health, Sarnak noted.

"Clinicians should be asking questions about sleep and educating patients about healthy sleep hygiene," he said.

"The Association of Sleep Duration and Quality with Chronic Kidney Disease Progression" (Abstract 3754).

Positive Results for Transplant Intervention and Liraglutide

By Bridget M. Kuehn

A safe, inexpensive pre-transplant intervention can reduce graft loss and mortality, according to late-breaking trial results presented during Kidney Week 2016.

During the late-breakers session at the meeting, the positive results from the REPAIR study of remote ischemic preconditioning (RIPC) were accompanied by reassuring data on the renal outcomes from the LEADER Trial of Liraglutide in type 2 diabetes. Other preliminary studies presented at the meeting found positive results for medications for lupus nephropathy and focal segmental glomerulosclerosis (FSGS), as well as some positive results for rapid withdrawal of steroids in transplant patients. But a trial of low-sodium dialysate did not find a benefit.

Transplant protection

Together, the rush of blood that flows into a newly transplanted kidney and the period of reduced oxygen just before transplant may permanently damage the organ. This damage may reduce kidney function and the life of the transplant.

But some evidence has suggested that preconditioning the organ by briefly limiting blood flow prior to the transplant can protect against these injuries by triggering the body's protective mechanisms (Veighey K and MacAllister R. *Pediatr Nephrol* 2015; 30:1749–1759). Now, Kristin Veighey, MB, MRCP, a nephrologist and research fellow at the University College London Centre for Nephrology, and her colleagues have shown that using a blood pressure cuff to briefly limit blood flow to the upper arm in the living donor and recipient just before surgery can reduce graft loss and substantially cut recipient mortality.

In the REPAIR study (http://repair.lshtm.ac.uk/), Veighey and her colleagues randomized 406 live donor/recipient pairs to placebo, RIPC just prior to surgery, RIPC 24 hours before surgery, or both. At the meeting, Veighey presented 5-year follow-up data that found sustained improvements in adjusted average eGFRs in patients who received early RIPC compared to placebo at 2, 3, 4, and 5 years, although the overall eGFR difference was not significant. The study also found reduced graft loss in the early RIPC group compared with placebo (5% vs. 6%), and reduced mortality in the early vs. placebo groups (2% vs. 5%). No adverse events were documented in the intervention groups.

"Based on the fact that this is safe, it is easy to deliver, and it is virtually cost-neutral at the point of delivery, we would advocate that this is something we should be offering to our patients as part of routine practice in this setting," Veighey said.

The potential benefits of RIPC were first shown in cardiology, and we are now starting to see them in nephrology, said Gretchen Brandt, MD, a nephrologist at Kaiser Permanente in Washington, DC. She noted that it is remarkable to see a clinically significant improvement in mortality and graft function in live donor patients, who already tend to do well.

"I'm very excited because this is a very low-tech, low-cost intervention," Brandt said. "We'll have to see if [the benefits] hold over the long haul."

If they do, the intervention could be widely applied even in resource-poor settings.

"It's on the cutting edge," said Brandt. "It's not yet standard of care."

Diabetes interventions

Diabetes drug Lirgalutide may have beneficial effects on the kidneys as well as the heart, suggest data from the LEADER trial presented by Johannes F. Mann, MD, of the University of Erlangen-Nürnberg in Germany. The cardiovascular outcomes of the LEADER trial, which enrolled 9340 patients with type 2 diabetes with high cardiovascular risk and randomized them to liraglutide or placebo were published in June (Marso SP, et al. *N Engl J Med* 2016; 375:311–322). The results showed a reduction in deaths from a composite of cardiovascular causes in patients taking the drug compared with placebo (4.7% vs 6%).

Mann and his colleagues found that the risk of a composite of negative renal outcomes was about 22% lower in patients taking liraglutide compared with placebo (HR, 0.787; p=0.003). But this result was driven by reductions in new onset macroalbuminuria alone, while there were no significant reductions in other renal outcomes including persistent doubling of serum creatine, ERSD, or death by renal cause. The eGFRs of liraglutide-treated patients also decreased less than placebo-treated patients, but the benefit was seen only in the subgroup of patients with an eGFR less than 60 mL/min. The drug was not associated with an increase in the risk of renal events.

"Liraglutide reduced the risk of nephropathy, cardiovascular events, and all-cause mortality relative to placebo," Mann said.

While the cardiovascular benefits were the trial's primary outcome, Brandt said it is nice to also see a benefit in nephropathy. "That's a 2-for-1," she said.

She noted that 3.84 years of follow-up is not a very long time, considering that diabetic nephropathy takes 17 to 20 years to progress. It may be possible that patients with lower eGFRs might show benefit after a longer period of follow-up.

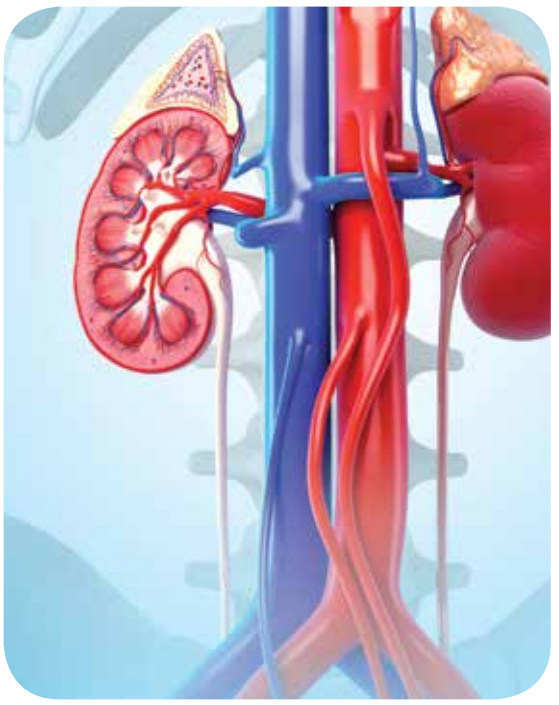
She did, however, note a few drawbacks to liraglutide. It is expensive, requires a daily injection, and is associated with gastrointestinal adverse events. She also noted that there is emerging evidence that cheaper, oral diabetes medications given at higher doses may also be useful for patients with stage 3 or 4 chronic kidney disease (CKD). She noted that in general clinicians are getting better at treating chronic diseases. So, whether switching to a new drug class or tightening up use of the existing armamentarium will be the best approach, "needs to be sorted out in the long haul," she said.

Other results

Cardiovascular disease is a major cause of death for patients with end stage renal disease (ERSD). It is a particular concern in patients receiving dialysis who often experience left ventricular hypertrophy, which may hasten death, according to Mark Marshall, MD, who is now director of medical affairs, renal, Baxter Healthcare in the Asia-Pacific region. In a single-blind, government-funded study, Marshall and his colleagues tested whether low-sodium dialysate (135 mM) reduced left ventricular hypertrophy in dialysis patients compared with standard dialysate (140 mM) in the phase 2 SoLID Trial. It did not. He and his colleagues have planned a larger trial.

"A lot of nephrologists are moving to low-sodium dialysate without a lot of evidence," cautioned Marshall. "This needs to be tested in a larger trial."

The trial was well designed, said Brandt, though she noted the trial used dialysate sodium levels that were on the ends of the spectrum to see a difference. At her institution, for example, she noted that the standard dialysate sodium level is somewhere is in the middle at 137 mM. She also noted that left ventricular mass is a surrogate marker and that it might be difficult to see a difference in a 9-month trial.



I wouldn't give up hope that there are future studies that see a difference 2 to 5 years out," Brandt said.

In the meantime, she suggested that clinicians watch for hypotension in patients during dialysis.

"Patients in the low-dialysate arm were often hypotensive," she explained.

Other studies presented at the meeting suggested benefits to rapid steroid withdrawal in low-risk kidney transplant patients, and provided preliminary evidence for the safety and efficacy of new agents for lupus nephropathy and FSGS.

- The HARMONY Trial, which enrolled 615 low-risk Caucasian kidney transplant patients, and tested the effect of rapid steroid withdrawal with standard immunosuppressive therapy, did not meet its primary endpoint of reduced acute rejections at 12 months. But rapid withdrawal did nearly cut diabetes among transplant recipients in half.
- The phase 2 AURA-LV trial of calcinurin-inhibitor voclosporin for lupus nephritis (LN) (n=265) met its primary endpoint, with 32.6% of low-dose treated patients and 27.3% of high-dose patients achieving complete remission at 24 weeks compared with 19.3% of the placebo group. It also met its secondary endpoints. But the treatment group also had more adverse events and a higher mortality rate than placebo. A phase 3 trial is planned.
- Sparsenta, a dual angiotensin II and endothelin type A receptor antagonist, had more of an effect on proteinuria, a surrogate endpoint, than angiotensin II antagonist with irebsartan in patients with focal segmental glomerulosclerosis in the phase 2 DUET trail, which enrolled 96 patients. Sparsartan was also well tolerated.

Higher BMI May Explain Womens' Lower Risk of End Stage Renal Disease Compared with Men

Lifestyle factors, particularly higher body mass index (BMI), appear to explain the lower risk of end stage renal disease (ERSD) in women compared with men, according to data from the Chronic Renal Insufficiency Cohort (CRIC) Study presented at Kidney Week 2016.

The incidence of ERSD is 1.5 times higher in US men than women even though women live longer and are more likely to have chronic kidney disease (CKD), said Ana C. Ricardo, MD, MPH, MS, assistant professor of medicine at the University of Illinois at Chicago. Some studies have shown that men with CKD progress more quickly (Neugarten J, et al. *Am Soc Nephrol* 2000; 11:319–29).

The effect of gender on CKD progression has been hotly debated for years. Until about 15 years ago there was a consensus that gender had no effect, then the prevailing view shifted to see female gender as protective, said Joel Neugarten, MD, JD, professor of medicine at Albert Einstein College of Medicine. A large meta-analysis published 2 years ago reignited the debate when it found no gender-based difference in CKD progression (Nitsh D, et al. *BMJ* 2013; 346:f324), a result Neugarten attributed to the high number of patients with diabetic renal disease in the study.

Now, Ricardo and her colleagues are wading in to the debate with an analysis of the relationship between gender and progression to ERSD (determined based on dialysis or transplant and estimated glomular filtration rate) in the Chronic Renal Insufficiency Cohort (CRIC). The CRIC study followed 1778 women and 2161 men for an average of about 7 years. The average age of study participants was 58; 42% were non-Hispanic black and 13% were Hispanic.

They found that at the start of the study women were more likely than men to be physically inactive (33% vs. 28%), never have smoked (53% vs. 39%), and have a higher BMI (33 vs. 31 kg/m^2). During the study follow-up period, 844 participants developed ERSD, and women's risk was lower, but nearly disappeared when the researchers adjusted for lifestyle factors, including smoking, physical activity, and BMI.

"In the unadjusted analysis, in men kidney function tended to get worse over time at a more rapid rate than women," Ricardo said. But after the researchers adjusted for baseline kidney function and markers of bone and mineral metabolism, the gender differences in progression became less significant. Adjusting for lifestyle factors also reduced the differences.

Adjusting for BMI alone appeared to attenuate the risk of ERSD on its own in women. This "obesity paradox" has also been documented in previous studies, Ricardo noted.

"We know that in the general population obesity is a risk factor for cardiovascular disease and death; however, in dialysis patients having higher weight or BMI is protective," she explained.

Higher rates of smoking among men did not appear to explain the differences.

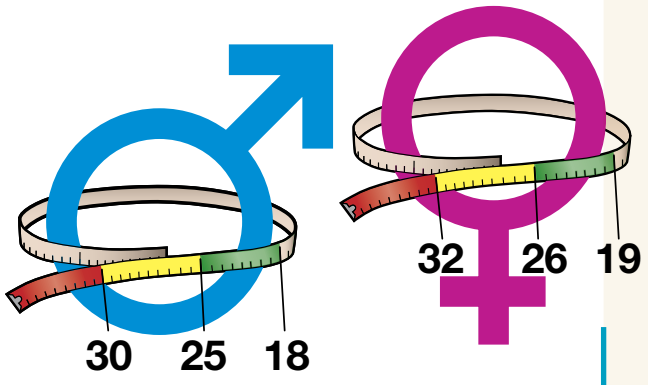
"In other studies, we've seen that smoking has a deleterious effect [on the kidney]," Ricardo said. "But for this particular study it didn't appear to play a significant role in terms of [gender] disparities."

The risk of mortality in women was 40% lower than in men, Ricardo said, so more women were not dying before reaching dialysis or transplant.

"It's a well-studied, well-followed cohort that confirms a relationship between gender and renal disease," said Neugarten.

But it also raises questions about the role of sex hormones in CKD progression. For example, if estrogen were protecting women from faster progression of renal disease you would expect younger women to be protected and older women to progress more quickly. "But younger women had accelerated progression compared to older women," Neugarten said. "That's contrary to what I would have predicted."

The findings on BMI were also surprising. There



isn't a clear mechanism to explain this relationship, Neugarten noted. Also, BMI as a measure is considered by many to be flawed, he said. But other studies that have used waist circumference or other measures of obesity have found contradictory results as well.

"The consensus is that high BMI accelerates renal disease, but many investigations have found that it is protective," he explained. "We don't know."

In future analyses, Ricardo and her colleagues plan to look at whether estrogen helps protect women from ERSD. They also plan to look at whether gender differences in endothelial function between men and women play a role.

In the meantime, she noted that many of the factors that appear to put men at greater risk based on her analysis are modifiable. For example, interventions might include management of phosphorus, calcium, or addressing issues related to socioeconomic status.

"We could potentially bring the risk of men down," Ricardo said.

She said her analysis also identified important disparities in the care women receive. Women were less likely to receive cardioprotective medications, like ACE inhibitors, angiotensin inhibitors, statins, or aspirin. They were also less likely to be seen by a nephrologist.

We nephrologists need to see if we are treating women the same way as men," she said.

Organoids Derived from Patients with Kidney Disease May Aid Research

Chicago—Stem cells from patients with polycystic kidney disease have been coaxed into growing into kidney-like structures, which may aid researchers studying the disease, according to a study presented at Kidney Week 2016.

Ryuji Morizane, MD, PhD, an instructor and scientist in the Brigham and Women's Hospital Renal Division in Boston, and his colleagues presented data on how they grew the kidney-like structures, called kidney organoids. They also described the features of the kidney organoids and the disease features they recreate.

Improvements in cell culturing technology have allowed scientists to coax stem cells into growing into organoids that recapitulate many of the features of kidneys, lungs, the gut, brain, and retina (Clevers H. *Cell* 2016; 165:1586–97). Scientists can use organoids to study organ development and disease processes in the laboratory, noted Hans Clevers, MD, PhD, professor of molecular genetics at the Hubrecht Institute in Utrecht, Netherlands, in his review. Organoids derived from the cells of patients with diseases, in particular, hold the promise to aid personalized medicine, he noted.

Morizane and his colleagues had previously developed a method to grow kidney organoids from human pluripotent stem cells that have the basic features of the kidney, including segmented nephron structures containing podocytes, proximal tubules, loops of Henle, and distal tubules juxtaposed to interstitial cells. Now, they have applied this method to pluripotent stem cells collected from patients with autosomal recessive polycystic kidney disease (ARPKD). The patients' cells grew into kidney organoids that had large cysts in the tubules, just like those seen in patients with ARPKD.

"Establishment of a novel platform to model ARPKD using human kidney organoids will facilitate studies on mechanisms of cyst formation and contribute to the development of chemical screening systems to find potential therapeutic agents for polycystic kidney disease," said Morizane.

The work may also lay the groundwork for one day growing transplantable kidneys in the laboratory.

"Our organoid system enables *in vitro* studies of kidney pathophysiology, nephrotoxicity assays, and disease modeling, and ultimately will lead to development of bioengineered kidneys for regenerative medicine," Morizane said.

Clevers said Morizane's study builds on work by another laboratory that has generated kidney organoids from human stem cells (Takasato M, et al. *Nat Proc* 2016; 11:1681–1692). It also demonstrates the potential of stem cells to form remarkably organ-like structures.

"This beautiful study builds on earlier work by Melissa Little and her colleagues in Melbourne," Clevers said. "It is amazing to witness again the self-organizing capacity of stem cells. The only thing missing from these mini-kidneys is the plumbing: blood vessels and ureter."

"Kidney organoids derived from human pluripotent stem cells contain multiple kidney compartments and model polycystic kidney disease" (Abstract 2139).

Fellows Corner

Raising Awareness during Nephrology Rounds

By Lourdes Gonzalez Suarez, MD, PhD

The US nephrology community has been concerned about lower numbers of trainees in Nephrology in recent years. A trend of fewer applicants to nephrology has been noted since 2011. Between 2013 and 2014, there were a slightly higher number of Nephrology Programs and fellowship positions opening. This led to a higher number of available positions than the number of applicants available to fill those positions in 2014 and 2015. This problem, if it remains unsolved, could translate into a possible future decline of the nephrology workforce and of nephrologists' ability to meet the needs of patient care in the US.

Fortunately, several measures are improving this situation. The fellowship Match timeline changed in 2013: Instead of choosing a specialty at some early point during PGY-2 and matching in the spring of that same academic year, we now have more time to choose a specialty up to the beginning of the PGY-3, and the Match has been delayed until December of that academic year. This change has allowed more time to evaluate options, which may be beneficial, especially for those residency programs where nephrology rotation may have been included at a later time in the PGY-2. Following institution of the ASN initiative for all nephrology fellowship programs to participate in the Match, and to fill all their positions through the Match, an increase in filled positions was seen for the 2016 academic year. There was a slight increase in the number of applicants during this year alone. If this trend continues, potentially in upcoming years this "crisis" of unfilled positions may become history.

As nephrology fellows, we may be able to contribute to solutions to the challenge of ensuring a robust nephrology workforce. We play an important role in introducing nephrology to medical students and residents. We usually spend more time with our team members in training than do our attending staff. Therefore, we have an additional opportunity to make an impact and inspire our peers to consider nephrology.

We need to remind ourselves of the particular aspects of nephrology that caught our attention and inspired us to pursue a career in the field. Our interest might have been piqued in different stages of our medical training. To some of us it occurred when we were medical students; to others it may have been while working as hospitalists for some years before deciding to train in Nephrology. This exercise may help us find key elements of our own experience in choosing nephrology that we may share with others.

Several small changes can make a difference in how the nephrology rotation is experienced. Here I summarize some of the most common scenarios that we can take advantage of to engage our peers in our specialty:

- **Take a walk.** During walking rounds, we may be able to take advantage of those moments in between patients to share our knowledge in a collegial and learning environment. Topics shared may vary according to the clinical cases being seen. Any spare moment may be full of fun facts about nephrology history, ranging from how the first dialysis came to be, to how the first transplants were performed. These facts and conversations may help increase interest in the field.
- **Ask questions.** It is important to keep questions short and to the point and to base them on clinical scenarios of patients seen by the team, especially those concepts that are tested. Asking questions may help our peers recognize possible gaps in knowledge, tailor their study sessions, and perhaps focus their interest. This will help in board exam preparation as well.
- **Engage in hands-on activities.** In many instances, it is better to practice skills than just learn the theory. Engage your team in the physical exam. At the bedside, teach them how to examine fistulas and how to differentiate them from grafts. This tool is specific to nephrology and may be interesting for our peers in training to familiarize themselves with. If a point-of-care ultrasound is available, take a look at the kidneys. Placing central venous access for hemodialysis may be another important skill to learn during nephrology rotation.
- Don't miss an opportunity to **use formulas.** Formulas are one of the most challenging parts of our specialty, and are certainly considered when deciding whether or not to apply to nephrology. Given the opportunity to practice them, our peers in training may feel more comfortable using these calculations and learning their merits. Some of the barriers to understanding may be overcome if time is spent working on these formulas and sharing tips on how to simplify and solve acid–base disorders, for example.
- **Visit the lab.** It should be interesting to all the members of the team to take a look at urine samples under the microscope to make a diagnosis. Urinalysis is a fundamental and inexpensive diagnostic tool, providing a great amount of information that can lead to diagnosis of certain pathologies. Visiting the lab is a good opportunity to emphasize the importance of our field.

Remember, if we are able to transmit our joy and passion for nephrology, we may inspire our peers to enter the field. The future of nephrology is now in our hands; let's make the best of it.

Lourdes Gonzalez Suarez, MD, PhD, is a third year nephrology fellow at Mayo Clinic in Rochester, MN.

Industry Spotlight

New Drug for Secondary Hyperparathyroidism Approved in Europe

Amgen's drug etelcalcetide (Parsabiv™) has been approved for marketing in Europe, through a decision by the European Commission announced in November 2016. Applications are also pending in the United States and Japan for etelcalcetide, which treats secondary hyperparathyroidism (SHPT) in adult patients with chronic kidney disease (CKD) who are on hemodialysis. In Europe, the prevalence of SHPT within dialysis populations ranges from 30% to 49%, Medscape reports. The EC approval covers 28 countries in the EU; Norway, Iceland, Liechtenstein, and members of the European Economic Area (EEA), can take corresponding decisions based on the EC decision.

The drug is the first calcimimetic agent to be given intravenously by a healthcare provider at the end of a hemodialysis session, three times weekly.

John Cunningham, MD, professor of nephrology at University College London Medical School, noted in Amgen's announcement that treatment failures among patients with SHPT are common. "Parsabiv provides a new tool that should give physicians more confidence that patients are getting the medication they need to treat their SHPT," Cunningham said.

In SHPT, excessive parathyroid hormone is secreted by the parathyroid gland and promotes phosphorus and calcium movement from bone, which can cause joint pain. The new medication binds to and activates the calcium-sensing receptor on the parathyroid gland and decreases parathyroid hormone levels.

The marketing application for etelcalcetide included data from three phase 3 studies, all of which met their primary endpoints, including two pooled placebo-controlled trials in more than 1000 patients and a head-to-head study comparing Parsabiv with cinacalcet (Sensipar, manufactured by Amgen).

Amgen submitted a new drug application for etelcalcetide to the US Food and Drug Administration in August 2015, but the FDA has yet to look favorably on the drug application. In August, the FDA issued a Complete Response Letter for the New Drug Application (NDA) for Parsabiv™.

According to the FDA website, a complete response letter provides a more consistent and neutral mechanism "to convey that our initial review of an application is complete and we cannot approve the application in its present form." The agency said the letter provides a more consistent approach to informing applicants of changes that must be made before an application can be approved, with no implications about whether the drug will ultimately be approved. Amgen says it is reviewing the Complete Response Letter and anticipates a meeting with the FDA late in 2016.

In January 2016, Japanese drugmaker Ono Pharmaceuticals filed a manufacturing and marketing approval application in Japan for etelcalcetide, for the same indication, PharmaLetter.com reported. Ono has been working to commercialize the medication since 2011, when it entered into an exclusive licensing agreement with former KAI Pharmaceuticals (now a subsidiary of Amgen) to develop etelcalcetide.

Practice Pointers

Dysproteinemias and Glomerular Disease

By Paisit Paueksakon and Agnes B. Fogo

What is the current terminology for dysproteinemia-related kidney disease?

Dysproteinemias are characterized by abnormal Ig molecules or fragments and result from clonal proliferation of plasma cells or B lymphocytes. Thus, an alternative term for dysproteinemia is plasma cell dyscrasia (PCD). PCDs are classified clinically on the basis of several external parameters, including percentage of plasma cells in the bone marrow, the presence of a monoclonal (M) spike on serum protein electrophoresis (SPEP) or urine protein electrophoresis (UPEP), osteolytic lesions on skeletal survey, and hypercalcemia. When the combination of findings meets precise criteria, patients may be classified as having multiple myeloma.

In 2012, the term monoclonal gammopathy of renal significance (MGRS) was introduced by the International Kidney Monoclonal Gammopathy Research Group. This approach distinguishes monoclonal gammopathy of undetermined significance, which has an isolated monoclonal spike on serum and/or urine electrophoresis without end organ damage, from MGRS, which is defined as kidney dysfunction due to monoclonal Ig (MIg) deposition.

Where do monoclonal proteins deposit in the kidneys?

PCDs can cause disease in any compartment of the renal parenchyma, including glomeruli, tubules, interstitium, and blood vessels. These distribution patterns are mostly determined by the physicochemical properties of the pathogenic MIg. Light chain cast nephropathy (LCCN) is a purely tubulointerstitial pattern of renal injury due to the precipitation of light chain (LC) initially in the lumen of distal tubules, causing inflammatory reaction and injury. Approximately 90% of patients with LCCN have multiple myeloma, often with a high tumor burden. In contrast, LC proximal tubulopathy (LC Fanconi syndrome) is characterized by proximal tubular injury and intracellular crystalline deposits of monoclonal LC. Occasionally, LC proximal tubulopathy occurs in combination with LCCN.

The spectrum of renal diseases induced by MIg also includes Ig-related amyloidosis (AIg); monoclonal Ig deposition disease (MIDD), which includes light chain deposition disease (LCDD), light and heavy chain deposition disease, and heavy chain deposition disease; most patients with immunotactoid glomerulopathy; and proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID). Many cryoglobulins also have a monoclonal component. Most of these diseases have glomerular deposits, with varying deposits elsewhere. Amyloid deposits have randomly arranged fibrils, usually only light chain (AL) but rarely with heavy chain components or light and heavy chain components. These deposits are predominantly present in glomeruli and blood vessels and occasionally present in the interstitium. Nonorganized, punctate, powdery deposits are characteristic of MIDD; classically, they are along the inner aspect of glomerular basement membranes (Figure 1), causing nodular sclerosis, and they are also seen on the outer aspect of tubules. Of note, LCDD may also have isolated tubular basement membrane deposits with no glomerular deposits. In immunotactoid glomerulopathy, the deposits are localized to glomeruli, causing focal proliferative or mesangioproliferative lesions, with microtubular substructure. PGNMID shows granular electron-dense mesangial and/or subendothelial deposits with no substructure, mimicking usual immune complex deposits, but composed of only a single light chain and β heavy chain subclass without tubular basement membrane deposits (1–11).

MIg may also trigger other injuries due to complement activation triggering C3 glomerulopathy or membranous nephropathy due to MIg reacting to the phospholipase A2 receptor (11). Of note, multiple patterns of paraprotein deposition frequently coexist in a single renal biopsy specimen. In our experience, almost 30% of patients with LCDD show coexistent LCCN. Combined AL amyloid and LCCN are also relatively common, whereas combined LCDD and AL amyloid are rare due to the underlying mechanisms promoting specific organization and deposition (e.g., β-pleated sheet formation in amyloid versus partial unfolding in LCDD).

How do patients with MGRS present?

The spectrum of renal manifestations in patients with PCDs is wide and varies according to the disease type and molecular characteristics of the pathogenic MIg. Acute kidney injury (AKI) and proteinuria with or without hematuria are the most common presenting findings. Patients with major glomerular involvement, such as AL amyloid, MIDD, immunotactoid glomerulopathy, and PGNMID, classically present with nephrotic-range proteinuria. Recently, a subset of patients with LCDD has been recognized to have limited proteinuria with dominant tubular deposits. Cryoglobulinemic GN often presents as mixed nephritic/nephrotic syndrome, often with systemic signs of vasculitis. In contrast, patients with LCCN present with less proteinuria and AKI, whereas those with LC proximal tubulopathy often show partial Fanconi syndrome. Of note, testing for monoclonal proteins in urine and serum (SPEP and/or UPEP) is a routine part of the prebiopsy evaluation of proteinuric adult middle-aged or older patients. However, in our practice, about 50% of patients undergoing renal biopsy with some evidence of a monoclonal protein had kidney disease unrelated to monoclonal protein.

What factors predict outcome?

To date, the clinical evaluation of free light chain (FLC) has been almost entirely on the basis of nephelometric immunoassays using sheep polyclonal antibodies against LC epitopes, which are exposed when the LCs are free but hidden when the LCs are bound. These assays, which have high sensitivity, suggest clonality by analyzing the concentration and ratio of κ to γ in serum. The FLC assay significantly improves the detection of monoclonal proteins in AL amyloid nephropathy. Additionally, a decrease in FLC also correlates with renal survival in AL amyloid and MIDD, because it likely is the best indicator of response to treatment. However, patients with PGNMID often do not have detectable monoclonal protein in serum or urine. Thus, improved biomarkers are needed in MGRS.

What treatment approaches are used?

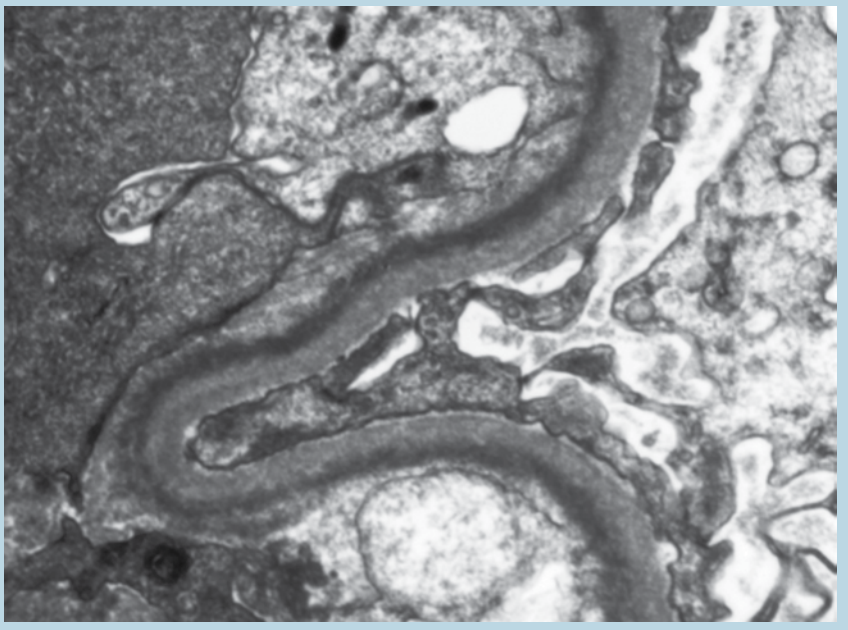
The goal of current treatment approaches for dysproteinemias associated with glomerular diseases is to eradicate the clonal plasma cells. High-dose intravenous melphalan followed by autologous stem cell transplantation to support bone marrow recovery had emerged as the most likely to remove the clonal plasma cells in AIg, although updated chemotherapy (or nontransplant) approaches may be at least as effective. In MIDD, a novel antimyeloma agent, bortezomib-based therapy, showed excellent hematologic and renal response rate, particularly when used early in the disease course. Rituximab therapy in addition to corticosteroids and angiotensin blockade may improve the clinical course of patients with PGNMID or immunotactoid glomerulopathy. Combined therapy with corticosteroid, plasma exchange, and rituximab is successful in MALT (mucosa associated lymphoid tissue) lymphoma with cryoglobulinemic GN. Combined therapy with dexamethasone and bortezomib may show benefit in decreasing the serum titer of IgG anti-CFH (complement factor H) autoantibodies in patients with C3 GN and monoclonal gammopathy, although bortezomib may cause drug-induced acute interstitial nephritis.

What novel therapies are emerging?

In AIg, the effectiveness of cytotoxic chemotherapy to suppress the pathogenic clone is often limited by dysfunction of the amyloid-infiltrated organs. About 20% of patients with AIg die within 6 months after diagnosis, before the delayed benefits of chemotherapeutic drugs may be realized. Thus, new treatments attempt to improve organ function by eliminating systemic amyloid deposits at the time of diagnosis. A clinical trial was designed to engage potent normal phagocytic clearance mechanisms involving the use of a small molecule drug, (R)-1-[6-[(R)-2-carboxy-pyrrolidin-1-yi]-6-oxo-hexanoyl]]pyrrolidine-2-carboxylic acid, to deplete circulating serum amyloid P component (SAP) followed by administration of a fully humanized monoclonal IgG1 anti-SAP antibody to activate macrophage destruction of the SAP-containing amyloid deposits in tissue. This novel therapy significantly decreased the amyloid load in the liver at 6 weeks. Reduction of amyloid load in the kidney and shrinkage of amyloid-laden lymph nodes were also shown. In the next clinical trial phase, patients with renal and cardiac amyloidosis will be studied. The patients will receive larger and if necessary, repeated doses of anti-SAP antibody, with the aim of achieving effective exposure in tissues that do not have highly permeable sinusoidal endothelium, like the liver and spleen.

Dysproteinemia causes a wide range of morphologic lesions in the kidney that can be diagnosed by renal biopsy. In addition to therapies aimed at eradicating the underlying plasma cell clone, disease-specific therapies are emerging (e.g., for AL amyloidosis).

Figure 1. Light chain deposition disease



Extensive powdery deposits along inner aspect of the glomerular basement membranes (transmission electron microscopy; original magnification, 5600).

Paisit Paueksakon, MD, is associate professor, and Agnes B. Fogo, MD, is professor in the Department of Pathology, Microbiology, and Immunology at Vanderbilt University Medical Center Nashville, TN.

Suggested Reading

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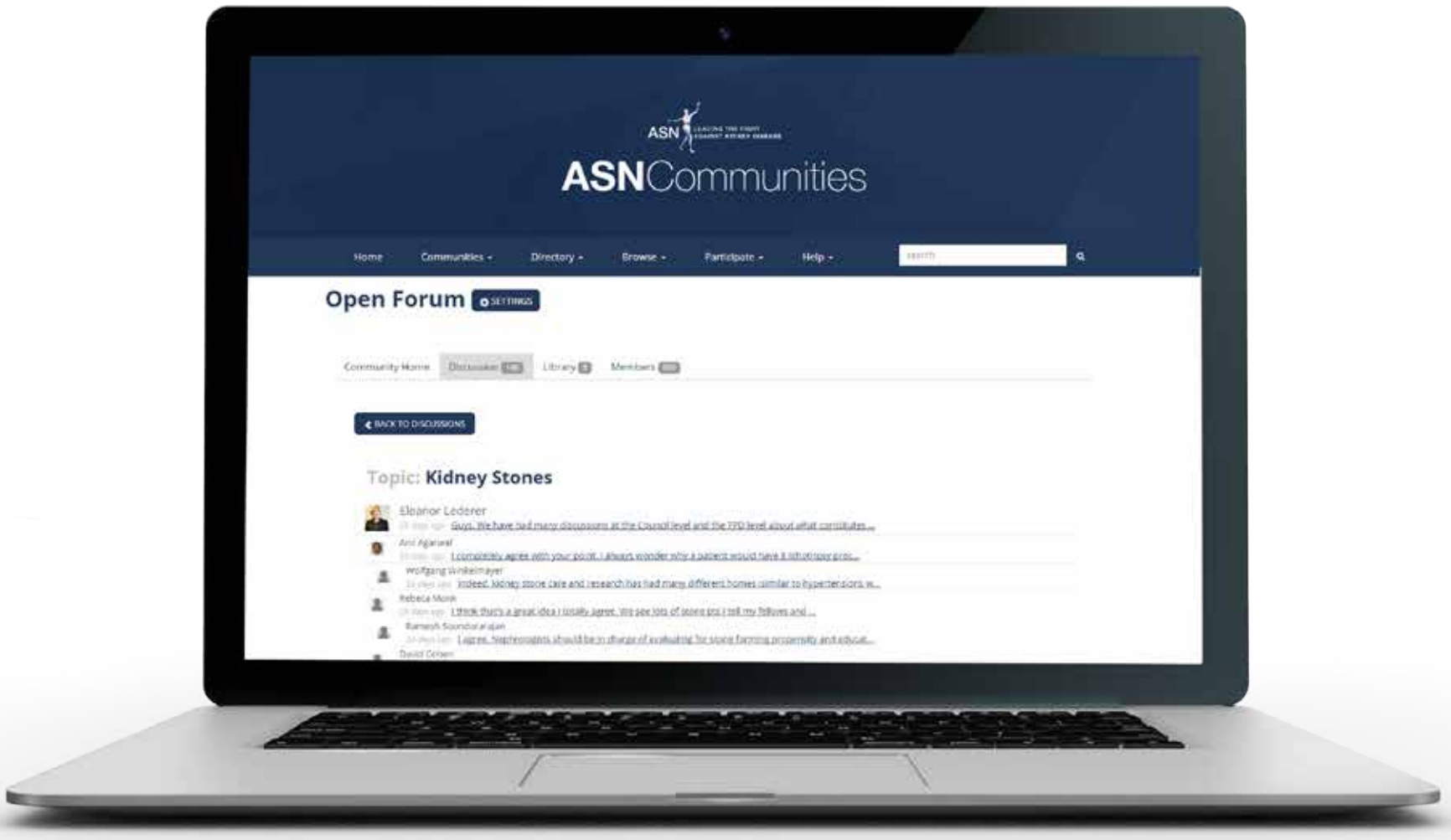

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