ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

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New Hints on Preeclampsia Mechanism Revealed

By Bridget M. Kuehn

The system that regulates blood cholesterol goes into overdrive in women who are experiencing preeclampsia, according to results of a recent study.

Published in the *Journal of Lipid Research*, the study provides the latest clue into what may cause preeclampsia, a condition in which women experience elevated blood pressure and protein in the urine during pregnancy (Mistry HD, et al. *J Lipid Research* 2017; 58:1186–1195). It also adds to emerging evidence linking cardiovascular disease risk to malfunctioning in the body's cholesterol flushing system.

Placenta problems?

Better understanding of this complex condition is critically important because it occurs in about 3%–5% of pregnancies in the United States, according to the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). It also accounts for about half of maternal deaths in the developed world, according to NICHD. Women who experience preeclampsia and survive have an elevated risk of cardiovascular disease and kidney disease. Their children also face a higher risk of heart disease later in life.

"We're still trying to work out what happens during preeclampsia and what causes it," said Hiten Mistry, PhD, a senior research fellow in the Division of Child Health, Obstetrics & Gynecology at the University of Nottingham's School of Medicine. "If we understand the mechanism, we can do something to prevent it."

Already, scientists know that the placenta plays an important role in preeclampsia. For example, a previous study by Mistry and his colleagues revealed signs of atherosclerosis in blood vessels in the placentas of women who had preeclampsia (Hentschke MR, et al. *J Lipid Research* 2013; 54:2658–2664).

This is the same kind of narrowing and hardening caused by a buildup of cholesterol seen in the arteries of people with heart disease. Atherosclerosis constricts blood flow and in people with heart disease may lead to heart attack, stroke, or death. In the placenta, this narrowing might compromise the flow of nutrients from the mother to the developing fetus and the flow of waste from the fetus to the mother. Such a constriction might explain why some babies born to mothers who had preeclampsia are smaller than expected.

"We know the placenta is involved," Mistry said.

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Diabetes Prevalence Data Herald High Rates of Kidney Disease in Years Ahead

By Timothy O'Brien

A recently released report on diabetes prevalence underscores the need for determined efforts to contain the burden of diabetes and diabetic complications in the years ahead.

The Centers for Disease Control and Prevention's (CDC) 2017 *National Diabetes Statistic Report* highlights the devastating impact of diabetes in the US, with estimates suggesting that 30 million Americans have diabetes and another 70 million meet criteria for prediabetes.

"More than a third of US adults have prediabetes, and the majority don't know it," said CDC Director Brenda Fitzgerald, MD. "Now, more than ever, we must step up our efforts to reduce the burden of this serious disease."

The aging US population and sky-high percentage of Americans with prediabetes mean diabetes-related complications will continue to be a concern moving forward. Based on a US Renal Data System report, more than 52,000 Americans developed ESRD with diabetes as the primary cause during 2014. Adjusted for age, sex, and race/ethnicity, the rate of diabetes-related

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Inside

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Preeclampsia

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Cholesterol implicated

Appropriate levels of cholesterol are necessary for both healthy adults and developing fetuses. It is used to build new cells for growth and repair, to protect nerves, and to make important hormones. But too much so-called bad cholesterol or low-density lipoprotein (LDL) cholesterol has been linked to heart disease and preeclampsia (Spracklen CN, et al. *Am J Epidemiol* 2014; 180:346–358).

Sufficient levels of a type of cholesterol called high-density lipoprotein (HDL) on the other hand have been found to be important for good heart health.

Low levels of HDL are associated with insulin resistance and other factors that may contribute to heart disease, so it has been hard to tease out HDL's role, noted Anand Rohatgi, MD, an associate professor and preventive cardiologist at the University of Texas Southwestern Medical Center in Dallas. One reason HDL may be helpful is that it helps the body remove LDL cholesterol and transport it to the liver where it can be eliminated. The first step in that process is called efflux.

Rohatgi and his colleagues found that people who are better at removing LDL cholesterol this way have a lower risk of having a heart attack, stroke, or other serious heart disease–related event (Rohatgi A, et al. *N Engl J Med* 2014; 371:2383–2393).

That study led Mistry to wonder whether this cholesterol flushing system also might play a role in preeclampsia.

Pregnant mothers need to supply their fetuses with cholesterol for development and they need it to aid their recovery after delivery, Mistry explained.

"It's getting the balance right," he said.

He and his colleagues suspected pregnant women with preeclampsia wouldn't clear cholesterol as efficiently as pregnant women without the condition. So they compared cholesterol efflux in pregnant women with and without preeclampsia. But they found that efflux is turned up in women with preeclampsia and in their fetuses. This may help the women try to mitigate the potentially harmful effects of elevated cholesterol.

"This study showed this is a compensatory mechanism for damage limitation," Mistry said.

The findings add some much needed information about efflux during pregnancy, said Rohatgi, but more studies are needed to understand whether efflux is a cause of preeclampsia or merely an indicator.

"I think this is provocative," Rohatgi said. "Because it is case controlled you get a link to efflux at the time of preeclampsia, but you don't know if it is causing preeclampsia."

In fact, the role of efflux in cardiovascular disease more generally is still being worked out. Some phase 2 trials are currently underway to test whether treatments that boost efflux would improve patient's cardiovascular disease outcomes.

"What has been established pretty well is that as a cardiovascular risk prediction marker efflux does work," Rohatgi said. "We still don't know what drives efflux—what makes it go up or down."

Emphasis on prevention

The findings may have important implications for protecting the long-term cardiovascular and renal health of mothers who experience preeclampsia, as well as the health of their children.

Women who have elevated cardiovascular risk are at higher risk of preeclampsia. After preeclampsia, a woman's cardiovascular risk is elevated substantially, noted study co-author Markus Mohaupt, MD, a nephrologist and head of internal medicine at Lindenhofgruppe, a foundation based in Bern, Switzerland, that supports research. Understanding these relationships may aid prevention and possibly treatment efforts.

"Is it a disorder that preexists the development of preeclampsia or a disorder that develops after [that contributes to the elevated cardiovascular risk]?" asked Mohaupt, who is also a professor at the University of Bern. "It could be either or both."

In addition to having an elevated risk of heart disease over the long term, women who experience preeclampsia are also more likely to undergo a renal biopsy, develop chronic kidney disease, and require treatment for kidney disease, Mohaupt said.

To help prevent such poor outcomes, Mohaupt recommended that clinicians monitor lipid levels in women with a history of preeclampsia, especially after menopause.

Rohatgi agreed that long-term monitoring for signs of cardiovascular disease is warranted. He also emphasized the importance of good prenatal care and managing conditions like high blood pressure or gestational diabetes that increase the risk of preeclampsia. "The low hanging fruit is simple prenatal care," he said.

Children whose mothers had preeclampsia are also at elevated risk for cardiovascular disease.

"The literature is scarce, but what is available tells us a story where the offspring may share the adverse cardiovascular risk factors with their mothers," said Ingvild Alsnes, MD, a PhD candidate at the Department of Public Health and General Practice at the Norwegian University of Science and Technology in Trondheim, Norway.

Alsnes and her colleagues recently compared the cardiovascular risk of siblings whose mothers had preeclampsia (Alsnes IV, et al. *Hypertension* 2017; 69:591–598). It turns out that the siblings have similarly elevated risks of cardiovascular disease regardless of whether their mother had preeclampsia during their own gestation.

"It might suggest that it is not the exposure [to preeclampsia] per se that gives an adverse cardiovascular risk profile, but perhaps genetics or lifestyle," she suggested.

Unanswered questions

Many unanswered questions remain about preeclampsia itself. Alsnes said it would be important to better understand if the cardiovascular risk profiles of women who had severe or mild preeclampsia are different.

"Perhaps they should not be subgroups, but different entities altogether," she said. "We also need to know whether cardiovascular disease is preventable in this patient group, and how or if they should be followed up or treated."

The heart risk may differ among women who have had preeclampsia—some may not have an increased risk—so it will be important to identify markers that distinguish those with an elevated heart risk, Rohatgi said.

"Efflux as a marker might help determine which ones are at risk," he noted.

Markers of elevated cardiovascular risk in women in general are needed, Rohatgi said. Most current heart risk calculators are geared toward men.

"There is a lot of room for improvement in picking out women who are at higher risk," Rohatgi said.

Early warning sign?

Mistry and his colleagues plan to monitor cholesterol efflux in women earlier in pregnancy to look at whether efflux is elevated before the condition is diagnosed. If so, it might be an early warning sign. They would also like to examine efflux prior to pregnancy in women with chronic hypertension or signs of kidney dysfunction who are at risk of preeclampsia. Rohatgi agreed that these types of studies will be helpful, as will studies that track the long-term cardiovascular outcomes of women who have had preeclampsia.

In the meantime, Mistry emphasized the importance of routine lipid monitoring during pregnancy. He also expressed optimism that elevated cholesterol efflux during pregnancy might one day prove to be a useful tool for monitoring women's cardiovascular health.

"In the future, it could be a predictor of heart disease later in life," he said. "If we know a woman is at higher risk, we can intervene early and prevent it."

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10.10 - OVER-THE-COUNTER PRODUCTS (OTCs)

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"…However, CMS will allow Part D sponsors the option to provide OTCs as part of their administrative costs structure."

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Stopping Preventable Infections in Dialysis

By Alan S. Kliger MD, NTDS Project Committee Chair, and Susan Stark, NTDS Director

It is now one year since Nephrologists Transforming Dialysis Safety (NTDS) began its work. The Centers for Disease Control and Prevention (CDC) awarded the American Society of Nephrology (ASN) 3 years of funding to sponsor NTDS, as part of its effort to improve infection-control practices in dialysis facilities across the United States.

The critical need to eliminate preventable infections in dialysis is shown in the dialysis databases. The PEER Report (2014) demonstrates only modest improvement in the rate of patient admission for infection between 2004 and 2014.

The USRDS 2016 Annual Data Report (vol 2, ESRD, Ch 5) shows hospitalization rates for dialysis patients, indicating that while all-cause and cardiovascular hospitalization rates have been declining from 2005 to 2014, hospitalization for infection has not improved substantially

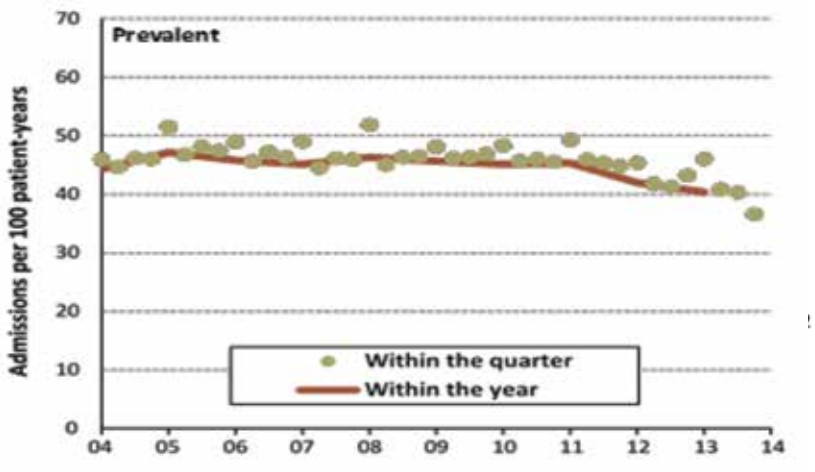
The 2014 PEER Report, "Cause of death in prevalent dialysis patients" shows that infection causes 9.5% of all deaths (1).

For several years, the CDC worked with dialysis companies to promote evidence-based best practices and useful tools to prevent bloodstream infections (BSI) and hepatitis C virus (HCV) infections. The NTDS project aims to more directly involve nephrologists as team leaders and as professional role models to reduce the burden of BSI and other healthcare-related infections in dialysis patients.

Building upon the foundational principles of the CDC's Making Dialysis Safer for Patients Coalition, the NTDS project is aimed at transforming dialysis care, to make infection prevention part of the fabric of everyday care for dialysis patients. The specific project aims include:

1. Adhere to CDC-recommended infection prevention practices
2. Screen and detect infections
3. Implement clinical protocols to ensure accurate detection and treatment of infections
4. Facilitate collaboration between nephrologists and state/federal healthcare-associated infection programs

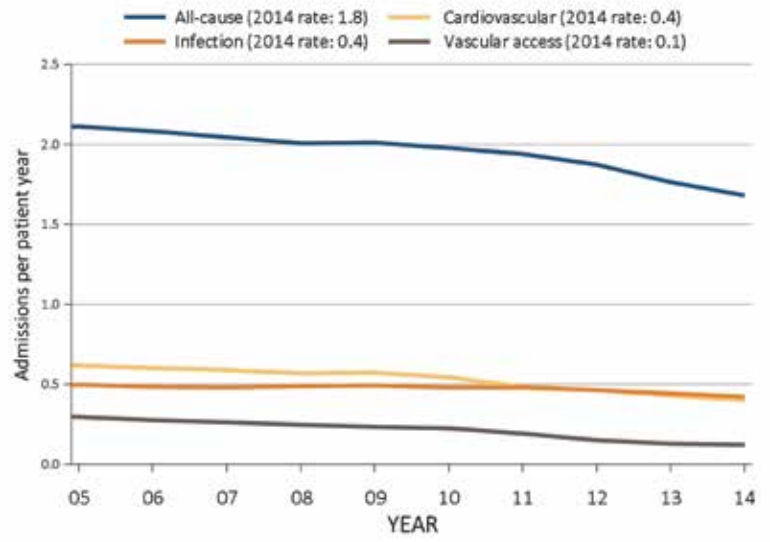
Figure 1. Annual & quarterly admission rates—infection as the primary discharge diagnosis



Patients prevalent on the first day of the year or quarter and rates within the year or quarter; patients aged 18 years or older.

Peer Dialysis Initiative, Peer Report: Dialysis Care and Outcomes in the United States, 2016, Chronic Disease Research Group, Minneapolis, MN, 2016. www.Peerkidney.org

Figure 2. Adjusted all-cause and cause-specific hospitalization rates for ESRD patients by treatment modality, 2005–2014



United States Renal Data System. 2016 USRDS annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health. National Institute of Diabetes and Digestive and Kidney Disease, Bethesda, MD, 2016. Vol 2, ESRD, Ch 5 https://www.usrds.org/adr.aspx

Year one achievements

NTDS believes that ending preventable infections requires a cultural change in dialysis facilities—where daily infection prevention is a priority, where caregivers and patients accept accountability for their part in stopping infections, and where a culture of safety encourages sharing and reporting of safety practices in a community that welcomes opportunities to correct and improve daily performance. Cultural change requires thoughtful planning and stakeholder input. In year one, NTDS successfully reached out to decision-makers across the nephrology community to incorporate their insights into the work of the Project Committee and Workgroups.

We then devised an implementation plan to determine best strategies for infection prevention and to garner feedback from the community on useful tools for leading improved practice. We led community meetings and focus groups to identify specific infection-control practices, barriers, and opportunities. We performed a root-cause analysis exercise among NTDS members, and augmented those insights during ASN's Kidney Week 2016. Contributing to this effort were 737 physicians, researchers, nurses and nurse practitioners, pharmacists, physician assistants, other healthcare professionals, and trainees. Barriers to infection prevention that were identified included lack of education and training; lack of policies, protocols, and procedures; absence of data; presence of central venous catheters; lack of leadership; and lack of governmental collaboration. NTDS synthesized these wide-ranging views, and developed a roadmap to guide each workgroup's activities. To support this work, NTDS launched a robust set of online resources. We created a series of NTDS webpages within ASN's website that includes a resource library of infection prevention tools.

One important objective was to prepare for the unknown. When the Ebola epidemic reached into the US, including the need to prevent infection spread during dialysis care, it became clear that the dialysis community needed to quickly learn new and critical methods for isolation, spent dialysate disposal, bloodline management, and possible Ebola exposure among our chronic dialysis patients. We were unprepared as a community to manage such virulent infection, and those few nephrologists who faced the challenge needed to deal with these challenges "on the fly." We want to be better prepared for the next epidemic. To this end, NTDS conducted a gap analysis to identify lessons learned by speaking with the nephrologists who managed the few cases of Ebola that required dialysis treatment in the US.

To reach a broad audience of dialysis caregivers, we launched an educational series, including webinars, regional lectures and interactive seminars, and seminars at ASN's Kidney Week. The first webinar, attended by nearly 500 nephrologists and other professionals, was titled "Targeting Zero Infections: Where Do We Begin?" This case-based conference stressed several key educational points, including the virulence of hepatitis C, the role of the nephrologist as a leader, and direction to the online resource library. Almost 100% of attendees found the webinar content useful and anticipate participating in Webinar 2, "Targeting Zero Infections: Combating Blood Borne Pathogens," scheduled for September 27, 2017. For ASN's Kidney Week 2017, NTDS will conduct several activities, including an Early Program seminar titled "The Dialysis Infection Crisis in the United States: A Call to Action," and a presentation during the annual meeting, "Infection Prevention: Are You Prepared for the Next Ebola?"

Engaging those who will make a difference to care requires a multi-dimensional approach. NTDS has es-

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Infection in Dialysis

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tablished a presence on several communication platforms, including:

1. Website URL: https://www.asn-online.org/ntds. This includes a resource library highlighting current topics, including data and quality improvement, identification and treatment of bloodborne pathogens, regulations, and leadership and culture
2. Facebook, administered by ASN: https://www.facebook.com/AmericanSocietyofNephrology: Posts including ASN President's invitation to the NTDS Town Hall, links to Kidney News Online articles, promotions for the NTDS website, and information about NTDS webinars
3. Twitter administered by ASN: Hashtags: #ASN_NTDS and #targetzeroinfections.
4. NTDS Community in ASN Communities: highlights have included NTDS Town Hall, regular glove use vs. sanitizer use, ClearGuard HD Antimicrobial Barrier Cap, and anti-infection or infection resistant surfaces.

If infection control practices are to become part of the fabric of daily dialysis care, the next generation of nephrologists and leaders will need robust education and practice patterns. NTDS identified several education and training needs:

1. Incorporate current guidelines: policies, procedures, and protocols
2. Fellow's Curriculum: infection prevention and leadership education and training
3. Hand hygiene
4. Human factors engineering, continuous quality improvement, and best practices
5. Credentialing
6. State/Federal healthcare-associated infections (HAI) program introduction and mandates

Antibiotic stewardship has been deployed in hospitals, but is not generally part of dialysis facility operations. These efforts improve outcomes in several ways. When antibiotics are administered only when there are clear indications for their use, fewer patients harbor antibiotic resistant organisms or develop multiple antibioti–resistant infections. Tailoring antibiotic administration to the agent appropriate for the organism and type of infection reduces the pressure on organisms to develop antibiotic resistance. In addition, it is now becoming clearer that the health-promoting gut microbiome can be permanently altered by multiple courses of antibiotics. Antibiotic stewardship reduces unnecessary exposure to antibiotics, and better preserves the normal gut microbiome. Dialysis patients are often prescribed courses of antibiotics, including wide spectrum agents. Antibiotic stewardship programs in dialysis facilities have the potential to substantially reduce unnecessary exposure of patients to these antibiotics.

NTDS identified several leadership mandates to facilitate. We will succeed only if we collaborate closely with dialysis organizations. We have engaged the leadership of the large and medium-sized dialysis companies, and seek ways to work together to enhance lines of communication, enhance training for medical directors, identify dialysis facility infection control leaders/coordinators, and collaborate with state/federal HAI programs and renal organizations. We also seek to reduce inconsistencies among government agencies and eliminate knowledge gaps between dialysis facilities and governmental HAI programs.

Year two plan

For the coming year, NTDS will continue to expand our education and physician engagement activities, present a series of articles in *Clinical Journal of the American Society of Nephrology*, complete and share a curriculum for trainees and medical directors to stop preventable infections, complete and share a guideline for anticipating and preparing for emerging threats, and encourage collaboration between dialysis professionals and state/federal HAI programs. In addition, NTDS will work with dialysis facilities to develop and refine programs to transform the dialysis culture to a culture of safety and individual accountability. By engaging nephrologists, dialysis facility owners, and other stakeholders in these many transforming activities, NTDS believes we can get to our target of zero preventable infections.

Reference

1. Cause of death in prevalent dialysis patients: Peer Dialysis Initiative, Peer Report: Dialysis Care and Outcomes in the United States, 2014.

Disclaimers

Peer Data: The data reported here have been supplied by the Centers for Medicare & Medicaid Services and the United States Renal Data System. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the US government. The Peer Kidney Care Initiative has no affiliation with the US government.

USRDS Data: The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government.

Diabetes Prevalence

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ESRD was 154.4 per 1 million persons.

The *National Diabetes Statistics Report* is a periodic update on diabetes in the US, with estimates drawn from CDC data systems and other sources. The 2017 report estimates that 9.4% of all Americans—and 12% of adults—are affected by diagnosed or undiagnosed diabetes. In the absence of a physician diagnosis, diabetes was defined as a fasting plasma glucose level of 126 mg/dL or higher, or an HbA1c level of 6.5% or higher. Prediabetes was defined as fasting plasma glucose of 100 to 125 mg/dL or HbA1c of 5.7% to 6.4%.

The estimates don't differentiate between type 1 and type 2 diabetes. "However," the report states, "because type 2 diabetes accounts for 90% to 95% of all diabetes cases, the data presented are likely to be more characteristic of type 2 diabetes." Overall prevalence appeared steady—the previous CDC diabetes statistical report, issued in 2014, estimated about 29 million Americans with diabetes, or 9.3% of the population.

In 2015, an estimated 1.5 million US adults received a new diagnosis of diabetes.

The prevalence data suggested that more women had diagnosed diabetes than men, but that differential may not mean much, as more men had undiagnosed diabetes (4.0 million men versus 3.1 million women). Also, most adults with diabetes were of working age: 4.6 million aged 18 to 44 and 14.3 million aged 45 to 64. At age 65 or older, total diabetes prevalence was 25.2%.

Analysis by race/ethnicity found that diabetes prevalence was highest for American Indians/Alaska Natives, 15.1%; followed by non-Hispanic blacks, 12.7%; Hispanics, 12.1%; Asians, 8.0%; and non-Hispanic whites, 7.4%. Within these categories, there were some important differences by subgroup: prevalence was 13.8% among Mexican Americans, 12.0% among Puerto Ricans, and 11.2% in Asian Indians.

Education, an indicator of socioeconomic status, was also related to diabetes prevalence: 12.6% for adults with less than a high school education, 9.5% for those with a high school education, and 7.2% for those with more than a high school education.

Estimates for prediabetes were staggering—33.9% of US adults in 2015, or 84.1 million people. That included nearly half (48.3%) of adults aged 65 or older. The figures were somewhat lower than in the 2014 report, which estimated that 86 million US adults had prediabetes.

Only 11.6% of adults with prediabetes were aware of their condition. In contrast to the situation with diabetes, there was no significant difference in the prevalence of prediabetes by racial/ethnic group.

High burden of complications and death

"Persons with diabetes are at higher risk of developing serious complications, including blindness, lower extremity amputation, and kidney failure," said Nilka Ríos Burrows, MPH, of the CDC's Chronic Kidney Disease Initiative, Division of Diabetes Translation. "However, people with diabetes can take steps (e.g., keeping blood sugar and blood pressure levels under control) to manage their diabetes and delay or prevent complications."

Diabetes was a listed diagnosis in 7.2 million hospital discharges in US adults in 2014, including 1.5 million discharges for cardiovascular disease: a crude rate of 70.4 per 1000 persons with diabetes. These included approximately 400,000 patients with ischemic heart disease and more than 250,000 with stroke. There were 108,000 hospitalizations for lower extremity amputations and 168,000 for ketoacidosis.

Diabetes was listed as any diagnosis in 14.2 million emergency department visits, including 245,000 visits for hypoglycemia and 207,000 for hyperglycemic crisis. Diabetes was the seventh-leading cause of death in the US in 2015, with a crude rate of 24.7 per 100,000 persons.

Total direct and indirect costs of diagnosed diabetes in the US were estimated at $245 billion in 2012, according to research by the American Diabetes Association. With adjustment for age and sex, average medical costs for people with diabetes were 2.34 times higher than for those without diabetes.

For nephrologists, the high prevalence of diabetes and prediabetes heralds high rates of diabetic nephropathy in the years ahead. "More than 30 million people in the United States are living with diabetes, placing them at risk of developing kidney disease," Ríos Burrows said.

A recent report by the CDC's Chronic Kidney Disease Surveillance Team estimated that 36.5% of adults with diagnosed diabetes had stage 1 to 4 CKD during 2011–2012. As reported last year in *ASN Kidney News*, that study found continued increases among African Americans. The authors highlighted the need for continued vigilance to lessen the impact of CKD in the population, including efforts on the part of nephrologists to promote better awareness and care among primary care clinicians.

"Claims data indicate that testing for urine albumin, the earliest marker of kidney disease in diabetes, is done in less than half of patients," Ríos Burrows said. "Testing for kidney disease among people who are at high risk for developing CKD—those with diabetes or with high blood pressure—has been shown to be a cost-effective tool to identify people with CKD. CDC's kidney team is currently designing an online tool to help primary care physicians and other health care providers evaluate a patient's need for and frequency of screening for CKD." The latest CDC National CKD Fact Sheet can be found at https://www.cdc.gov/diabetes/pubs/pdf/kidney_factsheet.pdf.

What are diabetes rates in your area?

The 2017 National Diabetes Statistics report includes age-adjusted, county-level data on adult diabetes prevalence, providing a unique snapshot of diagnosed diabetes, based on 2013 data from the US Diabetes Surveillance System.

Median county-level prevalence was 9.4%. Age-adjusted prevalence of diagnosed diabetes varied widely: from 3.8% in Eagle County, Colorado, to 20.8% in Lowndes County, Alabama. The data can be explored in depth at https://www.cdc.gov/diabetes/atlas/countydata/atlas.html.

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Nephrology and Palliative Care

Practice Pointers

In this issue,* Kidney News *Editorial Board member Edgar Lerma, MD, interviewed Christian T. Sinclair, MD, this month's special section editor, about palliative care in kidney disease. Dr. Sinclair is Assistant Professor in the Division of Palliative Medicine at the University of Kansas Health System in Kansas City, KS. We hope you enjoy this introduction to palliative care in nephrology, as well as the set of articles that follow. More articles will appear in the next issue.

Christian T. Sinclair, MD

Conservative care in ESRD seems to be in the limelight of late. However, this is not a new concept. How did interest in palliative care begin, and where are we right now?

It is important to note the official designation of hospice and palliative medicine as a new medical specialty in 2008 by the American Council on Graduate Medical Education (ACGME). Before then, research on quality of life, symptoms, and shared decision-making was often scattered across journals, specialties, and disciplines. Since 2008, with more clinicians practicing palliative medicine full time and more research being accumulated and incorporated into clinical care and educational programs, it has become much easier to see the opportunities for palliative care and nephrology to work together.

There is some confusion about palliative care and hospice, because there seems to be a lot of overlap. What are the differences and similarities?

The similarities between palliative care and hospice exist in the approach to care (quality of life, patient-focused, and with an emphasis on skilled communication) and by extension, in the training of clinicians in these skills. However, from a patient's point of view, these similarities do not really matter: just as ketchup and mustard are often paired, you use them in very different situations. The critical difference is that palliative care can be applied concurrently with hospice, even when a patient's goals are life prolonging or disease directed. We are seeing a big movement upstream in the care of people with serious illness. Hospice is consulted for symptom-directed care when comfort is the only goal.

Can you talk about time-limited trials of dialysis? Where do they fit into palliative and hospice care?

Time-limited trials are an important tool in conversations about goals of care. They allow patients and clinicians to acknowledge the uncertainty that exists in any outcome prediction, while implicitly acknowledging that there will be an opportunity in the future to readdress the goals. At that time, the patient and family will have a chance to see how well the patient tolerates side effects or if their function or quality of life changes as they thought it might.

What is advance care planning, and when and where does it come in, given the current behavioral patterns of patients and health care providers? When is the ideal time for it?

Claiming our right to control what happens to our bodies when we cannot decide for ourselves is something any competent adult should do, even if they do not have a serious illness. It should happen throughout our adult lifespan and be readdressed when major life events come up. The current thinking is moving away from clinicians highlighting advance care planning because someone has a serious illness. It is moving toward participation in advance care planning, because it is a responsibility to let people know who to talk with to share your values and goals. There are various tools that have different benefits and limitations, like living wills (values, goals, desired or undesired treatments), durable power of attorney (identifying a surrogate decision maker), and medical orders (e.g., DNAR [Do Not Attempt Resuscitation] and POLST [Physician Orders for Life-Sustaining Treatment]).

What do you perceive as barriers to conservative care from the patient's perspective? From the primary care physician's perspective? From the nephrologist's perspective?

One of the primary barriers for all of the above is that our health care delivery system is not necessarily well suited to make the choice for conservative care in ESRD visible. Upstream palliative care is beginning to make headway in clinics and in the community, but there are still far fewer providers compared with potential demand. In addition, each community may handle the interaction between nephrology and palliative care differently. Maybe your local palliative care clinics only see patients with advanced cancer or heart failure, or maybe you do not have outpatient palliative care beyond a few home health–based providers with limited specialty training or oversight.

Other barriers include balancing the time it takes to have these conversations, but with the new advance care planning codes approved, there is some reimbursement. Also, these conversations can take place over time and with different members of your nephrology team, like social workers. Two other common barriers are education and experience. If we do not get a chance to see this modeled in our training and if it does not exist in our community, it is much easier to stay on the same familiar paths instead of blazing a new trail. Therefore, I think it is essential that local nephrologists and palliative clinicians gather to discuss how they are serving their community together.

Can you discuss the concept of spirituality as it relates to chronic kidney disease?

Spirituality is such a critical part of many people's view of their world. Understanding how their faith influences their social support, hopes, fears, and even medical choices is important for us to acknowledge and explore in a respectful and supportive manner. Having access to a chaplain in a dialysis clinic or when working with a transplant team may be very helpful to make sure that these needs are being recognized.

What about the economics of conservative care in ESRD, e.g., insurance coverage?

One of the major challenges is the unique Medicare programs that cover dialysis and hospice care. Because they cannot both be accessed at the same time, it makes it challenging to work with patients in the transition off dialysis and onto hospice care. For more upstream palliative care support, the physician's role is covered by E&M codes, like any specialist physician. However, with the increased time-based billing and lack of procedures, there is not always a way to balance the salary. Therefore, health care systems and hospitals often support part of the salary. Add to this the lack of direct coverage for vital team support from nurses, social workers, and chaplains, and you can understand why palliative care has had such sporadic growth.

In a study published in 2003, the authors looked at octogenarians with stage 5 chronic kidney disease and showed 29- versus 9-month survival rates on dialysis versus not on dialysis (1). In another study published in 2007 involving patients 75 years or older, the authors looked at 1-year survival rates (84% versus 68% on dialysis versus not on dialysis), seeming to suggest that patients live longer on dialysis (2). As a nephrologist, I have been asked many times, "If I don't go on dialysis, how long do I have?" This is a very difficult question to answer. Can you suggest a constructive and informative way to answer this question?

My favorite topic in medicine is prognostication. We are fearful of the uncertainty inherent in predicting

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Continued from page 9

Practice Pointers

the future, but we are so dependent on it to make some of life's most important decisions. It is important to accept that, although we are not perfect at prognosis, clinicians, as a group, do have decent results when it comes to prognostication around end of life. To narrow down the accuracy for an individual gets much harder. I try to take a worst case, best case, and expected case approach. It allows for the uncertainty but gives a reasonable range for people to expect. It is also used to tell people how we are making this assessment. If it is because they are getting dangerously hypotensive during hemodialysis, it is important to share that concern. We should be basing these conversations on our clinical experience, published research, mortality calculators, and the data from our own organizations. And documenting what we said.

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Symptom Patterns in ESRD

By Chia-Ter Chao and Hung-Bin Tsai

Patient-reported outcomes in patients with chronic kidney disease (CKD)/ESRD have assumed increasing importance during recent years, because these factors also play a vital role in affecting outcomes, as do traditional survival determinants. A comprehensive understanding of measurements coming directly from patients is expected to assist physicians in improving patient care and facilitate patients in optimizing their decision-making processes. Incorporating patients' viewpoints and ameliorating their discomfort throughout the course of CKD and even the dialysis career constitute an important aim for optimal supportive care for renal patients. Furthermore, when CKD patients are required to choose between the option of dialysis or no dialysis when they face peaking creatinine levels, the totality of symptom burden frequently stands out as an important factor driving their thought process.

Patients with progressive renal dysfunction often have multiple comorbidities, leading to a plethora of symptoms. A systematic review disclosed that CKD/ESRD patients experience a disproportionately high prevalence of different physical symptoms, the most common of which include fatigue (49% to 100%), drowsiness (49% to 82%), pain (38% to 90%), pruritus (33% to 84%), dry skin (42% to 72%), and muscle cramps (26% to 74%) (1). In addition to physical symptoms, depression can be the most common psychological symptom among CKD/ESRD patients. Studies indicate that more than 20% of incident dialysis patients have increasing severity of depression within the first year of dialysis; this phenomenon was modified by their disease perception and understanding (2).

Patients with CKD/ESRD have, on average, 6 to 20 symptoms as shown by different assessment instruments (1). It is interesting to note that patients with stage 5 CKD reportedly might have a similar number of symptoms and impairment in quality of life compared with those with advanced cancer, although the pattern can be distinct in both groups of patients (3). In addition, the patterns of symptoms seem to differ depending on several clinical features. Those who are women, younger, or have longer dialysis duration tend to bear greater symptom burden (higher severity, frequency, and distress) than others (4, 5), but minimal evidence exists regarding the influence of CKD stages on symptom burden. Anecdotal reports suggest that cultural background might affect symptom severity. Finally, the prevalence of symptoms may be higher among advanced CKD patients before they receive dialysis than after dialysis commencement (6).

Symptom clustering is another important signature in patients with CKD/ESRD, because their symptoms frequently exhibit high correlation with each other and come in combination. Studies on hemodialysis patients in the United States revealed that four types of symptom clusters could be discerned, including energy/vitality-related symptoms, cardiac-related problems, pain/discomfort, and gastrointestinal system–related symptoms (7). Another larger study in The Netherlands disclosed that general symptoms of the uremia syndrome (dyspnea, faintness/dizziness, nausea, and appetite loss), neuromuscular problems (muscular ache and extremity numbness), and skin problems (dry, itchy skin) are the three most common symptom clusters identifiable in ESRD patients (8). Symptom clusters are more likely to emerge in those with less urine output, more severe depression, and lower hemoglobin levels (5). Uremic symptom clusters have been shown to independently predict all-cause mortality in a prospective cohort study among ESRD patients (9).

Fatigue or a sense of weakness is the most common symptom reported by CKD/ESRD patients. The presence of fatigue has been found to correlate with malnutrition, anemia, divalent ion imbalances, and chronic inflammatory status in these patients, and we recently discovered that ESRD patients reporting fatigue were at higher risk of low bone mass (10). More important, fatigue is an important component of and contributor to frailty, a degenerative phenotype resulting from the accumulation of multidimensional health deficits and an emerging risk factor for adverse outcomes in patients with renal failure (11).

Other components within the spectrum of symptom burden, such as dry skin, pain, and pruritus, worsen patients' quality of life and indirectly potentiate the development of frailty. ESRD patients with frailty are prone to have hypoalbuminemia, more complicated comorbidities, lower bone mass, and higher risk of vertebral compression fractures than those without frailty (12). Through a connection between symptomatology and frailty, these patient-rated complaints might serve as an intermediate, playing an under-recognized role in outcome determination. In this sense, assisting CKD/ESRD patients by helping them to understand the nature and causes of their symptoms, periodically assessing the severity, and providing optimal symptom management may not only improve their quality of life and enhance physician-patient communication and rapport but also lower the risk of adverse outcomes, including premature mortality, functional impairment, and frailty, indirectly leading to a potential reduction of health care spending.

Chia-Ter Chao, MD, FASN, is with the Department of Medicine, National Taiwan University Hospital Bei-Hu branch; the Nephrology Division, Department of Internal Medicine, National Taiwan University Hospital; and College of Medicine, National Taiwan University. Hung-Bin Tsai, MD, is with the Division of Hospital Medicine, Department of Internal Medicine, National Taiwan University Hospital and the College of Medicine, National Taiwan University.

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Depression and Anxiety in ESRD: **A Practical Guide for Nephrologists**

By Nicole Bates, Jane Schell, and Allison Jordan

Psychologic concerns are prominent in chronic illness, such as ESRD, in which patients face significant morbidity, mortality, and complex treatment decisions. However, these symptoms are often not recognized or effectively treated. Because rates of depression and anxiety increase in this population, there is a need for interdisciplinary team collaboration among nephrology, palliative care, and mental health. Here, we present a guide tailored to the kidney care team for identifying and managing depressive and anxious symptoms in ESRD patients.

Clinical relevance

One in five patients with ESRD is diagnosed with depression, which is higher than in kidney transplant patients (1). Risk factors include female gender, lower socioeconomic status, age >60 years old, and limited social support. Depression has been associated with worsening renal function, increased hospitalization, and all-cause mortality (2). Patients with depression are less likely to engage in treatment adherence, especially dialysis, which itself seems to drive decreased life satisfaction (3). Furthermore, cognitive and emotional aspects of depression may impair decision-making at particularly important points in care, such as when facing dialysis or transplant (4).

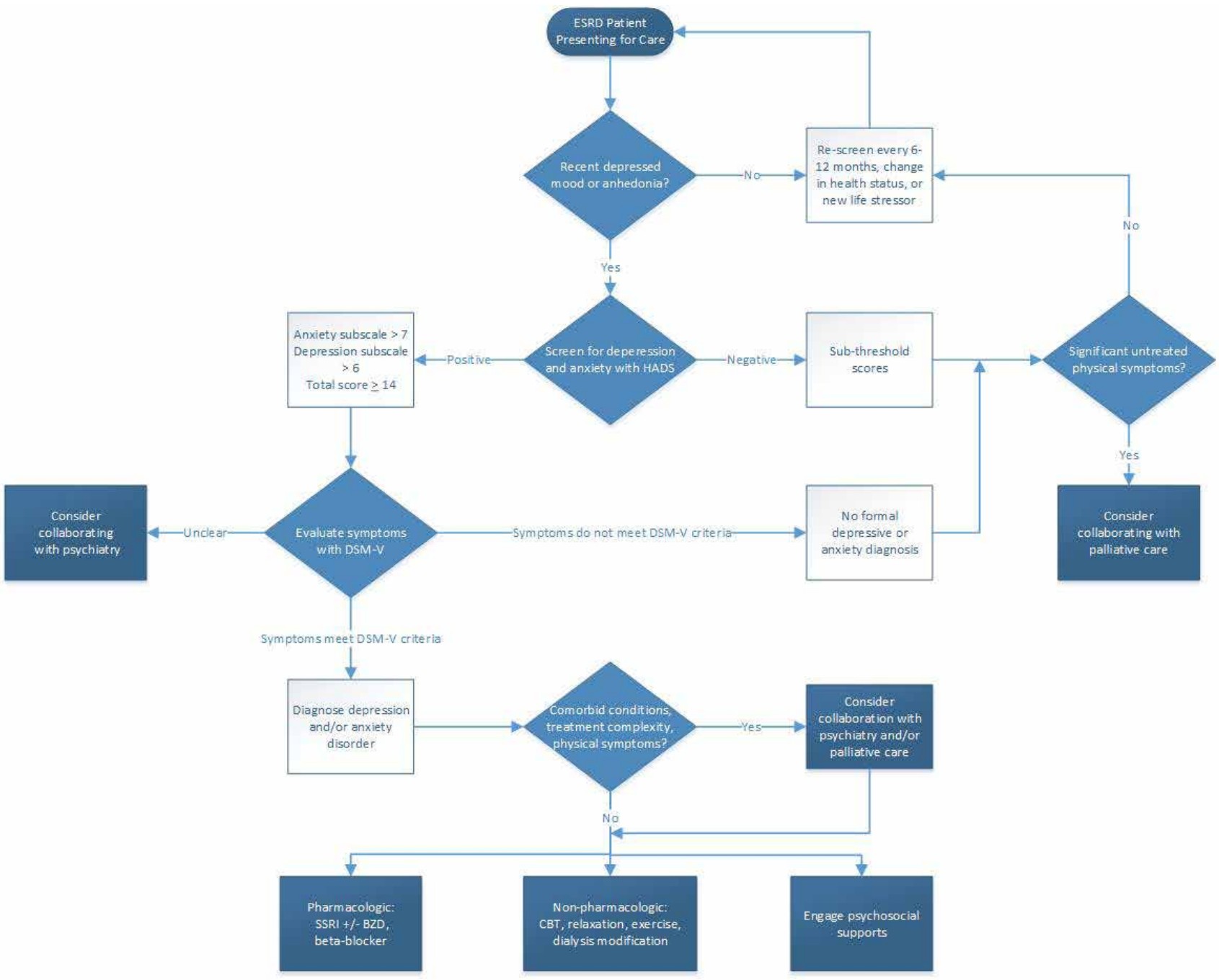
Anxiety disorders are common in ESRD, with rates reported in a range of 12% to 52%. Diagnoses include specific phobia, panic disorder, and generalized anxiety disorder (5). Symptoms vary by treatment modality: conservative care patients may suffer anxiety due to higher physical symptom burden (3), whereas dialysis patients face repeated traumas and a loss of control in the treatment environment. Significant anxiety often manifests as decreased treatment adherence or disruptive behaviors in clinic or dialysis centers, leading to frustration among patients and care teams.

Screening for depression and anxiety

When to screen?

Current guidelines recommend routinely screening ESRD patients at initiation of dialysis, every 6 months for the first year, and then annually (2, 5). Interval events, such as emerging major life stressors, change in health status or treatment plan, disruptive behaviors at dialysis, or a new mental health diagnosis, should prompt rescreening.

Figure 1. Clinical approach to depression and anxiety in ESRD



Abbreviations: BZD = benzodiazepine; CBT = cognitive behavior therapy; DSM-V = Diagnostic and Statistical Manual of Mental Disorders V; HADS = Hospital Anxiety and Depression Scale; SSRI = selective serotonin reuptake inhibitor.

How to screen?

First, we recommend using a two-question approach modified from the Patient Health Questionnaire: 1) In the past 2 weeks, have you been bothered by having little interest or pleasure in doing things? 2) Have you felt down, depressed? A positive response to either question should prompt screening to identify more specific depressive or anxious symptoms. We recommend the Hospital Anxiety and Depression Scale (HADS), which screens for both conditions. The HADS is particularly useful in ESRD, because it minimizes confounding by physical symptoms, has been validated in the ESRD population, and can be completed and reviewed quickly by patients and staff (6, 7). Other options include the Beck Depression Inventory, Patient Health Questionnaire-9, and Generalized Anxiety Disorder-7 (2, 5). Of note, all screening tools show limited sensitivity and specificity, and validation of screening tools has produced mixed results (6–8). A positive screen should prompt formal evaluation for depression or anxiety disorders.

Diagnosing depression and anxiety in ESRD

For consistency and accuracy, we recommend using Diagnostic and Statistical Manual of Mental Disorders V diagnostic criteria. Particularly relevant diagnoses in ESRD are major depressive disorder, panic disorder, specific phobia, and generalized anxiety disorder (8) (Figure 1). Diagnosis may be made by the nephrologist, trained kidney nurse, or social worker. However, accurately diagnosing depression and anxiety may prove challenging given symptom overlap with uremia, including pain, fatigue, sleep disorders, poor appetite, and reduced concentration (2, 4). Although not routinely recommended for diagnostic purposes, psychiatric consultation may be helpful in these more complex patients.

Treatment of anxiety and depression

Despite high prevalence and clinical implications, treatment of depression and anxiety is poorly studied in the ESRD population, in part due to exclusion of medically complex patients from treatment trials (2, 9).

Which medications to consider?

Selective serotonin reuptake inhibitors (SSRIs) are best studied; sertraline may be particularly advantageous, requiring no renal dose adjustments, and it is safe in patients with cardiovascular disease, who share many risk factors with ESRD patients (10). Limited data exist for fluoxetine, citalopram, escitalopram, and paroxetine, as well as for non-SSRI options, including mirtazapine, venlafaxine, and bupropion (2). For episodic anxiety, benzodiazepines and β-blockers may also be useful for short trials with caution for adverse side effects (5). Special considerations include adjusting doses for renal function, timing medications with dialysis, and minimizing drug-drug interactions. Furthermore, recent evidence suggests that hemodialysis patients and kidney care teams are resistant to initiating depression medications (9), emphasizing the importance of exploring beliefs about depression and antidepressant medications.

What nonpharmacologic treatments exist?

Cognitive behavior therapy (CBT), exercise programs, and increased dialysis frequency may decrease depressive symptoms and improve physical and overall function (2, 4). Chairside CBT in ESRD patients was associated with improved depression scores, improved quality of life, and decreased intradialytic weight gain (11). For patients with anxiety disorders, psychodynamic therapy, relaxation and mindfulness exercises, sleep hygiene education, and limiting caffeine and tobacco use are also recommended (5). Relaxation and psychoeducation interventions adapt well to the dialysis setting, which may promote adherence and reduce the need for additional appointments. All interventions may be combined with medications.

Team approach to managing psychologic issues

Members of the kidney care team caring for dialysis patients are well positioned to identify and screen patients at risk for depression and anxiety. We advocate a collaborative approach to explore mental, emotional, and physical symptoms, and to devise a management plan, which may extend beyond the renal setting.

Psychiatry and pharmacy teams can assist with evaluating complex psychiatric symptoms and providing medication advice given the adverse side effect profiles and complexity of drug dosing in dialysis (2). In addition to medications and therapy, psychiatry may help coordinate social work or case management support for both patients and their caregivers, who experience increased stress across the spectrum of ESRD care options (12).

Palliative care teams provide expertise in addressing physical symptoms contributing to mood or anxiety as well as strengthening communication and collaborative decision-making. For patients experiencing depressive symptoms as part of declining overall health, palliative care specialists can work alongside the kidney care team to help facilitate goals of care discussions that may include dialysis withdrawal and transition to hospice (4).

Nicole Bates, MD, is a psychiatry resident at Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center. Jane Schell, MD, MHS, is an assistant professor within the Renal-Electrolyte Division and Section of Palliative Care and Medical Ethics, University of Pittsburgh School of Medicine, University of Pittsburgh Medical Center. Allison Jordan, MD, HMDC, is medical director of palliative care services at Christian and Alton Memorial Hospitals and Associate Medical Director of BJC Hospice in St. Louis, Missouri.

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Acute Kidney Injury in Critical Patients and the Role of Palliative Care

By Yameena Jawed, MD

Offering patients life-prolonging treatments while at the same time improving their quality of life is a balancing act. With time, we learn that more care is not necessarily good care, that not every test or treatment available to the patient is needed, and that, at times, they may cause more harm than good.

A clinician must judge which treatment is quantitatively futile (it simply cannot physiologically work) or inappropriate. The latter is a gray zone and at times takes into consideration the clinicians', patients', and surrogates' personal conceptions about life and treatment goals. One such treatment is dialysis in a critically ill patient with acute kidney injury (AKI). Critically ill patients with AKI have a high mortality; of the 490 patients who required dialysis in the SUPPORT Trial (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments), only 27% survived after 5 months (1). Furthermore, dialysis was not shown to be cost effective in this population. Withholding or withdrawing a potentially inappropriate treatment in a critical patient can be particularly challenging, especially in an intensive care unit (ICU), where intense plans of support may be in place, indicating patients' or their families' unrealistic expectations of survival or quality of life. At times, other health care professionals may be in the same boat. What is then the best way to have these complex conversations with doctors, patients, and their families? Where do we start?

We must first equip ourselves with the knowledge of why and when we need to withdraw or withhold dialysis in a critically ill patient with AKI. Several factors make this clinical scenario more complicated than withholding dialysis in an ESRD patient: most of the patients in the ICU are incapacitated, surrogate decision-makers may not have a clear understanding of the goals of treatment and prognosis, and the reversible nature of the injury may bring up the option of temporary dialysis.

In 2000, the Renal Physicians Association (RPA) and the American Society of Nephrology (ASN) published a clinical practice guideline: "Shared decision-making in the appropriate initiation and withdrawal from dialysis. The Renal Physicians Association and the American Society of Nephrology" (2). Its goal was to provide evidence-based guidelines for clinical decision-making that can be tailored to a specific patient or situation. The nine recommendations include shared decision-making, informed consent or refusal of all available treatment options (including temporary dialysis), estimating prognosis, conflict resolution (between nephrologist and patient or other health care providers), advance directives, withholding or withdrawing dialysis, special patient groups (those with terminal illness due to nonrenal cause), time-limited trials of dialysis (if prognosis is uncertain), and palliative care (for those who forego dialysis). Addressing these nine factors can help physicians and patients reach an informed and ethical shared decision about initiating versus withholding or withdrawing dialysis.

Shared decision-making involves providing clear information about the risks and benefits of each treatment. The Choosing Wisely campaign, an initiative of the American Board of Internal Medicine, is intended to identify situations where the need for certain tests and treatment is questioned by encouraging open communication between physicians and patients (3). As part of this campaign, ASN has published guidelines about shared decision-making for chronic dialysis. There are modules that provide guidance to physicians about efficient patient communication. Per these recommendations, the four key interactional components that lead to better outcomes include "providing clear information; [c]reating mutually agreed upon goals for care; [p]atients taking an active role in their care; and [p]hysicians providing encouragement, empathy and praise" (3). We may apply the same communication strategies to discussions about dialysis for AKI in critical patients. We must be mindful that care in the ICU can often be challenging in terms of communication because oftentimes patients are debilitated and are not able to be fully involved in their care; therefore, we tend to have these conversations with surrogate decision-makers. Problems arise when there is poor communication regarding treatment goals, which should be an ongoing dialogue.

The expected outcome for and prognosis of critically ill patients with AKI should be addressed when making decisions pertaining to dialysis. As outlined in the RPA/ASN guidelines, it is reasonable to withdraw or withhold dialysis in patients facing terminal illness (life expectancy of 6 months or less secondary to nonrenal cause) who are not transplant candidates. These patients may include those with advanced malignancy not amenable to treatment, severe cirrhosis, heart failure, or end stage pulmonary disease. In other situations, criteria for the risk of renal failure, injury to the kidney, failure of kidney function, loss of kidney function, and end stage renal failure may be used to evaluate management and expected outcome (4). A prospective study performed in 2008 found six of the prognostic tools to be inaccurate in predicting hospital mortality or need for renal replacement therapy in ICU patients with AKI (5). Few studies have evaluated the long-term outcomes and quality of life of survivors. When the outcome is uncertain, patients may be offered time-limited trials of dialysis with a goal to withdraw dialysis if it does not provide benefit in the specified time. Objective ways to measure short-term benefit may include electrolytes and BUN.

Physicians who see chronic kidney disease patients in a non-ICU setting should discuss and document patients' wishes about initiating dialysis if they are likely to develop AKI during a hospitalization. In an ICU, patients who have decision-making capacity and refuse dialysis or have advance directives or appointed surrogates who concur should have their choices respected, and dialysis should not be initiated. On the other hand, some patients or their families may insist on dialysis even after it is considered quantitatively or qualitatively futile (e.g., a time-limited trial of dialysis is unsuccessful). This may pose an ethical and legal issue. Informed decision-making is an integral component when considering the legality of withholding or withdrawing dialysis; therefore, all discussions need to be documented. Because this is a shared decision-making process, involving a palliative care team or requesting an ethics committee consultation may be helpful to resolve conflicts between the provider and the patient.

In conclusion, taking care of critically ill patients can be challenging. Open communication with other caregivers, patients, and their families is an essential component of providing care and forms the basis of a strong relationship. Offering comprehensive care in a complex setting requires addressing a patient's prognosis, good clinical judgment about utilization of appropriate treatment options, adequate training of physicians in relevant communication skills, and ongoing collaboration with palliative care teams, as well as with patients and their families.

Yameena Jawed, MD, is a resident in the Department of Internal Medicine at the University of Texas, McGovern School of Medicine, Houston.

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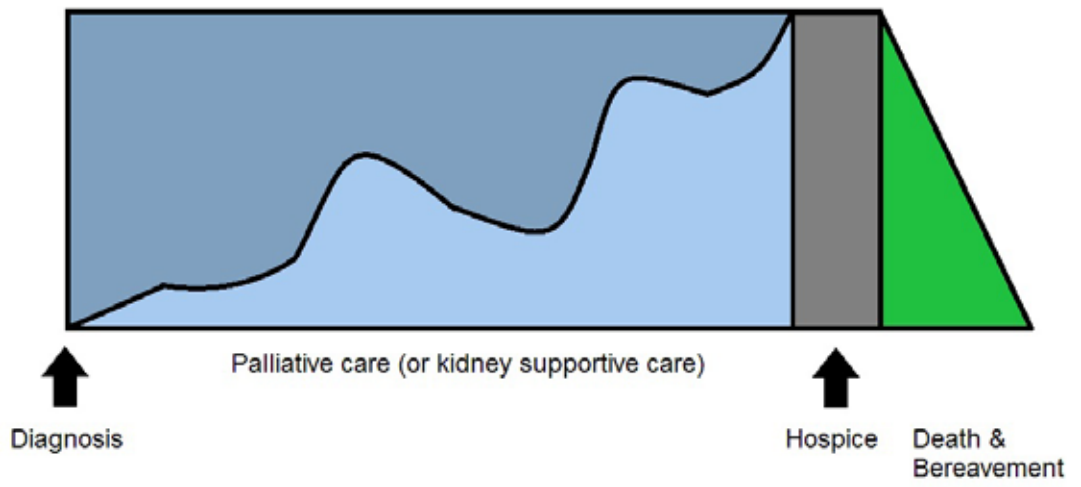
Palliative Care and Nephrology: Moving Upstream Together

By Daniel Lam

Patients with ESRD experience a high degree of symptom burden—physical symptom burden akin to patients with advanced cancer, along with emotional and spiritual suffering. In addition, ESRD patients on maintenance dialysis have the highest levels of medicalization at the end of life, surpassing what is experienced by their counterparts with other advanced chronic illnesses (1). Although high-intensity health care at the end of life may be goal concordant for a minority of patients, it is not on a population level. A large Veterans Affairs study evaluated family-reported quality of end-of-life care among 57,753 decedents and noted that quality of end-of-life care was significantly better for patients with cancer and dementia than for patients with ESRD, cardiopulmonary failure, or frailty (2). This quality advantage was mediated by palliative care consultation among other variables and is evidence for what many clinicians already know: there is a need to better integrate palliative care principles in ESRD care.

Palliative care is specialized interprofessional care for anyone with serious illness focused on relieving the symptoms and stress of that illness. The goal is to improve quality of life not only for the patient, but also for their friends and family. Within the field of nephrology, provision of palliative care for patients with advanced kidney disease is also known as kidney supportive care. The care is interprofessional precisely because patients suffer in multiple domains, including decision support for renal replacement therapy and assessment and treatment for emotional, physical, or spiritual and existential needs. This means that palliative care can and should be provided in conjunction with life-prolonging measures (Figure 1).

Figure 1. Disease-directed therapies (CKD management, treatment for primary renal disease, dialysis, transplantation)



Much of the literature on kidney supportive care focuses on conservative (nondialytic) management of ESRD. However, there are existing models in the United Kingdom and Australia of kidney supportive care programs that also provide concurrent palliative care for maintenance dialysis patients. For instance, Brown et al. (3) in Australia have established a Renal Supportive Care Clinic that sees not only patients on a nondialytic maximal conservative management pathway but also patients on maintenance dialysis in order to assist with advance care planning (ACP), goals of care, and complex symptom management (4). Clinician education programs have also been developed to better equip interprofessional staff to address these issues.

Murtagh and coworkers (5) in the United Kingdom developed the Renal Specific Advanced Communication Training program to improve communication skills for hemodialysis nurses and nephrologists. Currently, a multicenter study at Baystate Medical Center and the University of New Mexico is implementing a multimodal shared decision-making intervention for dialysis social workers and nephrologists who work with high-risk patients (6). The intervention will use the surprise question (Would I be surprised if this person died in 6 months?), which has been shown to be predictive of survival, to screen for the highest-risk patients. Dialysis social workers will be the primary facilitators of this intervention for improved end-of-life communication.

In reimagining how we can continue to improve the experience of dialysis patients and their friends, families, and caregivers, we can also learn from the oncology experience. In 2017, the American Society of Clinical Oncology published evidence-based recommendations regarding the integration of palliative care into standard oncology care. On the basis of the existing evidence, a recommendation was made that patients with advanced cancer should receive dedicated palliative care services early in the disease course concurrent with active treatment (7). One of the landmark trials of early palliative care supporting this guideline occurred in a population of patients with metastatic non–small cell lung cancer. Patients randomized to the early palliative care group had not only significant improvements in anxiety and depression but also a 2.7-month survival benefit—akin to the benefit of adjunctive chemotherapeutic agents in this population (8). The study used a palliative care intervention embedded within the oncology clinic—a model of care that could be adapted to the ESRD space.

In addition, ESRD Seamless Care Organization programs established through the Comprehensive ESRD Care Model present a unique opportunity to re-envision care delivery for dialysis patients, including better integration of palliative care. Innovative interventions have included nephrologist and dialysis social worker training to improve advance care planning (ACP) and end-of-life communication among staff, patients, and families. At Northwest Kidney Centers in Seattle, Washington, a novel Mobile Renal Supportive Care Team is being created to provide specialty-level palliative care in the dialysis facility and the home. Ultimately, the most successful strategies will leverage education to elevate interprofessional ability to provide primary palliative care—the palliative skills that every clinician should have—as well as improve access to specialty-level palliative care.

Because all ESRD patients have a serious illness and could stand to benefit from palliative care, how might we think of this heterogeneous group of patients? One could group patients in the following way: the older stable patient on dialysis, the patient with severe symptoms despite optimized dialysis, the patient considering dialysis withdrawal, and the patient with a poor prognosis. The strategy to meet their needs will be necessarily different: normalizing ACP and establishing long-term goals of care for future care planning in the first patient, ameliorating symptoms in the second patient, uncovering and addressing potential unmet palliative needs that may be driving a request for dialysis withdrawal and guiding through the process of withdrawal if goal concordant in the third patient, and expediting ACP in anticipation of approaching future decline in the fourth patient.

In summary, there are existing and emerging models of integrating palliative care principles into existing care delivery to meet the needs of the dialysis population. These include normalizing ACP earlier in the trajectory of disease and leveraging interprofessional training to improve meaningful ACP as well as formalized kidney supportive care teams to provide specialty-level palliative care for patients with the highest needs. In lieu of dedicated kidney supportive care staff, nephrologists can partner with local outpatient palliative care providers to address the needs of the patients they serve.

Daniel Lam, MD, is Clinical Assistant Professor of Medicine, University of Washington Department of Medicine, Division of Nephrology, and Palliative Care Medical Advisor at Northwest Kidney Centers, Harborview Medical Center, in Seattle, WA

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The Importance of Prognostication in the Patient-Centered Care of Chronic Kidney Disease and ESRD Patients

By Alvin H. Moss, MD

A foremost goal of American medicine for the 21st century to improve the quality of health care is individualized, patient-centered care. The recommended means to achieve this care is shared decision-making, a conversation process in which the physician communicates information to the patient about diagnosis, prognosis, and treatment options and the patient communicates to the physician about his or her history, values, and treatment preferences. Together, the two share responsibility in reaching a common understanding of the patient's preferred treatment course. This process has been called "the pinnacle of patient-centered care" (1).

Patient-specific estimate of prognosis

For patients to be able to participate in shared decision-making and express their preferences, they need to know their overall condition, their treatment options, and their prognosis. The clinical practice guideline *Shared Decision-Making in the Appropriate Initiation of and Withdrawal from Dialysis, 2nd Ed.*, recommends that each patient be given a patient-specific estimate of prognosis as part of the informed consent process for shared decision-making (2). This guideline recognizes that neither a clinician nor a prognostic score can predict with absolute certainty how well a particular patient will do with or without dialysis. However, evidence-based factors have been determined to be valuable in predicting prognosis in chronic kidney disease (CKD) and ESRD patients. Validated prognostic scores for ESRD patients have been constructed on the basis of the evidence to improve the accuracy of predictions of prognosis and to facilitate a patient-centered approach (3, 4).

Physician ethical obligation to disclose prognosis

Physicians have an ethical obligation to disclose prognosis to assist their patients in decision-making (5), and patients want to know their prognosis (6). Prediction of prognosis assists the nephrologist in recommending dialysis to patients with a good prognosis who are likely to benefit from it, and a conservative, nondialytic pathway to patients with a poor prognosis, for whom dialysis is unlikely to be a benefit. Physicians may be hesitant to conjecture a diagnosis because of considerable clinical uncertainty, but in such situations, patients may want to incorporate their extramedical values into the decision-making, and they appreciate physician candor about uncertainty.

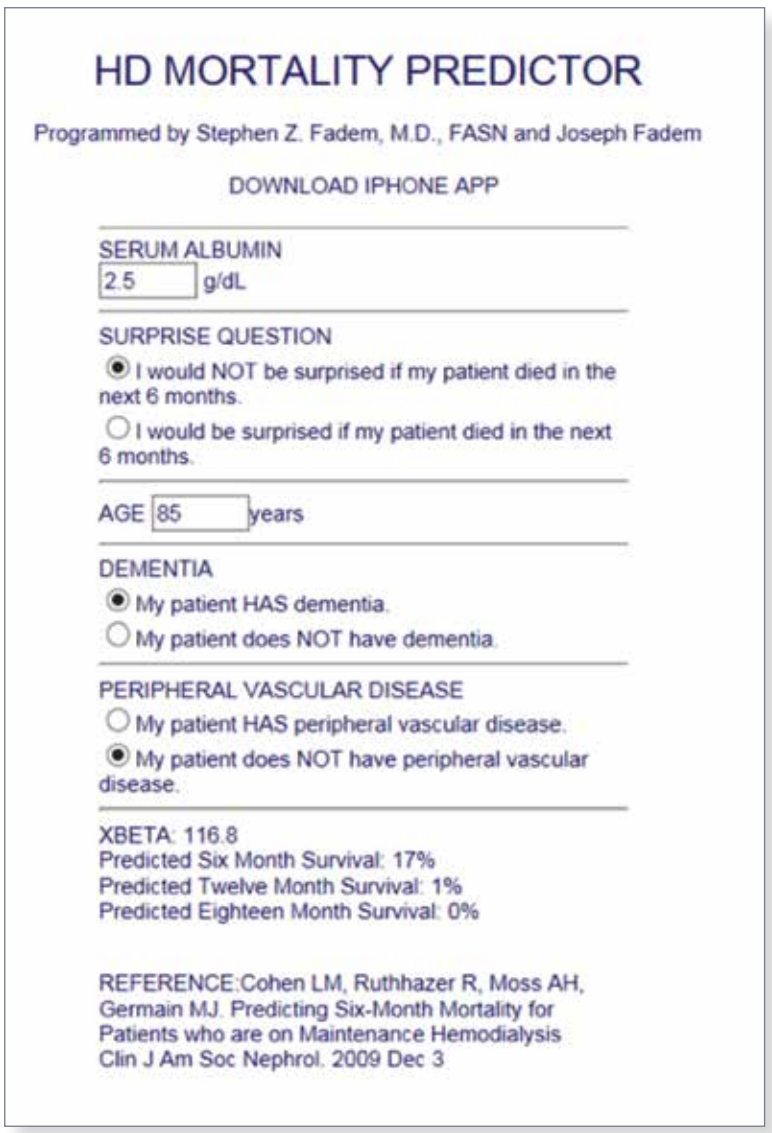
In one study of 62 dialysis patients, no patient reported a discussion of prognosis with his or her nephrologist, and patient and physician estimates of prognosis were profoundly discordant (κ=0.08). In this study, 60% of nephrologists said they would not disclose prognosis, even if their patients requested it. This is of concern from a patient-centered care perspective, because more than half of patients indicated a preference for comfort-focused care if they knew they were seriously ill (7). The authors concluded that interventions are needed to help nephrologists more effectively communicate with their dialysis patients about prognosis.

The advancing science of prognostication

The science of prognostication for patients with CKD and ESRD is advancing. There are several validated prognostic tools to predict 6-month to 1-year survival with an accuracy *C* statistic of 0.75 to 0.80 (4). One is an integrated prognostic tool that combines a subjective response to the surprise question—would you be surprised if this patient died in the next 6 months?—with objective variables to obtain 6- and 12-month predictions of survival with a *C* statistic of 0.80 (Figure 1) (3).

The systematic literature review for the clinical practice guideline on shared decision-making identified four statistically significant independent predictors of poor prognosis in dialysis patients: age, comorbidities, impaired nutrition, and impaired functional status (2). Since then, other factors, such as frailty, cognitive impairment, self-reported appetite, and independence in the ability to transfer, have been identified as potentially helpful variables that might improve the accuracy of prognostic scores if integrated into them (4).

Figure 1. Online integrated prognostic model calculator (http://touchcalc.com/calculators/sq).



Abbreviation: HD = hemodialysis.

The future of prognostication in the care of kidney patients

Validated prognostic scores with a high degree of accuracy can help calibrate nephrologists' estimate of prognosis. They are not meant to replace the shared decision-making process. The decision about dialysis is to be on the basis of the medical indications for it—the balance of benefits to burdens—and the patient's preferences. Estimates of prognosis can help in the assessment of the likely benefits versus burdens calculus. In the future, as dialysis decisions become more patient-centered, other outcomes important to patients beyond survival, such as predicted quality of life with or without dialysis, need to be incorporated into prognostic scores. Patients are being included in those framing the research agenda for the treatment of CKD and ESRD (8). There is reason to be optimistic that the future of treatment of patients with kidney disease will be more patient-centered and that patients will report more satisfaction with their experience of care.

Alvin H. Moss, MD, is a professor with the Center for Health Ethics & Law in the Department of Medicine, West Virginia University in Morgantown, WV.

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Difficult Communication in Nephrology

By Tamara Rubenzik, MD, and Holly Yang, MD

Effective communication is necessary when providing medical care but can prove challenging when attempting to match patients' values to therapies. Nephrologists often participate in difficult conversations with patients and their families, most commonly involving dialysis in patients with chronic kidney disease (CKD) and ESRD. Despite this, most nephrologists and nephrology fellows do not feel prepared for these difficult conversations (1–3).

In recent years, there has been an increasing focus on goals of care and utilization of a palliative approach in advanced CKD and dialysis care. The aim is to address the symptoms, pain, and stress of advanced kidney disease to improve quality of life. To accomplish these goals, nephrology care providers need to discuss prognosis and goals of care with their patients. There are few specific resources available to help guide nephrologists in these difficult conversations. These include journal articles, a 4-hour communication skills workshop geared toward nephrology fellows (Nephrotalk), and the Renal Physicians Association Clinical Practice Guidelines on Shared Decision-Making in Dialysis & Toolkit (1–5).

Trainees and practicing nephrologists should increase their efforts to use the resources available to help them tackle these discussions with their patients. Although the tendency might be to avoid these conversations due to discomfort or fear of upsetting patients, it has been shown that the majority of patients find it important to be informed about their medical condition, including prognosis (6). As a result, building skills in having difficult discussions will not only improve physician comfort and create more effective communication for future interactions but also meet important patient needs. The techniques taught in the 4-hour workshop provide basic skills for these discussions, including assessing understanding, giving information, responding to emotion, and matching patient values to treatment options. When it comes to giving bad news or assessing goals of care, the physician should start with open-ended questions, use a communication framework, and use the individual skills where appropriate (2).

Late-stage CKD: discussing whether to start dialysis

"Doctor, I know my kidneys aren't working well, but are you sure dialysis is my only option?" One of the most common scenarios that the nephrologist will encounter is whether to start dialysis in an elderly or debilitated patient. Presenting dialysis as a choice rather than the definitive next step in medical care should be discussed with all patients who have advanced CKD, but it is arguably most relevant in elderly patients and those with high levels of comorbidity. Data suggest that, although dialysis can prolong life in individuals older than 75, much of this time is spent either on dialysis or hospitalized, leading to a poor quality of life (7). In patients with high comorbidity scores and especially, ischemic heart disease, the survival advantage with dialysis might disappear (8). This prognostic information needs to be presented to patients to help guide decision-making regarding dialysis, but it is rarely discussed (3).

In addition to physician discomfort, insufficient time is likely contributing to this lack of communication between patients and their nephrologists. When a patient has progressive CKD, he or she is usually referred to classes to learn about kidney disease and dialysis when the nephrologist does not have sufficient time to accomplish this in the clinic. Unfortunately, these classes do not adequately address the option of conservative care for ESRD. Instead, they focus on hemodialysis, peritoneal dialysis, and renal transplant as the three options for patients with worsening kidney disease (9). Thus, if the physician does not mention conservative management, which can include palliative care or hospice care, then the patient may never know that it is an option. Many nephrologists might assume that dialysis education classes discuss the options of conservative management and do not realize the missed opportunity.

Nephrologists should discuss prognosis and conservative management, especially with those over 75 years old or with high comorbidity, during their clinic visit. Although lack of time might seem too great a barrier, both experience and use of various tools (Table 1) can lead to more succinct discussions. In addition, nephrologists should remember that they may be able to use time-based advance care planning codes (99497 and 99498) to be reimbursed for these discussions.

ESRD: Stopping dialysis, including what to expect afterward

"Doctor, my mother is so tired. She only gets out of the house to go to dialysis. I am not sure she wants to continue doing all this." The majority of dialysis patients are unaware of their prognosis, have not completed an advance directive, and have not discussed goals of care with their nephrologists (3). Given their high mortality rates, however, every patient on dialysis would benefit from a discussion regarding goals of care and should complete an advance directive with guidance from the medical team.

The impediments to having discussions about stopping dialysis are similar to those encountered when discussing dialysis initiation. In addition, physician uncertainty regarding both prognosis and life after dialysis cessation may also limit communication regarding stopping dialysis. Patients on dialysis with a poor 6-month survival can be identified with an online prognostic model (10). Alternatively, simply using the surprise question ("Would I be surprised if this patient died within the next year?") can identify patients at risk for higher mortality who would benefit from advance care planning (11). Discussing what life looks like after dialysis, including possible symptoms and their palliative management, likely prognosis, and access to supportive services, including hospice, may be challenging for nephrologists if they have not been trained in end-of-life management for renal patients.

Conclusion

Physician discomfort, insufficient time, lack of training, and medical uncertainty are roadblocks to effective communication with patients and can prevent difficult discussions from taking place. These obstacles may be lessened with education and curricular emphasis during nephrology fellowship programs in addition to meaningful continuing education for practicing nephrologists. Nephrologists should be empowered to discuss prognosis along with goals of care in patients with advanced CKD and ESRD. With skills acquisition and practice as well as utilization of the tools available to guide discussions and determine prognosis, nephrologists can help their patients improve their quality of life.

Tamara Rubenzik, MD, is affiliated with the University of California, San Diego, and with Scripps Health; Holly Yang, MD, is also affiliated with Scripps Health in San Diego.

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Table 1. Tips for discussing prognosis and goals of care in the clinic

- Discuss GOCs with all high-risk patients instead of select patients with challenging cases
- Have conversations about GOCs and prognosis over multiple visits
- Use the EMR to create a GOC template to guide the discussion using specific questions
- Use interactive software to document wishes regarding spiritual beliefs, medical care, and finances
- Have patients watch advance care planning videos to provide framework for further discussions

Abbreviations: EMR = electronic medical record; GOC = goal of care.

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Industry Spotlight

ARA Results and Plans

American Renal Associates Holdings (ARA) (Beverly, MA) launched an initial public offering in April 2016, and has now grown to 217 clinics serving more than 15,000 patients with 385 nephrologists.

Second quarter 2017 net patient service operating revenues increased 0.2% to $186.0 million, compared with $185.6 million for the prior year period.

ARA stated that 32 new clinics had signed with the company in the first half of 2017 and noted the large dialysis market presents a growing joint venture opportunity in the nephrology community. To date 4% of US nephrologists have joined with ARA. The company also noted that it has a "predictable de novo clinical growth model."

The company configures its partnerships such that a nephrologist owns a noncontrolling interest in an ARA clinic. Average ownership" is 53% by ARA and 47% by physician partners. The nephrologist's role in the clinic is oversight of clinic and staff, patient assessment, and patient care and treatment. ARA provides the backoffice support of the clinic's operations.

With 10,000 practicing nephrologists in the United States, and a dialysis market that historically grows at 3% to 5% per year, "we believe a significant portion (of nephrologists) treat patients at clinics in which they have no ownership interest" which demonstrates opportunity to grow as a joint venture model operator within the nephrology community, the company noted in a highlights slideshow.

Fresenius to Acquire Home-Dialysis Firm

Fresenius Medical Care (FMC), the world's largest provider of dialysis products and services, will buy NxStage, a home dialysis device maker, for $2 billion. Fresenius Medical Care North America and NxStage both have corporate headquarters in the Boston area, while FMC parent company is based in Bad Homburg, Germany.

The NxStage System One is cleared by the FDA for home hemodialysis and home nocturnal hemodialysis. NxStage has also established a small number of dialysis clinics.

The NxStage transaction is the latest in "a wave of deals across the medical-device industry in which companies increasingly look to bolster product suites and gain more leverage to resist pricing pressure from hospitals," Modern Healthcare wrote of the acquisition.

The deal give NxStage access to the resources of a larger company, and lets FMC further leverage its manufacturing, supply chain, and marketing competencies across the dialysis products, services, and care coordination businesses in a less labor- and capital-intensive care setting.

Practice Pointers

ANCA Disease: What's in a Name?

By J. Charles Jennette, MD, and Ronald J. Falk, MD

In Shakespeare's *Romeo and Juliet*, Juliet ponders, "What's in a name? That which we call a rose by any other name would smell as sweet." She seems to discount the importance of names; however, the play illustrates how names are very important with respect to how something is perceived and treated. The entire tragedy that befalls Romeo and Juliet was precipitated by preconceptions resulting from their names.

Should disease that is closely associated with, and likely caused by, antineutrophil cytoplasmic autoantibodies (ANCAs) be named (diagnosed as) ANCA disease (similar to antiglomerular basement membrane [anti-GBM] disease), ANCA vasculitis (similar to IgA vasculitis), or antineutrophil cytoplasmic autoantibody-associated vasculitis (AAV) as recommended by the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides (CHCC 2012) (1)?

Syndromic names on the basis of different clinicopathologic manifestations of ANCA disease also were defined by the CHCC 2012 (i.e., microscopic polyangiitis [MPA], granulomatosis with polyangiitis [GPA], and eosinophilic granulomatosis with polyangiitis [EGPA]) (1). The CHCC 2012 proposed that both the serotype and the clinicopathologic phenotype should be included in a diagnosis (for example, meyeloperoxidase-antineutrophil Cytoplasmic Antibodies (MPO)-ANCA GPA, PR3-ANCA GPA, ANCA-negative MPA, etc.) (1). However, some have advocated that the serotype alone is sufficient for a diagnosis and provides more guidance for management than the clinicopathologic phenotype (2, 3) and that the serology correlates better than the phenotype with genetic factors that relate to pathogenesis (4). Even in the short time since the publication of the CHCC 2012, further elucidation of the pathogenesis and genetic basis for ANCA disease has reduced the need for the precautionary adjective "associated." In fact, in some clinical settings in the United States, the term ANCA disease is being used more often than AAV. This also avoids confusing AAV in the vasculitis context with the standard use of AAV as an abbreviation for adeno-associated virus vectors used in genetic therapy. No matter what name is used for the clinical phenotype, inclusion of the serotype in the diagnosis is important (e.g., MPO-ANCA GPA, PR3-ANCA MPA, ANCA-negative EGPA).

Table 1 shows some of the differences between MPO-ANCA disease and PR3-ANCA disease. From a clinical perspective, the most important difference is the higher frequency of relapses that occurs in PR3-ANCA disease after induction of remission (2, 3). The greatest difference in symptoms is the higher frequency of ear, nose, and throat manifestations in patients with PR3-ANCA disease, although ear, nose, and throat involvement occurs in all phenotypes and serotypes of ANCA disease (2). Figure 1 shows the relationship between the clinicopathologic phenotypes of ANCA disease with MPO-ANCA and PR3-ANCA in the context of patients with crescentic GN (CGN). Renal-limited ANCA disease is included with MPA in this diagram. In addition to ANCA disease, patients with CGN may have anti-GBM disease or immune complex disease as the cause for CGN. The size of the different immunopathologic categories represents the relative frequency of these categories among patients with CGN in the southeastern United States. In this geographic location, MPO-ANCA CGN is more common that PR3-ANCA CGN (2), and anti-GBM CGN is less common than ANCA CGN or immune complex CGN. The overlaps of the immunopathologic domains indicate the concurrence of more than one immunopathologic category in the same patient. For example, approximately 25% to 30% of patients with anti-GBM CGN are ANCA positive, usually for MPO-ANCA. Note that a small proportion of patients with ANCA disease have both MPO-ANCA and PR3-ANCA, which occurs most often in drug-induced ANCA disease (e.g., secondary to hydralazine, propylthiouracil, levamisole in cocaine, etc.) (5). The colored domains represent the distribution of ANCA disease clinicopathologic phenotypes relative to the ANCA specificity in the southeastern United States. It is important to recognize that these relationships differ in different geographic locations. In the United States and Europe, MPO-ANCA disease and MPA are more frequent in the south, and PR3-ANCA disease and GPA are more frequent in the north (6). In Asia, MPO-ANCA disease is much more frequent than PR3-ANCA disease, even in patients with GPA (6).

Given that both the ANCA serotype and the clinicopathologic phenotype provide useful information about what is happening and what will happen in patients, when possible, designations for both should be included in a diagnosis (e.g., MPO-ANCA GPA).

What is the differential diagnosis for ANCA disease?

The diagnosis of ANCA disease requires distinguishing it from other forms of GN and small vessel vasculitis (SVV) that can cause signs and symptoms that are indistinguishable from those of ANCA disease (7). For example, a patient with GN and purpura (Figure 2) may have MPA, GPA, IgA vasculitis (formerly Henoch–Schönlein purpura), cryoglobulinemic vasculitis, or other forms of SVV that can cause purpuric leukocytoclastic angiitis in the skin. Even nonvasculitis diseases, such as hemolytic uremic syndrome and atheromatous cholesterol embolism, can mimic SVV with acute kidney injury, hematuria, proteinuria, and cutaneous lesions resulting from vascular occlusion. Table 2 provides a comparison of likely signs, symptoms, and laboratory observations that can help differentiate among diseases that are in the differential diagnosis for ANCA disease.

Does ANCA cause disease?

There is strong clinical, in vitro, and in vivo animal model evidence that MPO-ANCA causes disease (8). There is similar clinical and in vitro evidence that PR3-ANCA causes disease, although no convincing animal model of PR3-ANCA–induced disease has been developed. The lack of an experimental animal model may relate to the difference in the biology of PR3 in animals compared with humans. If PR3-ANCAs are pathogenic, genetic studies suggest that the pathogenic mechanism may involve different mediator pathways compared with those in MPO-ANCA–induced disease (4).

A mouse model of ANCA disease that is produced by injecting anti-MPO antibodies intravenously in mice supports a pathogenic mechanism that initially involves ANCA-induced activation of primed neutrophils by Fc receptor engagement by ANCA bound to ANCA antigens followed by activation of the alternative complement pathway by factors released from activated neutrophils. C5a engagement of C5a receptors on neutrophils generates an inflammatory amplification loop that attracts and activates more neutrophils and monocytes (8). This process takes place at thousands of sites in numerous small vessels, usually in multiple organs. Each acute lesion evolves in 1 or 2 weeks into a chronic lesion with monocytes, macrophages, and lymphocytes replacing neutrophils followed by scarring. Until remission is induced, additional acute lesions continue to form and accrue to the overall tissue injury. Thus, the outcome depends on how quickly and effectively initiation of new acute lesions can be prevented.

How should ANCA disease be treated?

If ANCA disease is caused by ANCA and if the injury is mediated by acute inflammation, therapies that eliminate circulating ANCA and quell acute inflammation are called for. Historically, ANCA disease was treated with a variety of regimens of high-dose corticosteroids and cytotoxic immunosuppressive treatments (9). The downside to this treatment includes multiple adverse events, especially increased risk for morbidity and mortality from infections (10). Facilitated by the discovery of ANCA, which helped identify and classify patients for clinical trials and suggested more targeted therapeutic approaches, there have been steady improvements in induction and maintenance of remission, prevention, and treatment of relapse and reduction of adverse events in patients with ANCA disease (9).

In patients who are dialysis dependent or have severe renal insufficiency or pulmonary hemorrhage, remission can be induced by a regimen of methylprednisolone, cyclophosphamide (oral or intravenous), and plasmapheresis along with a course of prednisone. If a patient has less severe renal diseases and no pulmonary hemorrhage, a regimen of methylprednisolone, cyclophosphamide, and prednisone without plasmapheresis is appropriate. Rituximab (a mAb that targets B cells) has been shown to be noninferior to cyclophosphamide for induction of remission (11, 12) and thus, is an option if this is practicable.

Remission can be maintained using low-dose glucocorticoids plus additional therapy with azathioprine, rituximab, or mycophenolate mofetil. Rituximab may be more effective than azathioprine for preventing relapse (13). Continued use of cyclophosphamide after induction of remission increases risk for adverse events (10). PR3-ANCA patients are more likely to have refractory disease than MPO-ANCA patients, and they may require a longer or modified induction regimen (e.g., switching from cyclophosphamide to rituximab or adding plasmapheresis) (14). After 12 to 18 months in remission, maintenance immunosuppression should be discontinued, although the patients should have sufficient follow-up to detect disease recurrence. If a patient is dialysis dependent for more than 4 months or toxicity risks are too high, immunosuppression should be terminated.

Clinical trials continue to identify more effective and less toxic regimens with existing therapies as well as with novel therapies that have been identified through basic and translational studies of ANCA disease (9). For example, avacopan (also known as CCX168), which is an orally administered small molecule that inhibits the engagement of C5a with the C5aR on neutrophils, was shown to prevent the induction of GN by anti-MPO antibodies in mice (15). On the basis of this observation, a recent randomized, placebo-controlled trial evaluated the efficacy of avacopan in treating human ANCA disease. Avacopan effectively replaced high-dose glucocorticoids for induction of remission in ANCA disease patients, with a lower incidence of glucocorticoid adverse effects (16).

As our knowledge of ANCA disease continues to grow, there will be further improvements in the diagnosis, monitoring, and treatment of patients with ANCA disease, no matter what name we choose for the disease.

J. Charles Jennette, MD, is the Kenneth M. Brinkhous Distinguished Professor and Chair of Pathology and Laboratory Medicine and executive director of the University of North Carolina nephropathology division at the University of North Carolina at Chapel Hill. Ronald J. Falk, MD, is the Nan and Hugh Cullman Eminent Professor and Chair of Medicine and director of the University of North Carolina Kidney Center at the University of North Carolina at Chapel Hill.

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Figure 1. The circles in black represent the relative proportions of patients with crescentic GN caused by antineutrophil cytoplasmic autoantibody (ANCA) disease, antiglomerular basement membrane disease, or immune complex disease in the southeastern United States. Note that the overlaps indicate concurrence of more than one cause. The colored ovals indicate how often patients with different phenotypes of ANCA disease have evidence for one or more of the immunopathologic categories.

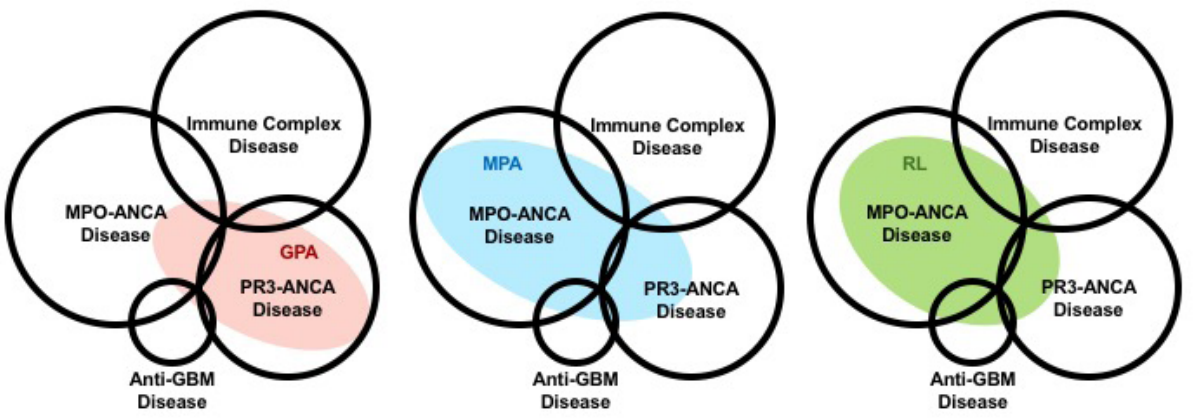

Figure 2. Lower extremity purpura indicating some form of small vessel vasculitis.

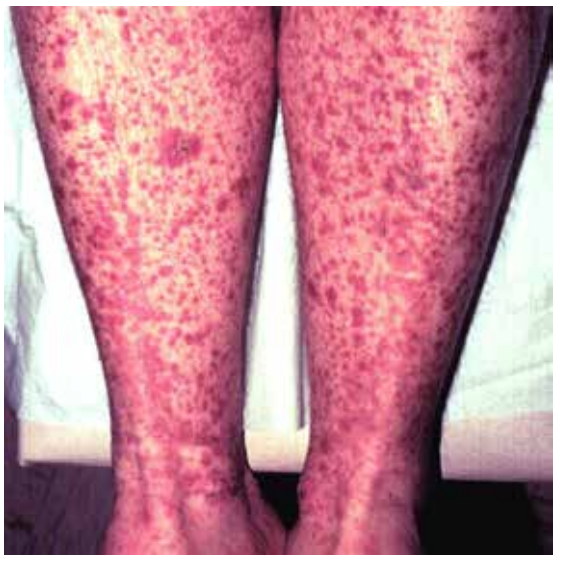

Table 1. Differences in ANCA disease with renal involvement in patients with PR3-ANCA versus MPO-ANCA

	PR3-ANCA	MPO-ANCA
Renal limited	Much less	Much more
MPA	Less	More
GPA	More	Less
EGPA	Much less	Much more
Lung disease	More	Less
ENT disease	Much more	Much less
Remission	Harder	Easier
Relapse	More	Less

Table 2. Useful parameters for resolving the differential diagnosis for patients with clinical features suggesting systemic small vessel vasculitis

Glomerular Cause of Acute Kidney Injury	Hematuria & Proteinuria	Purpura	Pulmonary Hemorrhage	ENT Disease	Neuropathy	Reduced Complement
ANCA disease	+++	+++	+++	++	++	+
Anti-GBM disease	+++	o	+++	o	o	o
Cryoglobulinemic Vasculitis	+++	+++	+	o	++	+++
IgA Vasculitis	+++	+++	o	o	o	o
Hypocomplementemic Urticarial Vasculitis	+++	+	o	o	o	+++
HUS Thrombotic Microangiopathy	++	+	o	o	o	+
Cholesterol crystal embolism	+	o	o	o	o	+

+++, >50% of patients; ++, 25%–50% of patients; +, <25% of patients; o, rare or absent

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Mineral and Bone Disorders in CKD – New KDIGO Update

What's the latest evidence affecting clinical management of mineral and bone disorder in chronic kidney disease? Updated recommendations by the Kidney Disease: Improving Global Outcomes (KDIGO) Global Network are now available.

The 2017 KDIGO Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) guideline update has implications for diagnosis, evaluation, prevention, and treatment of secondary CKD-MBD in children and adults. The full guideline has been published as a supplement to *Kidney International;* an Executive Summary appears in the July issue of *Kidney International*.

Updating the previous guideline published in 2009, the revision reflects new research related to management of CKD-MBD. In a key change, it recommends against routine use of calcitriol or vitamin D analogs for treatment of abnormal parathyroid hormone (PTH) levels.

That change reflects a continued lack of data on the optimal PTH level for patients with CKD G3a to G5. Meanwhile, the 2017 Update Working Group believes that modest rises in PTH may be an "appropriate adaptive response" to decreased kidney function.

"Randomized controlled trials have not really shown a benefit and perhaps harm because of hypercalcemia," said Michael J. Germain, MD, Professor of Medicine, Tufts University School of Medicine and Nephrologist/Partner, Western New England Renal & Transplant Associates, PC, Springfield, Mass. Calcitriol and vitamin D analogs "do a good job in terms of suppressing PTH, but they haven't shown a benefit in terms of other outcomes, [including] cardiovascular outcomes."

The update suggests that calcitriol and vitamin D analogs "not be routinely used" in adults with CKD G3a-G5 not on dialysis. Although there was no "uniform consensus" regarding this recommendation, it reflects a lack of data showing benefits of these older drugs on patient-level outcomes.

The revised guideline mentions a potential new alternative for secondary hyperparathyroidism. Extended-release (ER) calcifediol (Rayaldee) was recently approved for use in adults with stage 3 or 4 CKD and serum total 25-hydroxyvitamin D less than 30 ng/mL. Approval was based on trials showing that ER calcifediol reduced intact PTH while increasing 25D. Effects on calcium and phosphorus were similar to placebo.

"This is a medication that can be used in predialysis patients," said Dr. Germain. "It has the advantage, as opposed to the activated vitamin Ds, of doing a good job in replacing nutritional 25D in the body and normalizing the blood level. By its mechanism of action, it does prevent catabolic pathways from breaking down vitamin D." The data on ER calcifediol were published after the KDIGO evidence review, and do not include patient-level outcomes.

Extended-release calcifediol is not indicated for dialysis patients. OPKO, manufacturer of Rayaldee, states that it "plans to start a Phase 2 trial in dialysis in partnership with Vifor by the end of the year."

Dr. Germain notes that calcimimetics are "a reasonably good treatment" for the more severe hyperparathyroidism seen in dialysis patients. He points out that the intravenous calcimimetic etelcalcetide (Parsabiv) was approved for use in dialysis patients earlier this year.

An updated recommendation states that it's "reasonable" to reserve calcitriol and vitamin D analogs for patients with CKD G4-G5 with severe progressive hyperparathyroidism. In children, these drugs "may be considered" to maintain serum calcium in the normal range for age.

Other revised recommendations address:

CKD-MBD Diagnosis. Recent studies have added evidence that measuring bone mineral density (BMD) predicts fractures in patients with CKD, as in the general population. On that basis, BMD assessment is suggested to assess fracture risk in CKD G3a-G5D, if the results will affect treatment decisions.

Bone biopsy is considered "reasonable" if information on the type of renal osteodystrophy will affect treatment. Dr. Germain cites that recommendation as an example of how guidelines based on literature reviews may provide limited guidance for nephrologists in practice. "The problem is that very few people can get biopsies" due to the lack of specialized pathology personnel and equipment. "If [KDIGO] are going to recommend [bone biopsy], they really have to acknowledge the fact that it's impossible to get for probably 95% to 99% of nephrologists."

Serum phosphate and calcium. Recent studies have linked higher serum phosphate levels to increased mortality, but there's still a lack of evidence that phosphate-lowering therapy improves patient outcomes. The revised guideline removes a previous recommendation to maintain phosphate in normal range, instead focusing on treatment for hyperphosphatemia. It also discusses new data on calcium-containing versus calcium-free phosphate binders.

Antiresorptive and other osteoporosis therapies. Recommendations for antiresorptive and other osteoporosis treatments were broadened from CKD G3a-G3b to G3a-G5d. Treatment choices should consider specific side effects and the accuracy of the underlying diagnosis.

Kidney transplant bone disease. The update addresses the use of BMD testing to assess fracture risk. Evidence supports treatment suggestions for the first 12 months, but not thereafter.

The KDIGO Working Group notes that its updated guideline still reflects a "dearth of high-quality evidence…in several areas pertaining to CKD-MBD."

Research priorities "need to be very focused on the patient's experience," Dr. Germain believes. "I would concentrate more on bone health and what the patient experiences, so they feel better." He thinks that nephrologists treating MBD need to "know a little bit more about what the patient's symptoms are in dialysis and what could be related to the hyperparathyroidism.

"And then, does treatment actually improve their symptoms and their day-to-day life?" He emphasizes the need for studies focusing on patient-reported outcomes and giving patients more choices and input into treatment decisions—notably including choices about phosphate binder therapy.

Suggested Reading

KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl*. 2017; 7:1–59.

Ketteler M, et al: Executive summary of the 2017 KDIGO Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) Guideline Update: what's changed and why it matters. *Kidney Int*. 2017; 92:26–36.

Sprague SM, et al: Use of extended-release calcifediol to treat secondary hyperparathyroidism in stages 3 and 4 chronic kidney disease. *Am J Nephrol*. 2016; 44:316–325.

Findings

In Black Patients with Type 1 Diabetes, HbA1c Underestimates Mean Glucose

Glycated hemoglobin (HbA1c) levels may underestimate mean glucose level in African Americans with type 1 diabetes, reports a study in *Annals of Internal Medicine*.

The T1D Exchange Racial Differences Study Group analyzed data on 104 non-Hispanic black and 104 non-Hispanic white patients with type 1 diabetes, enrolled at 10 US centers. (Individuals with anemia or hemoglobinopathy were excluded.) All subjects were at least 8 years old and had had type 1 diabetes for at least 2 years. Mean glucose concentration was measured by continuous glucose monitoring, and racial differences in the relationship between glucose and HbA1c were assessed.

In this population with type 1 diabetes, mean HbA1c was 9.1% in black subjects compared to 8.3% in white subjects; mean glucose concentration was 191 versus 180 mg/dL, respectively. At a given mean glucose concentration, HbA1c was 0.4 percentage point higher in blacks compared to whites. The results were similar on analysis of subjects with a higher number of continuous glucose monitoring measurements.

The racial difference in mean glucose–HbA1c relationship also persisted on stratified analysis by age under 18 years versus age 18 or older. Glycated albumin and fructosamine were highly correlated with HbA1c, with no clinically significant difference by race.

Studies have consistently reported higher HbA1c levels in black compared to white adults and children with type 1 or 2 diabetes. Although this could indicate poorer glycemic control in black patients, it might also reflect racial differences in glycation of hemoglobin.

This study suggests that HbA1c overestimates mean glucose concentration in black patients with type 1 diabetes. While this could reflect racial differences in hemoglobin glycation, race only partly explains the observed difference in HbA1c. The authors write, "Future research should focus on identifying and modifying barriers impeding improved glycemic control in black persons with diabetes" [Bergenstal RM, et al. Racial differences in the relationship of glucose concentrations and hemoglobin A1c levels. *Ann Intern Med* 2017; doi:10.7326/M16-2596].

Policy Update

ASN Pushes for Adjustments to the Quality Payment Program for 2018

By David White

Quality and value care reimbursement: Where is it going in the next couple of years? There has been a great deal of talk and action to move health care from volume-based to value-based reimbursement. Most notable has been the creation of the Quality Payment Program (QPP) to implement the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA) and replace the Sustainable Growth Rate (SGR). The program began this year with Medicare designating 2017 as a transition year with Merit-based Incentive Payment System (MIPS) clinicians getting to "pick your pace." For 2017, the first year, clinicians are only required to report on one measure to avoid a penalty.

The proposed rule was released on June 20, 2017, and the American Society of Nephrology (ASN) submitted its comments and recommendations in a letter on August 21. The proposed rule focused on updates in three primary areas:

- Making participation easier for small (and possibly rural) practices,
- Easing clinicians into reporting requirements, and
- Recognizing the diversity of practices, practice settings, patients, and care models.

Here are some of the highlights from the proposed rule for 2018.

Merit-based Incentive Payment System (MIPS)

The Merit-based Incentive Payment System (MIPS) is one of the two pathways to participation in the QPP. The other pathway is Advanced Alternative Payment Models (AAPMs).

Low-volume exemptions

The Centers for Medicare & Medicaid Services (CMS) has proposed to raise the low-volume threshold in MIPS in 2018. Clinicians would be excluded from MIPS if they do not bill over $90,000 in Medicare Part B allowed charges or do not have over 200 Part B beneficiaries.

Performance Threshold

CMS proposes to set the performance threshold at 15 in 2018. All clinicians in MIPS are able to earn a score between 0 and 100 awarded based on the clinician's reporting in four areas: Quality, Costs, Advancing Care Information, and Improvement Activities. Within that range, Medicare selects a number reflective of a base level of performance it believes a clinician should be able to achieve—that number is the "performance threshold." A score above the performance threshold could result in a bonus adjustment in reimbursement. A score below the performance threshold will result in a negative, downward adjustment in reimbursement. An exact score in the performance threshold will result in no adjustment up or down—neutral.

Zero weight for costs category

The proposal recommends maintaining the weighting of costs at 0% in 2018 as it was in transition year 2017. This was done in large part because the episode groups that CMS intends to use to calculate cost effectiveness are not yet complete. The proposed rule has an alternative proposal placing the weight at 10%. ASN has strongly urged CMS to adopt the primary proposal of 0% and use the time between now and December 31, 2018, to transparently develop episode measures applicable to nephrology caregivers.

Hierarchical Conditions Category Bonus

CMS proposes to add a complex patient bonus, limited to three points, to the final score for the 2020 MIPS payment year for MIPS clinicians who submit data for at least one performance category. CMS proposes to calculate the average Hierarchical Condition Category (HCC) risk score for a clinician or group by averaging HCC risk scores for beneficiaries cared for by a clinician or group during the second 12-month segment of the eligibility period, which spans from the last 4 months of a calendar year 1 year prior to the performance period followed by the first 8 months of the performance period in the next calendar year (September 1, 2017, to August 31, 2018, for the 2018 MIPS performance period). The proposed rule also contains an alternative proposal, in which CMS would apply a complex patient bonus based on the ratio of patients who are dual eligible.

Because patients with kidney diseases are among the most complex in clinical practice, ASN encouraged CMS to continue working on this issue as there are several aspects of the proposal that need further refinement. The point bonus does not appear robust enough nor does the proposed process sufficiently consider patient population size, as smaller patient populations are statistically problematic. ASN has offered to work with CMS to further refine this recommendation.

Topped-Out Quality Measures

In 2019 and beyond, CMS proposes that any measure identified as topped-out for two consecutive years would not provide more than six measure achievement points in the second consecutive year it is identified as being topped-out. After three years of being identified as topped-out, the measure would be considered for removal through the rulemaking process. ASN does not object to this proposal.

The statistical definition CMS uses to define topped-out measures is exceedingly difficult to reach given the high numbers as, with large populations or numbers of facilities, clinically insignificant differences can be statistically significant. Nephrology's experience with the Quality Incentive Program (the first mandatory pay-for-performance program within Medicare, implemented in 2010) suggests that even if a measure does not meet CMS's statistical definition of being topped-out, there are many circumstances, particularly given the relatively low numbers of patients at each dialysis facility in relation to the much larger number of facilities, where measures are 'clinically' topped-out. When this occurs, the measure may no longer achieve the goal of incentivizing and rewarding quality care but rather prevents individualized patient-centered care.

ASN urges CMS to pursue a robust process to evaluate and remove topped-out measures to ensure optimal patient care and success of the QPP and emphasizes that assessment of whether a measure is 'clinically' topped-out is essential for all metrics.

Continuing Medical Education

CMS included language in the proposed rule to explicitly recognize Continuing Medical Education (CME) as an Improvement Activity (IA) in MIPS. ASN welcomed this inclusion.

Virtual Groups

In 2016, ASN urged CMS to create virtual groups for performance year 2017. ASN supported CMS moving forward on virtual groups for 2018 in the hopes that this will be a helpful path for solo practitioners and small practices.

Data Completeness

CMS proposed that clinicians who report on measures that do not meet data completeness standards receive one point as opposed to three points currently, although small practices will continue to receive three points. Recognizing that the QPP is a young, evolving program, ASN urged CMS to not make this change and maintain the current formula so clinicians will have the opportunity to learn how to interact optimally with this developing program.

Advanced Alternative Payment Models (AAPMs)

Advanced Alternative Payment Models (AAPMs) are the second pathway to participation in the QPP.

As noted in its comment letter from 2016, ASN remains concerned about the relatively small number of Advanced Alternative Payment Models available for clinicians, particularly those who care for patients in multiple settings without focusing on dialysis. While the ESRD Seamless Care Organization program offers one option to nephrologists, it is limited to dialysis care, thereby excluding the nearly 40 million Americans with CKD not yet on dialysis as well the hundreds of thousands who have received kidney transplants who could benefit from integrated care. ASN continues to urge CMS to use every available mechanism to foster the development of AAPMs, including models that span rather than silo stages of kidney diseases and incentivize optimal transitions across care settings.

The QPP also created the Physician-Focused Payment Model (PFPM) Technical Advisory Committee (PTAC) to consider and recommend new models, but the small number of AAPM proposals submitted to the PTAC demonstrates how early in development this path in the QPP remains.

Nominal Risk

For AAPMs, CMS proposed that the definition of nominal risk be just the 8% revenue standard—8% of the average total Medicare Parts A and B for an entity. ASN maintains that 8% is still high and could serve as a barrier to increasing the number of AAPMs—particularly PFPM AAPMs. In 2016, ASN recommended several alternative options:

- Limiting risk on using revenues received by a practice as a metric instead of a percent of total expenditures for patients (at least in some models).
- Not requiring payments back to CMS if the APM entity falls short of its anticipated revenues, as calculated by the physicians, for at least the first 2 years. Simply not receiving a bonus may be sufficient incentive for improving the ability to calculate risk, as physicians learn how to work with the new paradigm.
- Allowing certain APMs to operate for a pre-specified time period as one-sided risk (long enough to test whether a new care delivery model is promising in terms of cost and outcomes) but with the expectation that it would transition into two-sided risk if it were to be expanded/extended.

ASN restated its position that it sees the QPP as an evolving system that needs input and participation from all sectors of health care as all parties move forward.

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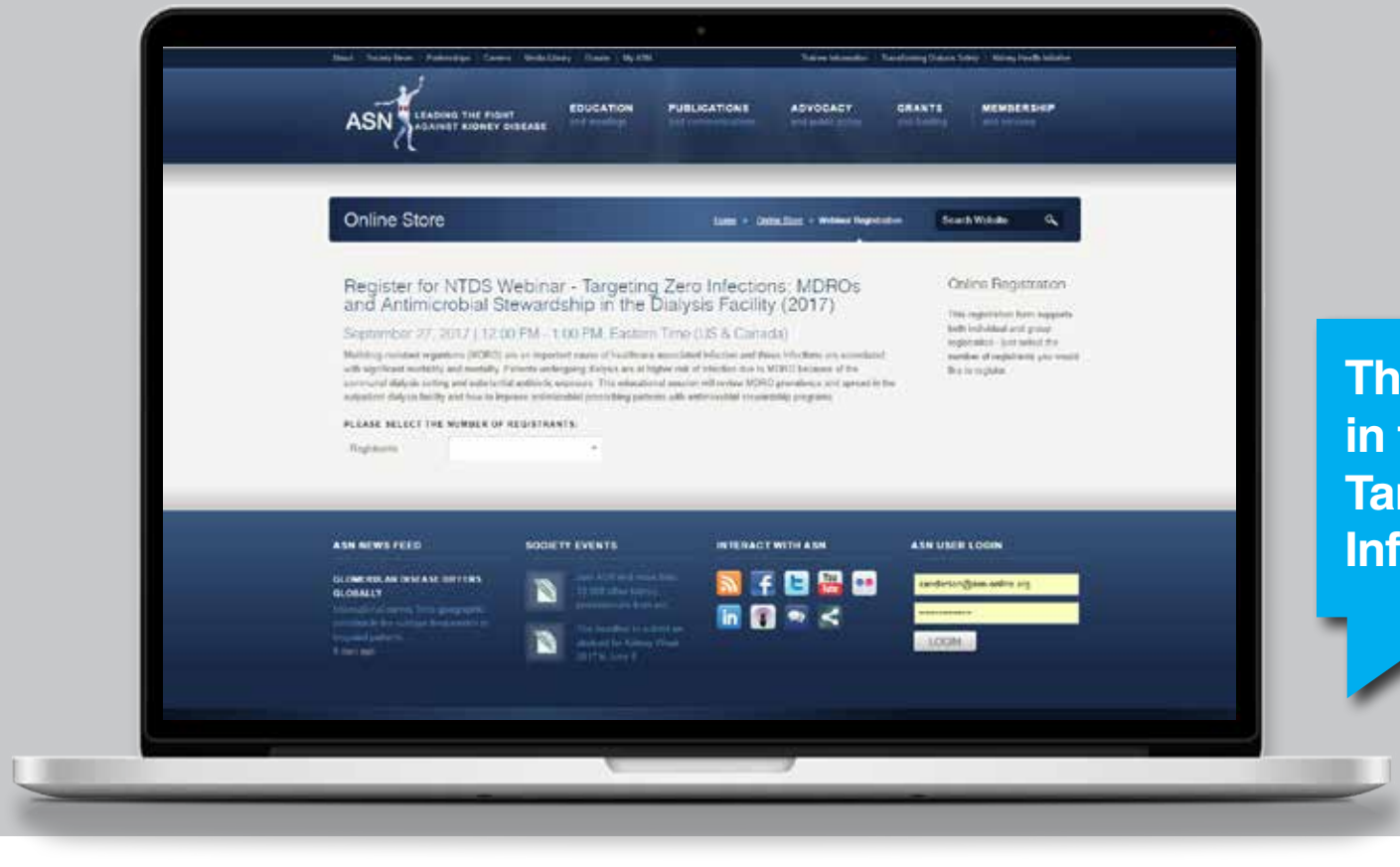

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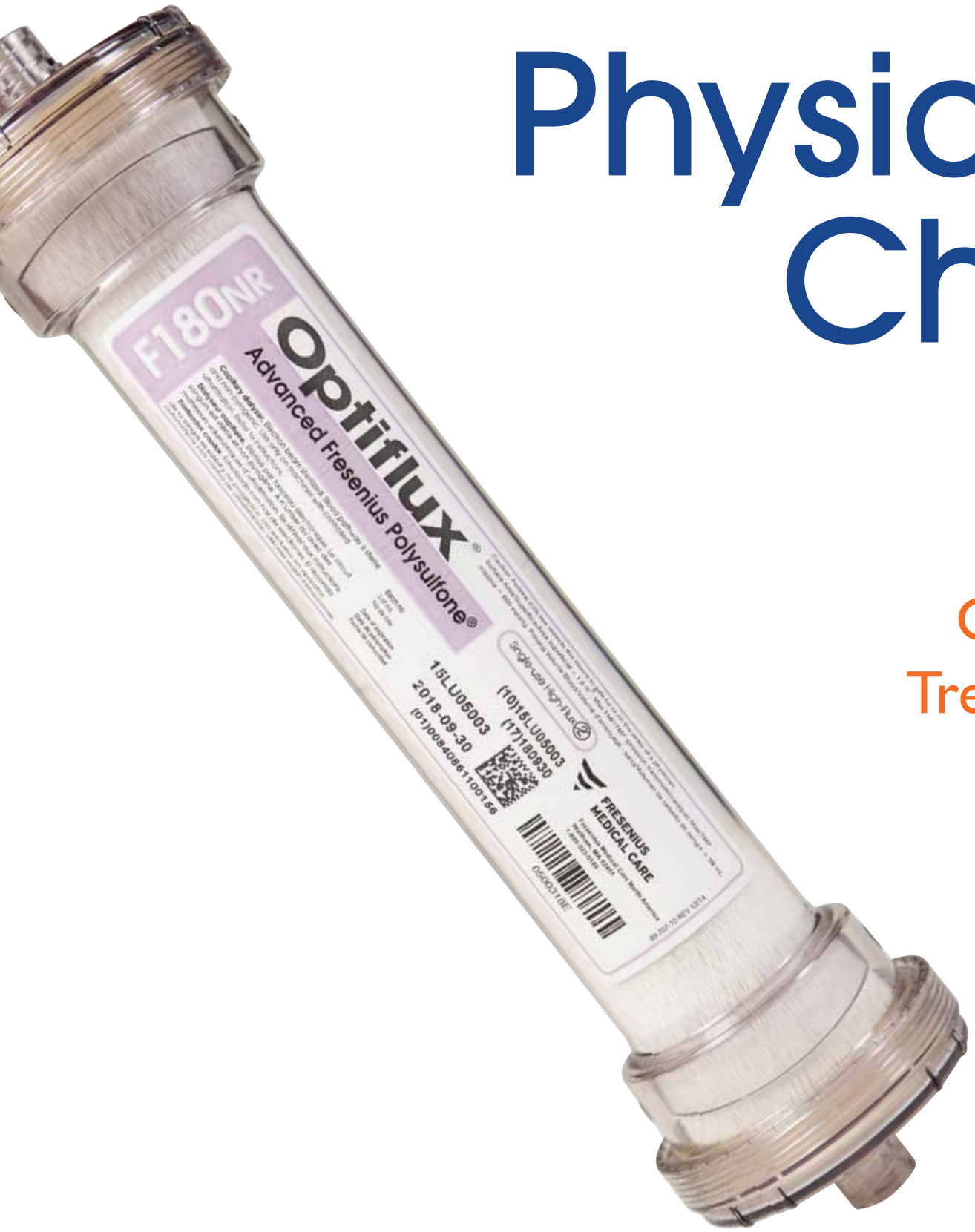

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