ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Kidney News

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Kidney Experts Address End-of-Life Care

Advanced care planning and end-of-life discussions are never easy, but for nephrologists they are a necessary part of caring for ESRD patients. As the general population ages and the incidence of CKD continues to climb, more researchers and clinicians are reassessing the role of palliative care in ESRD.

Jean Holley of the University of Illinois at Urbana-Champagne College of Medicine offered practical suggestions for having advanced care planning discussions in her talk "Creating an Efffective Advanced Care Plan for End Stage Renal Disease Patients" at Renal Week 2010 in Denver.

"A contemporary view of advanced care planning can be seen as preparing patients and surrogates to participate with clinicians to make the best possible in-the-moment decisions," she said.

She suggested starting with the patient's values and priorities—does the patient prefer prolonging life or a higher quality of life? Begin the discussion by talking about proxies: If you are unable to speak for yourself in the future, who will best represent your views and values? Have you given any thought to what kinds of treatment you would want or not want if you become unable to speak for yourself?

Surveys show that most patients believe that physicians should be the one to bring up these topics, but patients then prefer to have discussions about the topics with their families. As to when a physician should initiate these conversations, she pointed to the useful "surprise question" as in, "Would you be surprised if this patient died within the next six to 12 months?"

A useful opener for an end-of-life conversation is to talk in terms of goals: Given the severity of your condition, what is important for you to achieve? What are your greatest fears? Greatest hopes? Is it more important for you to live as long as possible, despite some suffering, or to have the best quality of life with little or no pain? What makes life worth living for you right now? Have you seen someone have a particularly good death or a particularly bad death?

Noting that one study showed physicians interrupt patients after an average of 18 seconds, Holley urged physicians to take the time to listen to patient concerns and wishes. She showed a slide of a typical ESRD patient trajectory—patients experience a slow decline in health over time that is interrupted by dips, or sentinel events, which return to a lower baseline. These sentinel events, she said, often result in a hospitalization and a change in health status, which makes each episode an appropriate time to talk about and revisit advanced care planning.

The successful use of physician-order advance directives such as a Do Not Resuscitate (DNR) or a Physician Order for Life-Sustaining Treatment (POLST) can benefit from educating patients about the realities of CPR survival rates and other interventions.

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Urinary Protein Analysis Promises Early Prediction of Diabetic Kidney Disease

By Daniel M. Keller

Analyzing the pattern of protein fragments in the urine may be a way to predict a risk for developing diabetic kidney disease years earlier than now possible, allowing therapeutic interventions to prevent or slow down irreversible kidney damage.

The results of a study presented at the 46th Annual Meeting of the European Association for the Study of Diabetes in Stockholm, Sweden, this fall suggest that collagen fragments are major components of this so-called "proteome analysis," looking at the presence and amount of as many as 273 different polypeptide chains.

Lead investigator Peter Rossing, MD, DMSc, chief physician at the Steno Diabetes Center in Gentofte, Denmark, reported results showing that urinary proteome analysis can provide early and sensitive detection of diabetes-associated renal pathology as early as four years before a rise in urinary albumin levels. Furthermore, this method can follow the progression of disease.

Initial efforts were aimed at finding individual molecular markers in the urine to predict future diabetic

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Inside

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End-of-Life Care

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"On television, 75 percent of patients survive CPR, and usually by the end of the episode," Holley quipped. "And of those, 67 percent survive to hospital discharge." In the real world, on the other hand, only 30–40 percent of patients survive CPR and only 15 percent to discharge. In addition, CPR in this patient population carries risks of undesirable outcomes such as prolonged ventilation, fractures, pneumonia, and neurological damage.

Holley suggested openers for DNR conversations, too, such as: "If you suddenly stopped breathing or your heart stopped, we could try to revive you by CPR. Are you familiar with CPR? Have you given thought to if you would want it?" Or, "Given the severity of your illness, CPR would likely not be effective, so I would recommend that you not choose it. But, how do you feel about it?"

The POLST document, usually a brightly colored page in a patient's chart, converts patient preferences into medical orders signed by a physician. It is available, or will be soon, in several states. It usually includes a CPR designation, comfort measures, limits to interventions, whether antibiotics should be given, and whether tube feeding or fluid nourishment should be given. It may also have timing attached to certain measures to accommodate a major life event for the patient such as attending a daughter's marriage.

Stopping dialysis

Lewis Cohen, director of the Baystate Renal Palliative Care Initiative and psychiatrist at Tufts University School of Medicine in Springfield, Mass., spoke about the tricky issue of stopping dialysis. He noted that in the New England region, currently more than 40 percent of deaths of ESRD patients result from stopping dialysis.

In 2000, his group initiated a prospective study to find out who these patients were, their reasons for stopping dialysis, and what kind of death they had. Families reported 85 percent of the deaths as "satisfactory," but pain was present in 42 percent of deaths and agitation in 30 percent during the final day of life. Death occurred an average of eight days after the last dialysis treatment.

Forty-seven percent of these patients experienced a good death, defined as one that occurred within eight days of stopping treatment, was painless, in the company of loved ones, peaceful, asleep, at home, and with the patient mentally alert. Only 15 percent experienced a bad death.

"It's time for us to sharpen up the prognostic tools and focus on those doing poorly and likely to die in the next six months. How do they want to make use of that time?" asked Cohen. "Patients need to know that stopping dialysis does not mean the end of further care. It's not about dying, but about the living that comes beforehand."

Holley, Cohen, and other speakers in the Renal Week session "Palliatiative Care in ESRD" encouraged nephrologists at dialysis centers to determine who within their staff, such as social workers and nurses, would be best equipped to help facilitate these discussions. But one doctor in the audience had the final word: "It's not just the social worker's job or the nurse's job, it's our job [to talk about death]. If you are a nephrologist, you got here because you've seen patients sick and dying. Death is part of what we do."

At the end of Lewis Cohen's talk, audience members had several questions about handling tricky situations that crop up in their daily practice or within their own dialysis centers—usually revolving around stopping or not initiating dialysis and the end of life. Cohen offered his perspective on these scenarios.

Q: You said you felt that it was not a good death if it occurred more than eight days after removal of dialysis, but we all know of cases where patients have some residual renal function and continue to live for even up to a year longer. How do we deal with that?

A: We all know the story of Art Buchwald, the Pulitzer Prize winner who was very vocal about what happened when he was taken off dialysis. It was the time of his life, until he got thrown out of hospice because he didn't die. At the same time, I recall a family in California who wrote to me about the agony of the prolonged period their loved one was going through that stretched into months. These are working attempts to come up with a quality of dying measure, but the

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Kidney News

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End-of-Life Care

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field is having a tough time finding one that works across the board. We should continue to figure it out.

Q: Say you have a young patient on the transplant list who asks you, "Is stopping dialysis committing suicide?" How do you answer that?

A: I stand here as a psychiatrist and that's the very question that got me interested in this subject. It can, for some people, be the same thing and so I'm always careful to look for someone with a past history of suicide attempts or depression. But for all the rest, the vast majority of folk, it's a different kettle of fish that is something very different from suicide.

Most Western religions have looked at the matter and determined that stopping extraordinary measures are not sins of suicide. So you can dispel concerns of someone bothered by that thought, and I have involved the hospital chaplains in those conversations.

Q: Sometimes the family is pushing hard for dialysis, but the patient doesn't want to. How do you deal with that?

A: When the patient and family are not on the same page—usually a loving family saying we don't want you to die—the ethics at the moment is pretty clear. It's not the family's decision to make if the patient can make it on their own. It's a cultural thing as well. In this country, the individual has the right to make decisions for themselves. They are the one suffering and they have both the ethical and legal right to say they want to stop treatment.

What's a strategy for helping the family and patient get on the same page? You can tap a social worker to join the conversation. Also, very few family members actually sit in dialysis centers and see what the person is experiencing. [If they did,] they might understand better.

Q: Could you talk about the memorial service performed at [your center] Baystate, and what good has come from it?

A: This is something we've been doing for a number of years and it's worth considering bringing to your dialysis centers. We send out invitations to the bereaved families of people who have died within the last year for an ecumenical service of remembrance. Families get the opportunity to say thank you to those who've cared for their loved ones over the years and the staff get to hear about how the person actually died.

Again, it's about changing the culture. All the staff that come are affected by this. During the candle lighting ceremony, you see that, wow, there are 50 candles here and that changes the staff and how they practice. The atmosphere is much more conducive to having these [end-of-life] discussions with patients and families.

Symptom Management Near the End of Life

Drew Rosielle keeps the memory of a patient from his training days in his mind when thinking about end-of-life (EOL) palliative care. The 69-year-old woman with type 2 diabetes and ESRD on dialysis developed a painful rash called calciphylaxis.

"She spent the last two weeks of her life in the hospital, twitching and writhing with a pain score of 8–10 and we as her physicians worried constantly about overdosing her on pain medications," said Rosielle, a palliative care physician at the University of Minnesota Medical Center Fairview in Minneapolis. "It was a big example to me of the suffering our patients go through and our feelings of being helpless."

Luckily, the good news is that ESRD patients at the EOL can get tremendous relief now for their physical symptoms. Rosielle noted that while there is some evidence that guides first-choice agents to use, his usual mode of operation when treating someone near the EOL is to "try something to see if it works, and move on to the next thing in a very rapid, careful management."

For acute symptoms, he recommends using rapid-acting formulations like IV and subcutaneous injections or oral doses, not IV drips that take hours to take effect. For opioid pain relief, Rosielle recommends using fentanyl and methadone (see box at right) for ESRD patients, either with or without dialysis. He says patient and provider concerns or hopes that using opioids will hasten death are misguided because there is no evidence to support this. "Instead, just tell them it will only make them more comfortable," Rosielle said.

He also notes that families concerned about delirium and the patient not eating or drinking can be reassured that this is a normal part of the process of dying and to be expected.

Although only a few percent of patients have intractable suffering, characterized as pain, nausea, dyspnea, and agitation that does not respond to usual drug therapy, those patients can benefit from sedation with benzodiazepines at the EOL. The worse cases may need continuous deep sedation (medically induced coma) but this should be performed by a palliative specialist familiar with the procedure. If intractable suffering is a major patient worry, you can reassure them that there are options for relief.

Rosielle's session was titled "Maximizing Quality of Life: Symptom Management near the End of Life."

Treatment recommendations for EOL symptoms

Pain relief: nonopioids

Acetominophen is safe and may be synergistic with lower-dose opioids

Glucocorticoids, such as low-dose dexamethasone, are fairly safe (not worried about bone loss in these patients) and include the benefits of a modest energy and appetite boost as well as being an antiemetic

NSAIDS are not safe to use in these patients

Pain relief: opioids

Codeine, meperidine, morphine, hydrocodone: best to avoid in ESRD patients; negative side effects such as worsening pain, agitation, delirium, twitching due to their metabolites building up in renal patients

Oxycodone, hydromorphone: may be okay for patients still on dialysis because metabolites are dialyzable; may not be the best option if need high doses for weeks for patients not on dilaysis

Fentanyl: transdermal patch is the long-acting opioid of choice for these patients, it is 100 percent metabolized by the liver, it does take 18-24 hours to start working, but is essentially steady-state after a week; for fast-acting needs, transbuccal tablets or lozenges are available but these are an expensive option

Methadone: good for ESRD patients with or without dialysis, 100 percent metabolized by liver; both short- and long-acting and its half-life can last up to a week, so best managed by physicians with experience with it

Dyspnea: evidence that a fan or other air blowing in the face is effective; opioids and benzodiazepines are the best drug options

"Death rattle" secretions: after differentiating from pulmonary edema, use suction and repositioning in bed

Nausea: same treatment as for other patients

Delirium: important to reassure families that this is a normal part of the process of dying; if distressing for the patient, can treat effectively with neuroleptics

Urinary Protein Analysis

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nephropathy, but using a wide array of markers may be a better answer. "We have analyzed urines from a lot of different patients, some having diabetic nephropathy and some being control subjects," Rossing said. "The pattern in a patient with chronic kidney disease is different from the pattern in a control." The current work compares patterns of many markers to integrate them into a risk score. "So you try to sum up the differences. Some polypeptides are increased and some are decreased," Rossing added.

Using stored urine samples, the researchers could go back and check the patterns of protein fragments in the samples from individuals they knew developed kidney disease and compare them with individuals who did not. They discerned which protein markers were most informative and then validated their model on samples from another group of patients.

Testing the predictive model

The first part of the study compared the urinary proteomes from 64 type 2 diabetes patients with nephropathy and 81 without nephropathy. Patients were well matched for age, gender, and duration of diabetes. When samples were unblinded, the proteome analysis had a sensitivity (ability to detect disease when truly present) of 95.3 percent and a specificity (correctly identifying the people without the condition) of 85.2 percent.

For a prospective, blinded test set of 110 cases with a variety of kidney diseases and 34 healthy controls, the sensitivity was 85.2 percent with 100 percent specificity. When the data were unblinded, all the controls and 94 patients with CKD were correctly classified.

The researchers tested the model by following type 2 diabetes patients with initially normal urinary albumin excretion levels for several years to see if they could use proteome analysis to predict which patients would eventually develop abnormal levels of albumin excretion, an indicator of kidney disease. Samples were collected approximately once a year for 10 years. Samples (n = 187) were classified in a blinded manner.

Of the patients the investigators followed, 10 proved to have progressive kidney disease and nine did not. "The interesting thing is that this risk marker based on the polypeptide pattern is increased several years before you start to increase the albumin excretion rate," Rossing said.

The use of the biomarkers pattern predicted the beginning and progression of diabetic nephropathy an average of 4.1 years before urinary albumin levels increased. Rossing concluded that the data support the researchers' earlier hypothesis that collagens have an important role in the development of diabetic nephropathy and may be very suitable targets for diagnosis and superior to the currently used albumin excretion rate.

The study is remarkable for the length of time that patients were followed and the large number of patients, Rossing said. He is currently working to extend the findings to patients with type 1 diabetes.

Although proteome analysis would be more expensive than a simple urine test for albumin, it appears to be more predictive of kidney damage and further advanced than albumin testing.

In talking with *ASN Kidney News*, Rossing suggested that if abnormal protein patterns become evident in the urine of a diabetic individual without nephropathy, more aggressive treatment could be in order, including the use of statins, antihypertensive medications, glycemic control, and renoprotective agents such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Looking to the future, Rossing said that protein markers in urine could also be a clue to targets for drug development.

Renal Week 2010 Findings

Chronic Kidney Disease Clinical Trials Yield Promising Results

By Kendall Powell

Positive results from two clinical trials of medications for chronic kidney disease (CKD) patients were presented during the "Late-Breaking Clinical Trials" session at Renal Week 2010. The trials represented potential good news for millions of CKD patients at risk of end stage renal disease and with increased risk of cardiovascular events.

Pablo Pergola, research director for Renal Associates PA and of the University of Texas Health Science Center, San Antonio, presented findings from a Phase IIb trial of bardoxolone methyl in CKD patients with type 2 diabetes.

Bardoxolone methyl is an antioxidant inflammation modulator that activates the novel Nrf2 anti-inflammatory pathway. In the study sponsored by Reata Pharmaceuticals and Abbott, 227 adults with type 2 diabetes and moderate (stage 3b) to severe (stage 4) CKD were randomized to receive either placebo or bardoxolone methyl in doses of 25, 75, or 150 mg/day. The patients were an average age of 67 years, with long-term diabetes for an average of 18 years, and 75 percent were obese. They were all receiving standard-of-care treatment for CKD, and almost all of the patients were taking an ACE inhibitor or ARB and had well-controlled blood sugar and blood pressure levels.

Change in estimated glomerular filtration rate (eGFR) at week 24 of a 52-week protocol— for either the pooled bardoxolone methyl doses or placebo— was the primary endpoint. Patients on bardoxolone methyl had a statistically significant 10.1 mL/min improvement in GFR compared with a 0.1 mL/min improvement in the placebo group. The improvement in GFR began as early as week 4 and continued until week 12 when it leveled off. In addition, 59 percent of bardoxolone methyl patients improved their CKD stage, compared with only 16 percent on the placebo.

"Current treatments for CKD only slow, but do not reverse progression of the disease," Pergola said during a press briefing on the trial. "These results suggest that bardoxolone methyl has the potential to change the treatment landscape of CKD."

Patients on bardoxolone methyl did experience certain adverse events more frequently compared with the placebo group, such as muscle spasms (described as charley-horse-type cramps), nausea, hypomagnesemia, and decreased appetite, but Pergola noted that all of these side effects could be effectively managed clinically. He also noted that the 52-week data will be analyzed in January 2011, and that these initial results merit the initiation of a Phase III study of 1500 patients.

Members of the audience expressed skepticism about how quickly the drug acted to change eGFR, with some suggesting that rather than representing an improvement in kidney structure based on reduced inflammation, the results were due to a simple increase in fluid flow, or "hemodynamic" effect, that in the long run would not be protective for kidneys.

One audience member questioned Pergola: "Are you concerned that the increased eGFR might actually hasten renal deterioration?" Pergola said that he hopes the question of hyperfiltration would become a moot point after the 52-week and phase III results came out showing both increases in renal survival and patient survival. He also noted that previous studies had shown that bardoxolone methyl reduced levels of urea nitrogen, phosphorus, and uric acid in the blood, other indications of improved kidney function.

Tomas Berl, of the University of Colorado, Denver, and past president of ASN, heard the presentation and commented, "I, too, have concerns about the dramatic increase in GFR reported with bardoxolone in such a short-term study. This is more likely to represent a functional, rather than a structural improvement [in the kidney]."

Sharp results for SHARP trial

Patients taking Vytorin compared with those on a placebo had a 17 percent risk reduction for experiencing a major atherosclerotic event (MAE), according to highly anticipated results from the largest trial of kidney patients to date, the Study of Heart and Renal Protection, or SHARP trial.

The trial, which was designed and run by researchers at the University of Oxford with funding by Merck, the British Heart Association, and the UK and Australian governments, followed 9270 CKD patients for approximately five years to test whether lowering their LDL cholesterol levels with the Merck drug Vytorin, a combination of the drugs ezetimibe and simvastatin, would reduce their risk of MAE, defined as a major coronary event, a nonhemorrhagic stroke, or any revascularization procedure.

CKD patients have a higher risk of cardiovascular events, but previous trials of LDL-lowering therapies in this group have been inconclusive. As Colin Baigent, professor of epidemiology at Oxford, said, "I'll let the results speak for themselves," as he put up the lines representing risk ratio in the placebo group and the treatment group. Thousands of audience members erupted in applause.

Of note, the LDL-lowering had no effect on the progression of CKD to end stage renal disease. Importantly, as Martin Landray, a Reader in epidemiology at Oxford and clinical coordinator of SHARP, presented, there was no increased risk of cancer for the patients taking Vytorin. Although 850 cancers occurred in the patient pool, there were no significant differences in incidence or types of cancers seen in the treatment group compared with the placebo group. There was also no increased risk of myopathy, liver disorders, or nonvascular mortality.

Landray also noted that overall compliance in the treatment group was only about two-thirds, indicating that the results were an underestimate of the true value of risk reduction.

"These patients were taking a tablet that they didn't know would work and if it was safe, and they are already taking 10–20 other tablets. Now they might be more invested, to know that it does indeed work and it is safe," Landray said at the press briefing. "Full compliance would be expected to reduce the risk of major atherosclerotic events by 25 percent. In the U.S., that would prevent tens of thousands of events each year, and a quarter million worldwide."

One audience member, noting that the effect was independent of the amount of LDL-lowering, asked, "Should we be using this drug in everybody with CKD?"

Baigent responded, "I would say that you treat any patient that you believe would be better off from a risk level, who could afford it, and who wants to take a drug on a daily basis. I would not use cholesterol measurements as a measure of risk. The bottom line is that it works, gives a benefit, and will do so safely."

Pablo Pergola presented "Effect of Bardoxolone Methyl on Renal Function in Patients with Chronic Kidney Disease (CKD) and Type 2 Diabetes Mellitus" and Colin Baigent and Martin Landray presented "Should We Reduce LDL Cholesterol in Patients with Chronic Kidney Disease? The Results of the Study of Heart and Renal Protection (SHARP)" during the "Late-Breaking Clinical Trials" session on Saturday, November 20, at Renal Week 2010.

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Renal Week 2010 Findings

Maternal Obesity and Diabetes Linked to Increased Risk of Childhood Chronic Kidney Disease

Are some children born at increased risk of kidney disease? Research presented at Renal Week 2010 suggests that maternal obesity and diabetes are independent—and perhaps modifiable—risk factors for childhood chronic kidney disease (CKD).

"We aimed to determine whether the development of CKD in childhood and young adulthood is determined prenatally, "said lead investigator Christine Hsu, MD (University of Washington, Seattle), a pediatric nephrologist. "Our results show that maternal diabetes and overweight/obesity are associated with the development of childhood CKD, with the strongest association between maternal diabetes and congenital kidney abnormalities."

Hsu and colleagues analyzed Washington state birth records linked to hospital discharge data through the Comprehensive Hospital Abstract Reporting System. Using these population-based data, the researchers identified 4063 cases of childhood CKD diagnosed before age 21.

The cases were matched to 20,032 non-CKD controls, with maternal and infant data available for both groups. The researchers analyzed maternal diabetes mellitus and overweight/obesity as primary risk factors for childhood CKD.

From 1987 to 2008, the overall prevalence of childhood CKD was 258.1 cases per 100,000 births—more than 1 out of 400 children born in Washington state was diagnosed with CKD before age 21.

Children born to mothers who had diabetes mellitus or above-normal body weight during pregnancy were at higher risk of developing CKD. The association was strongest for maternal pregestational diabetes after adjustment for length of gestation. A smaller but still significant increase in risk was noted for children born to mothers with gestational diabetes.

Maternal obesity was another independent risk factor for CKD in offspring. Risk also tended to be higher in children born to overweight mothers, although not significantly so.

In subgroup analyses, maternal pregestational diabetes was associated with a sharply increased risk of renal aplasia/dysplasia in offspring. Children of pregnancies complicated by gestational diabetes were at increased risk of obstructive uropathy. Maternal obesity and overweight were also risk factors for obstructive uropathy.

"Congenital renal/urinary abnormalities are the most common causes of childhood chronic CKD," said Hsu. However, there are surprisingly few data on factors associated with an increased risk of CKD in children. To the researchers' knowledge, theirs is the first study to evaluate maternal diabetes, overweight, or obesity as risk factors for childhood CKD.

The results show that maternal diabetes and obesity are significantly and independently associated with CKD developing before adulthood. For women with diabetes before pregnancy, the risk of giving birth to a child with renal aplasia/dysplasia is elevated more than sixfold.

Because the study was based on hospital discharge data, it could not identify children with CKD who had not been hospitalized. "Identification of cases depended on having a kidney disease diagnosis in the list of hospital discharge diagnoses," Hsu noted.

Do the new associations present opportunities for prevention? Previous studies have linked maternal diabetes to an increased risk of congenital abnormalities. "However, with strict control of maternal diabetes, rates of congenital malformations are similar to those of nondiabetic mothers," said Hsu.

"This implies that perhaps stricter diabetic control and decreased rates of overweight/obesity in women may decrease the risk of their children developing CKD," Hsu said. "This would have to be evaluated in future research."

Diet and Sleep Emphasis Benefit Kidney Patients

Targeting dietary habits and sleep patterns can improve kidney disease patients' health, according to two studies presented at Renal Week 2010.

The negative effects of a Western diet go beyond the obesity epidemic and its related health consequences. A diet rich in wheat flour and animal protein also produces an acidic environment in the body that worsens with age as kidney function declines. This acid load can be detrimental to a variety of tissues and processes.

Nimirit Goraya, MD (Texas A&M College of Medicine and Scott and White Healthcare), and colleagues designed a study to see if consuming a diet high in base-inducing fruits and vegetables that counteract this acidity might improve the kidney health of 40 patients who had moderately reduced kidney function (stage 2 chronic kidney disease) due to hypertension.

A 30-day dietary regimen high in fruits and vegetables reduced urine excretion of three indicators of kidney injury: albumin, transforming growth factor β, and N-acetyl-β-D-glucosaminidase.

"We support exploring this dietary intervention as an adjunctive kidney protective strategy to blood pressure reduction and ACE inhibition in patients with hypertension-associated kidney disease," said Goraya, who noted that because the study tested a 30-day dietary intervention strategy, long-term implications of the results are not clear. Other factors in addition to or instead of added fruits and vegetables might have contributed to the benefit seen. These factors might include better medication compliance and/or an increase in physical activity that patients decided to undertake with dietary changes.

Another study investigated the potential of the hormone melatonin, which regulates sleep/wake rhythms, for improving dialysis patients' sleep. The need for sleep interventions in this population is great, because sleep disorders are common in kidney disease patients on dialysis due to a disturbance in their biological clock.

Previously, researchers found that melatonin can improve dialysis patients' sleep over a short period. These same investigators, led by Marije Russcher and Birgit Koch, PhD (Meander Medical Center, Amersfoort, The Netherlands), recently looked to see whether the benefits of 3 mg melatonin on sleep persist over the long term and whether the hormone has any effects on patients' quality of life.

In this randomized, double-blind, placebo-controlled trial, 70 dialysis patients received melatonin or a placebo for 1 year. Objective sleep measurements were taken at 0, 3, 6, 9, and 12 months. Quality of life parameters were measured by the Medical Outcomes Study Short Form-36 questionnaire. Melatonin concentration curves were sampled in saliva at 0 and 6 months.

Administration of exogenous melatonin resulted in higher endogenous melatonin levels. At three months, the previously shown beneficial effect of the short-term use of melatonin on sleep onset was confirmed. Trends in improvement were seen for sleep efficiency, actual sleep time, and actual awake time. In contrast, at 12 months, none of the measured sleep parameters differed significantly from placebo. Melatonin had a positive effect on social functioning and improved mentality.

"The short-term effects of melatonin on sleep were confirmed; however, we found no indication that melatonin's effects persist during 12 months of melatonin use," said Russcher.

The study abstracts "Adding Dietary Fruits and Vegetables Reduces Kidney Injury in Subjects with Moderately Reduced GFR" and "The Long-Term Effects of Melatonin on Sleep and Quality of Life in Hemodialysis Patients" were presented at Renal Week 2010.

H1N1 Vaccination Policies for Patients Posttransplant Fall Short

A single dose of H1N1 vaccine as well as booster vaccination are not sufficient to induce a protective immune response in renal transplant patients, new data suggest.

In healthy individuals, between 80 percent and 95 percent of adults develop a sufficient immune response after a single vaccination against the H1N1 virus, but no corresponding data have been available for immunosuppressed patients.

Susanne Brakemeier (Charite, Berlin) and her colleagues studied the immune responses to the H1N1 vaccine (Pandemrix) in 60 patients—12 females and 48 males—who received a kidney transplant at least six months

Racial and Socioeconomic Disparities Persist in Kidney Transplantation

Considerable barriers must be overcome to ensure fair and equal access to kidney transplantation, according to three research presentations at Renal Week.

Among the findings: The lower an individual's income, the less likely that individual was to donate a kidney to a loved one. Blacks are less likely to be placed on transplant waiting lists before they start dialysis, but early care by a nephrologist diminished this disparity. Finally, in a study of pediatric patients, blacks had a 50 percent increased risk for graft failure compared with white non-Hispanics.

The number of living kidney donors in the United States has decreased in recent years. Jagbir Gill, MD (St. Paul's Hospital, University of British Columbia, Vancouver, BC, Canada), and colleagues broke down this trend by income level, examining the rates of kidney donation based on median household income between 2000 and 2007. Their analysis included data from the Organ Procurement and Transplantation Network/United Network for Organ Sharing and the 2000 U.S. Census.

Rates of living kidney donation declined in all income groups over time; however, the lower the income, the lower the rate of living donation. In the lowest income group, living donations decreased by five per million population between 2004 and 2007. The rates decreased by one donor per million population in the two highest income groups, making the absolute decrease in living donor rates fivefold greater in the lowest income group compared with the highest income groups.

"Removing financial disincentives to living kidney donation may be an important strategy to prevent ongoing retraction of living kidney donation," the authors concluded. Gill added that minimizing these barriers is also necessary so that everyone who wishes to donate a kidney to a loved one has the opportunity to do so. Lower socioeconomic status is associated with a higher incidence of end stage renal disease (ESRD) yet reduces access to living donor kidney transplantation.

Another study identified disparities in placing kidney disease patients on transplant waiting lists pre-emptively, or before they start dialysis. Blacks are less likely than whites to be wait-listed pre-emptively. Nancy Kutner, PhD (Emory University, Atlanta, GA), and colleagues examined whether these racial disparities exist even among patients who have had discussions with nephrologists about kidney transplantation before starting dialysis.

Between 2005 and 2007, the investigators surveyed 1634 incident dialysis patients aged ≥18 years from 296 randomly selected clinics in the United States Renal Data System (USRDS) Comprehensive Dialysis Study. Participants were asked, "Was kidney transplantation discussed with you before you started your regular treatment for kidney failure?"

A total of 813 (49.8 percent) patients reported that kidney transplantation had been discussed with them before starting dialysis. Only 60 (7 percent) of these patients were wait-listed pre-emptively; 29.3 percent of the patients wait-listed pre-emptively were black, compared with 26.6 percent of patients not wait-listed pre-emptively.

Patients who were wait-listed pre-emptively were more likely to be employed and to have private insurance and less likely to have diabetes and cardiovascular comorbidities. They also had higher average levels of hemoglobin, serum albumin, and serum creatinine and were more likely to have received care from a nephrologist before starting dialysis.

Among the 813 patients who reported having discussed predialysis transplantation, more patients who were wait-listed pre-emptively had received early nephrology care (98.3 percent versus 79.4 percent), and they were more likely than patients who had not been wait-listed pre-emptively to begin renal replacement therapy on peritoneal dialysis (25.9 percent versus 9.4 percent).

Early kidney transplant discussion and higher hemoglobin level were significant predictors of pre-emptive waiting list placement. Early nephrology care and serum albumin had borderline significance. Blacks and whites had similar likelihoods of being placed on transplant waiting lists before starting dialysis.

"Although black patients are often disadvantaged at multiple steps in the kidney transplant process, in this study population, patients' early discussion of kidney transplantation as a treatment option, linked with early nephrology care, appeared to diminish barriers to black patients' placement on a kidney transplant waiting list before dialysis start," said Kutner.

Examining the effects of race and socioeconomic status on graft failure in children, Rachel Patzer (Emory University) and colleagues conducted a study of all pediatric (<21 years) incident ESRD patients in the USRDS and the United Network for Organ Sharing who received a kidney transplant between January 2000 and September 2006. The investigators followed the patients for transplant outcomes through September 2008. Patients' residential zip codes were linked with poverty data from the 2000 U.S. Census.

Of the 4320 patients in the study, 18.4 percent experienced allograft loss within an average follow-up time of 3.6 years. Blacks had nearly twice the risk of graft failure at any given time versus white non-Hispanics. Hispanic whites had a 23 percent reduced risk versus non-Hispanic whites. After taking demographic, clinical, and socioeconomic factors into account, this racial disparity remained high, with blacks at a 50 percent increased risk for graft failure versus white non-Hispanics. Increasing poverty also increased patients' chances of graft failure: those from the poorest neighborhoods had a 20 percent greater risk than patients in the wealthiest neighborhoods.

"Racial and poverty disparities exist in pediatric kidney allograft survival, with black pediatric ESRD patients and those living in poor neighborhoods having a shorter time to graft failure," the authors concluded. "These differences deserve further exploration to identify modifiable risk factors for graft loss and to ensure health equity." Advocacy and education programs that are targeted to poorer neighborhoods may help improve posttransplantation outcomes.

The studies "The Retraction of Living Kidney Donation Is Most Marked among the Poor," "Race, Predialysis Transplant Discussion, and Preemptive Wait Listing in a National Cohort," and "Racial Disparities and Neighborhood Poverty in Pediatric Renal Allograft Survival" were presented at Renal Week 2010.

earlier and were taking immunosuppressive medications (mycophenolate in combination with either tacrolimus, cyclosporine, everolimus, or sirolimus). Twenty-two healthy individuals served as controls.

Two transplant patients had elevated antibody titers before being immunized. Of the remaining 58 patients, only 34.5 percent developed a titer of 1:40 or more, which is considered sufficient to be protected against the H1N1 virus, after a single dose of Pandemrix (3.75 µg per dose, adjuvanted). In contrast, 91 percent of the control group developed a protective titer of 1:40 or more. The other 65.5 percent of transplant patients showed no or only a weak response.

Among a subgroup of transplant patients who received a booster vaccination 21 days after the initial immunization, 42 percent mounted a sufficient immune response.

Underweight dialysis patients have increased mortality risk

Obesity is an important risk factor for cardiovascular disease and mortality among those on dialysis; however, differences in mortality between young and elderly dialysis patients have not been well addressed.

Ellen Hoogeveen, MD, PhD (Jeroen Bosch Hospital, Den Bosch, The Netherlands), and colleagues investigated whether the association of body mass index (BMI) and mortality differs between younger (<65 years of age) and older (>65 years of age) dialysis patients.

The researchers divided 1749 dialysis patients into eight categories based on their baseline age and BMI: <20 (7.5 percent), 20 to 25 (47 percent), 25 to 30 (34.5 percent) and ≥30 (11 percent) kg/m^2. After their first dialysis treatment, patients were followed until death, transplantation, or a maximum of seven years.

Compared with patients with a normal BMI, both young and elderly dialysis patients who were underweight had an approximately twofold increased risk for mortality, although this may be due to reverse causality. Young patients with obesity had an approximately 1.5-fold increased risk of dying compared with both young patients with a normal weight and elderly obese patients. "Identification of modifiable risk factors for survival opens the door to targeted prevention and is important to improve life expectancy," said Hoogeveen.

Renal Week 2010 Findings

Autoantibodies, AKI's effects on vital organs, and coronary revascularization in CKD highlight grant recipients' talks

Among the current and former ASN grant recipients who spoke at Renal Week 2010 are Laurence H. Beck, Jr., MD, PhD, recipient of a Halpin Foundation-ASN Research Grant, Sarah Faubel, MD, and David Charytan, MD, MSc, recipients of a Carl W. Gottschalk Research Scholar Grant.

"The Human Membranous Antibody: Mechanism and Monitoring" was the topic of Beck's talk. Funded by the Halpin Foundation-ASN Grant, Beck's line of research on autoantibodies to the phospholipase A2 receptor (PLA2R) is expected to lead to a better understanding of idiopathic membranous nephropathy, and ultimately to better and safer treatments for individuals with this disease. Beck is assistant professor of medicine at Boston University School of Medicine.

Faubel is investigating systemic effects of acute kidney injury, particularly the role of IL-6 in mediating lung injury after acute kidney injury. Faubel said this research may lead to specific interventions that will reduce the high mortality of this complication in patients with acute kidney injury. Her talk was titled "Adverse Effects of AKI on Vital Organs." Faubel is associate professor of medicine at the University of Colorado School of Medicine.

Charytan discussed "The Role for Coronary Revascularization and Type of Revascularization in CKD." The Gottschalk Grant helps fund his study of the role that myocardial microvasculature plays in CKD and cardiovascular outcomes. Charytan is assistant professor of medicine at Harvard Medical School and Brigham and Women's Hospital.

The ASN grants portfolio comprises career development grants for young investigators; interim funding for established investigators' grants for medical student research; and travel support for ASN members, residents, and medical students.

ASN directs a large portion of funds to career development grants, including the Carl W. Gottschalk Research Scholar Grant, the Norman Siegel Research Scholar Grant, and the John Merrill Grant in Transplantation. ASN also partners with the Halpin Foundation to fund the Halpin Foundation-ASN Research Grant, and with the Association of Specialty Professors (ASP) to fund the ASN-ASP Junior Development Grant in Geriatric Nephrology. These grants help young investigators develop independent research initiatives, hire staff, purchase critical supplies, and other activities that are essential to successful applications for individual federal funding.

Under the leadership of ASN Grants Review Committee Chair Detlef O. Schlondorff, MD, and with the assistance of ASN Grants and Development Associate Evelyn Shapiro, in 2010, ASN awarded nine career development grants to young investigators, seven Student Scholar Grants to medical students, and three M. James Scherbenske Grants to established investigators. ASN also awarded over $200,000 in travel support for Renal Week 2010. For more information on grants and travel support, please visit www.asn-online.org.

Letters

***ASN Kidney News* accepts letters to the editor in response to published articles. Please submit all correspondence to kidneynews@asn-online.org**

Moderate drinking may benefit transplant recipients

It's commonly believed that kidney transplant recipients should refrain from drinking alcohol. Clinicians fear that alcohol might adversely interact with patients' immunosuppressive drugs. Yet moderate alcohol consumption can have positive effects in the general population (e.g., it reduces one's risk of diabetes and premature death).

Dorien Zelle (University Medical Center Groningen, The Netherlands) and colleagues conducted a study to determine whether alcohol's anti-diabetes and survival benefits hold true for kidney transplant recipients as well.

The researchers studied 600 transplant recipients, following them for several years posttransplant. Of these, 288 (48 percent) were abstainers, 94 (16 percent) were sporadic drinkers, 210 (35 percent) had moderate alcohol intake, and 8 (1 percent) were heavy drinkers. Moderate alcohol drinkers were 0.33 times less likely to develop diabetes than other types of drinkers and nondrinkers. During an average follow-up of seven years, 33 (15.7 percent) moderate alcohol drinkers died, whereas 26 percent of abstainers, 24.5 percent of sporadic drinkers, and 25 percent of heavy drinkers died. Moderate alcohol drinkers were 44 percent less likely to die than other types of drinkers and nondrinkers.

These results suggest that drinking moderate amounts of alcohol may protect against diabetes and premature death in kidney transplant recipients, similar to the effects seen in the general population. "To our knowledge, this is the first study to report on alcohol consumption, posttransplant diabetes, and all cause mortality in renal transplant patients," said Zelle. "There seems no reason to advise renal transplant recipients to use no alcohol after transplantation."

The studies "Obesity Is a Risk Factor for Mortality, Especially among Younger Dialysis Patients," "Sudden Cardiac Arrest Risk Associated with Low Calcium Dialysate in Hemodialysis Patients," and "Moderate Alcohol Consumption Is Associated with Low Prevalence of Post-Transplant Diabetes and Reduced Risk for Mortality in Renal Transplant Recipients," were presented at Renal Week 2010.

Recommended dialysate calcium concentration may increase cardiac risk

Another study looked at the effects of recommended dialysate calcium levels that are meant to protect hemodialysis patients, in whom the leading cause of death is sudden cardiac arrest. Because vascular calcification has been linked to increased cardiovascular mortality in hemodialysis patients, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative suggests that the dialysate calcium concentration should be lowered to 2.5 mEq/L among patients who receive oral calcium.

To see whether this recommendation is warranted, Patrick Pun, MD (Duke University), and colleagues studied 502 dialysis patients who experienced a sudden cardiac arrest and 1632 randomly selected matched dialysis patients who did not, comparing the calcium concentrations in patients' dialysis fluids. The investigators found that lower concentrations of calcium in dialysis fluids actually increased patients' risk of experiencing a sudden cardiac arrest. Patients whose dialysate calcium concentration was ≤2.5 mEq/L were 1.5 times more likely to experience sudden cardiac arrest than those with higher dialysis calcium concentrations. Concurrent exposure to QT-prolonging medications and low potassium dialysate conferred additional risk. "This suggests that arrhythmic risks in addition to calcium absorption and bone turnover should be taken into consideration in determining the optimal dialysate calcium prescription," Pun said.

Albumin in Urine Increases Risk for Cognitive Decline

Clinically "Insignificant" Levels Predict Faster Cognitive Decline in Elderly Women

Individuals who excrete even low levels of the protein albumin in the urine are at increased risk of experiencing cognitive decline, according to two studies presented at Renal Week 2010.

Albuminuria and low estimated glomerular filtration rate (eGFR) have both been found to increase an individual's risk of developing cognitive impairment, but the joint associations of these commonly measured kidney disease markers with cognitive decline had not been studied.

Manjula Kurella Tamura, MD (Stanford University, Palo Alto, CA), and colleagues studied clinical data from 19,442 individuals participating in the Renal Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, a nationally representative, population-based cohort of individuals who are 45 years and older. Kidney function was estimated using serum creatinine, and albumin to creatinine ratio (ACR) was measured on a single-voided urine sample, both obtained at baseline. Cognitive function was assessed each year.

A total of 1575 participants (8.1 percent) developed cognitive impairment over an average follow-up of 3.5 years. Individuals with albuminuria (ACR ≥10 mg/g) were 1.23 times more likely to become cognitively impaired compared with patients without albuminuria. Those with eGFR <45 mL/min/1.73 m^2 were 1.36 times more likely to become cognitively impaired compared with those with higher kidney function. Cognitive impairment occurred in 6.7 percent of individuals with neither condition, 10.1 percent of those with albuminuria, 18.8 percent of those with low eGFR, and 13.4 percent of those with both. Compared with individuals with neither condition, those with albuminuria were 1.25 times more likely to develop cognitive impairment, those with low eGFR were 1.78 times more likely, and those with both conditions were 1.41 times more likely.

The results indicate that albuminuria—which is common and potentially modifiable—predicts the development of cognitive impairment independent of low eGFR. "The findings should help clinicians identify patients at high risk for subsequent cognitive decline and dementia," said Kurella Tamura.

Another study found that low levels of albuminuria (<5 µg/mg of creatinine) that are not traditionally considered clinically significant strongly predict faster cognitive decline in older women.

Very few data are available on how the presence of albumin in the urine may relate to changes in cognitive function over time. Julie Lin, MD (Brigham and Women's Hospital, Boston, MA), and colleagues studied more than 19,000 women aged ≥70 years who participated in the Nurses' Health Study and were phoned every two years for three cycles. Participants were tested for general cognition, verbal memory, verbal fluency, and working memory.

The apparent effect of ACR ≥5 µg/mg was cognitively equivalent to that seen with two to seven years of aging. In other words, women with an ACR ≥5 µg/mg at the start of the study experienced cognitive decline two to seven times faster than that attributed to aging alone. The strongest association was seen with a decline in verbal fluency score, which is attributed to progression of small vessel disease in the brain. Lin noted that this is consistent with the theory that albuminuria reflects vascular disease.

"The presence of low levels of albumin in the urine is widely considered to be an indicator of vascular disease as well as a predictor of progressive kidney disease and a risk factor for cardiovascular disease and death. These data suggest that albuminuria may also be associated with quality of life parameters such as cognitive function decline," said Lin. Screening for albuminuria as an independent predictor for subsequent cognitive decline may be warranted in the elderly.

The studies "Albuminuria, Kidney Function and the Incidence of Cognitive Impairment in US Adults" and "A Prospective Study of Albuminuria and Cognitive Decline in Women" were presented at Renal Week 2010.

Intensive Glucose Control in Type 2 Diabetes Protects Kidneys, ADVANCE Trial Finds

By Daniel M. Keller

Intensive glucose control with target HbA1c levels of 6.5 percent or less protects kidney function for patients with type 2 diabetes mellitus (T2DM), according to results of new analyses of the ADVANCE (Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation) study.

Because the risk of end stage kidney disease is 12-fold higher among patients with T2DM, and because renal disease is a strong independent predictor of cardiovascular risk, prevention and management of renal disease has to be a major effort in the care of patients with T2DM.

In the ADVANCE trial, 11,140 patients ≥55 years with T2DM were randomly assigned to standard glucose control or to intensive glucose control using gliclazide MR and other therapy as required to achieve the target HbA1c level. Urine albumin-to-creatinine ratio, a measure of kidney damage, was determined at study entry (baseline), at 24 and 48 months, and at end of follow-up.

The typical transition rate among patients with T2DM from a normal level of albumin excretion in the urine to small amounts (microalbuminuria) to large amounts (macroalbuminuria) is approximately 2 percent per year. Therefore, lead investigator Sophia Zoungas, of the University of Sydney in Sydney, Australia, said the primary endpoint of the trial was new or worsening nephropathy, including new onset macroalbuminuria. Secondary endpoints were new onset microalbuminuria, progression of albuminuria by at least one stage, and regression of albuminuria by at least one stage. Zoungas presented her study results at the 46th Annual Meeting of the European Association for the Study of Diabetes in Stockholm, Sweden, in September 2010.

At baseline, 69.3 percent of participants had normal albumin excretion, 26.9 percent had microalbuminuria, and 3.8 percent had macroalbuminuria. The largest group of patients (40.6 percent) had normal albumin excretion and fell in the middle of the range of kidney function as measured by estimated glomerular filtration rate.

At the final visit at 66 months of follow-up, the intensive blood glucose control group had significantly better glucose control than the standard control group. Both groups started with an HbA1c level of 7.5 percent. The intensive control group reduced that to 6.5 percent, compared with 7.3 percent for the standard control group, a significant reduction of 0.67 percent ($p < 0.001$).

Tighter glucose control translated into better outcomes. "Total renal events were significantly lowest... in favor of intensive glucose control," Zoungas reported. The intensive control group also had significantly less new microalbuminuria, new macroalbuminuria, and new or worsening nephropathy. The prevalence of end stage kidney disease was very low in both groups and did not differ significantly between them.

"Looking at the progression and regression of albuminuria... [there was] a 10 percent further reduction in the chance for progression with intensive glucose control, and if you look at regression of albuminuria there was a 15 percent further likelihood of regression [by at least one stage] in the intensive as compared to the standard control arm," Zoungas said. "There was a 20 percent increase in regression to normoalbuminuria among patients assigned to intensive glucose control."

The effect of intensive control on total renal events was beneficial across all subgroups regardless of baseline HbA1c levels, with an overall risk reduction of 21 percent for all renal events.

In summary, Zoungas said intensive glucose control was associated with a 21 percent reduction in major renal outcomes, a 10 percent reduction in progression of albuminuria, 15 percent regression of albuminuria, and an 11 percent reduction in total renal events.

Therapy to Protect Kidneys Preserves Blood Vessels in Type 2 Diabetes

Patients with type 2 diabetes mellitus are prone to vascular disease in large and small blood vessels, including in the kidney. Intensive therapy to protect the kidneys also has far-reaching benefits in vessels throughout the body, according to findings presented at the European Association for the Study of Diabetes in Stockholm, Sweden, in September 2010.

Using Doppler ultrasound to measure blood flow in small vessels (microcirculation) and ultrasound techniques to measure the thickness of the walls of large blood vessels, the researchers showed advanced atherosclerotic changes ("hardening of the arteries") in larger vessels and decreased microcirculation in the skin of type 2 diabetes patients with nephropathy, compared with patients without diminished kidney function. Large vessel ("macrovascular") disease can eventually manifest as ischemic heart disease or cerebral stroke. After 36 months of therapy with drugs often used to protect the kidneys, further changes in large vessels were prevented, and microcirculatory abnormalities in the skin regressed.

The researchers, led by Malgorzata Waluś-Miarka, MD (Department of Metabolic Diseases, Nephrology, and Internal Medicine, University Hospital Krakow of Jagiellonian University, Krakow, Poland), studied three groups of patients with type 2 diabetes. One group consisted of 48 patients with nephropathy, and a control group of 22 patients lacked any vascular complications. A third group of 25 patients with nephropathy was examined after 36 months of intensive nephroprotective therapy, mainly with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and statins, as well as diet.

The study group, control group, and 36-month study group were well matched for age (mean age 60–64.8 years) and were fairly well matched for diabetes duration (mean age 13.5, 10.5, and 14.2 years, respectively).

As vessel changes progress in diabetes, the vessels become stiffer, more so than in individuals without diabetes. To follow these changes, the investigators used pulse wave velocity. The stiffer the vessel, the faster the pulse wave, similar to the way in which a ping-pong ball would bounce off a concrete floor compared with a carpet. Thickening of the inner and middle walls of arteries is an indication of damage and was assessed using ultrasound. Circulation in the small vessels of the skin of the forearm was measured under various conditions.

The group with nephropathy had significantly higher pulse wave velocities, indicating stiffer vessels, and greater vessel wall thickness in their neck arteries compared with the control group ($p < 0.010$). They also had slower flow in their microcirculation at rest ($p < 0.010$), as well as lower peak flow as blood re-entered the smalls vessels after a restrictive occlusion was released ($p = 0.05$).

Referring to the group that received intensive nephroprotective therapy, study presenter Katarzyna Cyganek, MD, a diabetologist at Jagiellonian University, said, "We detected improvement in microcirculatory flow at three years. . . . We can, after intensive therapy, improve microvascular and macrovascular parameters."

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Policy Update

ASN Testifies at FDA Meeting on Future of ESAs

By Daniel Kochis and Rachel Shaffer

Representatives convened at a crucial Food and Drug Administration (FDA) meeting of the Cardiovascular and Renal Drugs Advisory Committee (CRDAC) recently to determine the future of darbepoetin. ASN Public Policy Board member Wolfgang Winkelmayer, MD, ScD, FASN, presented testimony on the currently available evidence regarding erythropoiesis-stimulating agents (ESAs).

FDA convened the CRDAC meeting to discuss the risks and benefits of the use of ESAs to treat anemia in patients with chronic kidney disease (CKD) based on results from the recent "Trial to Reduce Cardiovascular Events with Aranesp® Therapy" (TREAT). CRDAC reviews and evaluates available data concerning the safety and effectiveness of drug products for use in the treatment of cardiovascular and renal disorders and makes recommendations to the Commissioner of Food and Drugs.

FDA approved darbepoetin in 2001 for the treatment of anemia associated with chronic renal failure, including for patients not on dialysis. In light of TREAT, which failed to demonstrate cardiovascular benefit—and showed risk—when patients with chronic renal failure and anemia were treated with ESAs to target hemoglobin concentrations higher than the current recommended range of 10 to 12 g/dL, FDA requested that the CRDAC provide advice about the benefit-risk profile of darbepoetin, feasibility and necessity of future trials on Aranesp dosing, and on labeling revisions. FDA prepared five specific questions for the panel to vote upon, which will inform FDA's final decision on this issue.

"The TREAT trial evidence raises considerable doubt about the safety and advisability of using darbepoetin in this manner to raise the hemoglobin in patients with anemia associated with CKD," concluded FDA's internal review of evidence in advance of the CRDAC meeting. "No large randomized trial results support the hypothesis that targeting a higher hemoglobin/hematocrit results in an improved cardiovascular or renal outcome."

Prior to voting, CRDAC heard testimony from Aranesp sponsor Amgen; TREAT principal investigator Marc Pfeffer, MD; internal FDA experts; and public speakers including Winkelmayer. Reviewing the implications of currently available evidence, Winkelmayer's testimony focused on three key points.

First, all four large ESA trials have shown that if a population is being treated to a target hemoglobin above the upper limit of the current label, 12 g/dL, no meaningful benefits arise and adverse outcomes may occur. Second, he argued that TREAT does not provide evidence

that would support reducing the current lower range of the labeled target hemoglobin below 10 g/dL. TREAT intended to study a population of patients with advanced chronic kidney disease and anemia, with the expectation that the patients' kidney function and—correspondingly—anemia would deteriorate during follow-up. Thus, the inferences that can be made from TREAT about the optimal label range are limited and any justification for a label change based on TREAT is inherently weak. A comparison of achieved mean hemoglobin concentrations among the four large ESA trials puts the low hemoglobin groups in each of them well within the range of the current label.

Third, adjusting a label to a reduced lower hemoglobin boundary could result in more patients receiving transfusions, thereby reducing their likelihood of receiving and maintaining a functioning kidney transplant. Importantly, lowering the labeled hemoglobin target would put women and minorities at particular risk. Overall, Winkelmayer's testimony on behalf of the society supported the current label, noting that it "is grounded in the best evidence currently available and has been adequate to support individualized treatment decisions among patients and their physicians."

In addition to testimony by Winkelmayer, the panel also heard from other providers and patient advocacy organizations as well as from dialysis patients. Patients primarily urged the panel to strongly weigh quality of life issues when considering any changes to EPO dosing guidelines. One patient told the panel, "I'm hoping, along with hundreds of thousands of kidney patients like me, that the recommendations you make today will not hinder our ability to live full, meaningful, and productive lives."

ASN Public Policy Board member Glenn Chertow, MD, FASN, also testified, answering questions from the panel about what, if any, dosing changes the recent clinical trials support for ESAs. Chertow summarized his commentary by stating, "Patients and their physicians need to balance the known risks of ESAs with the potential benefits, including avoidance of transfusion, when deciding whether or not to use these drugs. Patients awaiting kidney transplantation may be those most likely to benefit from transfusion avoidance."

After hearing testimony, CRDAC considered five prespecified FDA questions relating to darbepoetin dosing guidelines. The first question asked whether based on available evidence the indication for darbepoetin for the treatment of anemia associated with chronic renal failure should be withdrawn; the panel voted 15–1 with one abstention not to withdraw, stating that the scientific evidence available does not support such a move at this time. The panel also voted not to recommend darbepoetin alfa be avoided for all patients with a prior history of stroke. The panel voted no on questions two and four, which asked whether the control arm of the TREAT trial be used as the dose-schedule for use for controlling the anemia associated with CKD in dialysis and nondialysis patients, respectively. Question three asked the panel to describe a prudent approach to designing the next trial for safer use of ESAs in patients with CKD. The panel suggested any future trial would need to study EPO use in patients with CKD versus a true placebo group—an arrangement that, it pointed out, raises serious ethical questions since patients in the placebo group may not suffer unnecessary risks and lower quality of life than the non-placebo group.

While the FDA is not obligated to follow the recommendation of the CRDAC, it is highly unlikely they would not. Following the meeting, current dosing practices remain in effect, with the panel strongly supporting an EPO regimen individualized for each patient through discussions between patients and their physicians on the risks and benefits of drugs that treat anemia associated with CKD. ASN continues to closely monitor the debate over EPO dosing, supporting guideline decisions that take into account patient safety as well as quality of life and the integrity of the patient-physician relationship. To view ASN's complete comments to the CRDAC please visit ASN Public Policy webpage.

Dialysis Facilities Reverse CMS Predictions, Opting for Full Bundle Over Blended Payments

By Rachel Shaffer

Dialysis facilities nationwide overwhelmingly opted to begin receiving a fully bundled payment for dialysis treatments beginning on January 1, 2011. Over 90 percent of facilities elected to be paid entirely under the bundle in 2011, upending the Center for Medicare and Medicaid Services' (CMS) projection that just 43 percent of dialysis facilities would choose the full bundle in its first year, according to a recent survey of nearly 4500 facilities (Table 1). The difference between estimate and outcome will likely affect the amount of the "transition adjustor" payment cut applied to facilities during the phase-in of the bundle (which lasts from January 1 to December 31, 2010).

CMS was required by the Medicare Improvements for Patients and Providers Act (MIPPA) of 2008 to give dialysis facilities the choice of receiving fully bundled payments in the first year of the new bundled payment system, or to transition into the new system over four years, receiving a blended payment amount of what a payment would have been under the current composite rate system and the new bundled payment amount (Table 2). Facilities had until November 1, 2010, to make a one-time election to opt into the fully bundled payment system. Facilities that did not communicate to CMS a choice to receive fully bundled payments will automatically receive the blended payments until the termination of the transition period (January 1, 2014), when all facilities will be paid the bundled amount.

During the transition period, CMS is also required by MIPPA to maintain budget neutrality (to ensure that costs during the transition period are not greater than they otherwise would have been in the absence of a transition). CMS calculated that it needed to impose a 3.1 percent reimbursement rate reduction known as the "transition adjustor" on all facilities—both those paid entirely under the bundle and those receiving a blended payment—in 2011 to achieve budget neutrality. However, these calculations were based on its assumption that just 43 percent of facilities would opt to receive bundled payments.

Because far more facilities will receive fully bundled payments in 2011 than CMS estimated, many in the kidney care community are calling for the agency to revise the transition adjustor. According to recent estimates by the Moran Company—a Washington, DC-based consulting firm—in order to maintain budget neutrality CMS should set the transition adjuster at approximately 0.39 percent, rather than 3.1 percent.

Working with providers and other kidney care organizations, ASN has been advocating for key members of Congress to recalculate the transition adjustor based on the actual number of facilities that will receive blended payments. In late October, eight Senators sent a letter to CMS Administrator Donald Berwick, MD, conveying concerns that a 3.1 percent transition adjuster might have a negative impact on patients and access to quality care if not recalculated.

To access more resources on bundled payments and other coming changes in the Medicare ESRD program, and to read ASN's analysis of the ESRD Final Rule, please visit www.asn-online.org.

Table 1

CMS projection for percentage of dialysis facilities opting into bundled payments in 2011 versus actual facility decisions

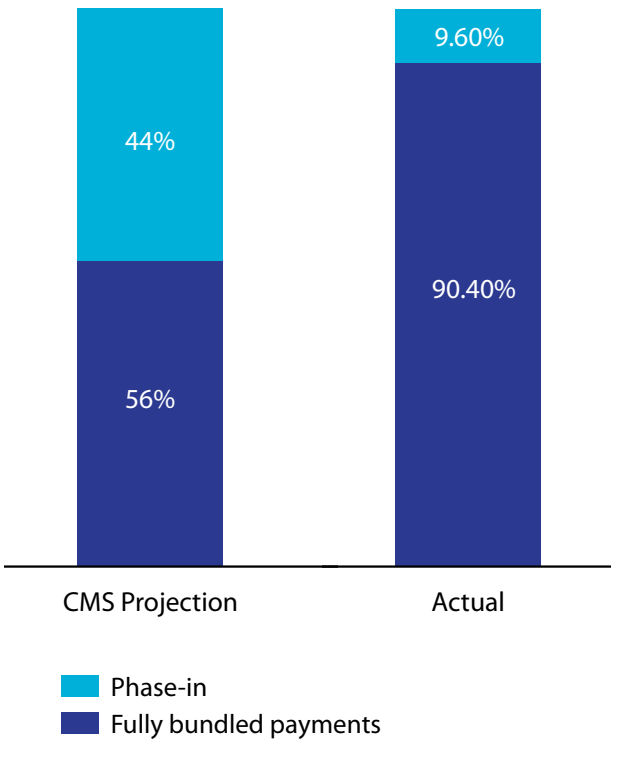
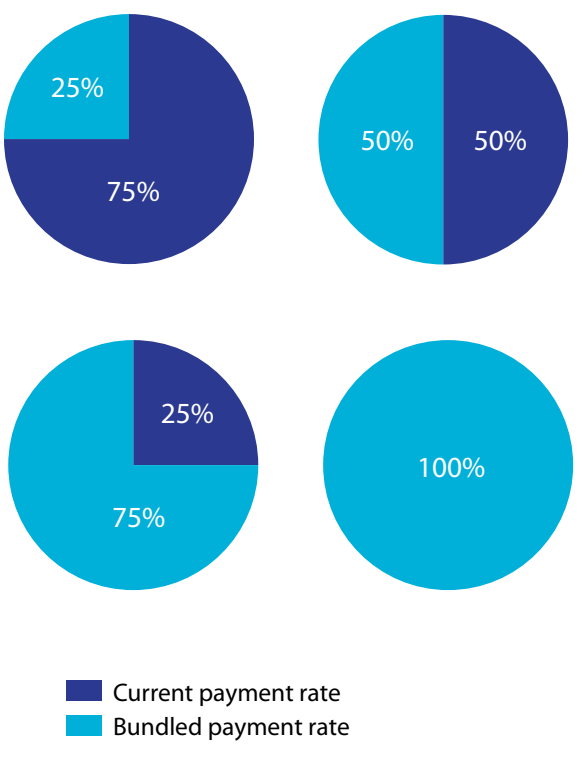


Table 2

Transition period "phase-in" payments



Industry Spotlight

Bicoastal Deal Forms Third Largest Dialysis Company

Liberty Dialysis will combine with Renal Advantage to form the third largest U.S. provider of dialysis services.

This is the latest, largest instance of a merger in this bustling industry. In fact, it was just in January 2006 that Fresenius Medical acquired Renal Care Group, what was then known as the third largest U.S. dialysis provider.

Financial terms of the Liberty-Renal Advantage deal weren't disclosed, and the new company will remain private.

Liberty, which has 112 dialysis clinics, was founded in 2002 by Mark Caputo and Bob Santelli with investment partner Bain Capital. It has received funding from investment firms Bain Capital, KRG Capital Partners, and Ignition Partners. These partners are also contributing to the newly merged company, Liberty Dialysis Holdings, Inc.

Renal Advantage brings to the deal 154 dialysis clinics in 19 states in the Midwest, Southeast, and West.

The dialysis clinics will continue to operate under their pre-merger names.

Together, Liberty, based in Mercer Island, Washington, and Renal Advantage in Brentwood, Tennessee, will employ 5300 people serving more than 19,000 patients in 260 locations in 32 states, according to the *Seattle Times*.

Liberty CEO Mark Caputo, who will remain as top executive of the holding company, said the deal should be complete by year's end. The newly combined company is expecting sales of nearly $1 billion next year, he said.

For context, Dow Jones Newswire noted that Fresenius has projected sales above $12 billion this year, while analysts anticipate DaVita will post sales of $6.4 billion. Fresenius Medical Care North America provides dialysis treatment for more than 128,700 patients and has a network of more than 1700 facilities in the United States, according to the company.

The start of a new Medicare bundled payment method in January makes scale more important, at a time when payments for each patient will become similar, rather than tailored to the specific care a patient receives in dialysis, Caputo said. Because of these regulatory changes, performance-based payments by CMS to dialysis companies are expected to decline by 2 percent next year, industry observers say.

A veteran of the dialysis merger world, Joe Cashia sold the dialysis chain National Renal Alliance to Renal Advantage two years ago. Reflecting on the Liberty-Renal Advantage deal, he told Nashville's newspaper *The Tennessean,* "You've got to be very efficient, and larger providers are certainly able to purchase more efficiently, contract more efficiently, and utilize their labor costs more efficiently."

FDA Focuses on Contrast Agent Effects

This fall, the U.S. Food and Drug Administration (FDA) issued a directive for new warnings on labeling for some contrast agents commonly used during magnetic resonance imaging because of toxicity to kidneys. Contrast agents are used to delineate organs, tissues, and other structures during imaging.

Gadolinium-based contrast agents (GBCAs) now have to carry a warning about "the risk of a rare and potentially fatal condition"—nephrogenic systemic fibrosis (NSF)—if the drug is given to certain patients with kidney disease. Advice for health care professionals wanting to learn more can be found at: http://www.fda.gov/Drugs/DrugSafety/ucm223966.htm

These label changes, which come after a series of earlier but milder warnings, are to help ensure that patients at risk for NSF who receive GBCAs are monitored for symptoms of NSF. "Symptoms include scaling, hardening and tightening of the skin; red or dark patches on the skin; and stiffness," the FDA noted. NSF may also cause fibrosis of internal organs, a condition that can become fatal. Unfortunately, there is no effective treatment for NSF.

Patients at greatest risk for developing NSF after receiving GBCAs have impaired elimination of the drug; this group includes individuals with acute kidney injury or chronic, severe kidney disease (with a glomerular filtration rate <30 mL/min/1.73 m^2). "Higher than recommended doses or repeat doses of GBCAs also appear to increase the risk for NSF," the FDA warned.

Three GBCAs—Optimark, Magnevist, and Omniscan—are associated with a greater risk of developing NSF than other related agents. Thus, the FDA has said these three drugs should not be used in patients with acute kidney injury or chronic, severe kidney disease. The FDA noted several other contrast agents that could be used with care.

The manufacturers of the three contraindicated drugs are dealing with this latest warning in different ways. Covidien, which makes Optimark, said it would voluntarily discourage use of the drug in kidney disease patients, and that effort began in November a year ago. Bayer Healthcare, the manufacturer of Magnevist, said it would respond to the FDA within the 30 days allowed in the agency's letter and that Bayer is "committed to the appropriate and safe use of its products." According to the *Wall Street Journal*, GE Healthcare, which makes Omniscan and similar drugs, said the drugs still are "a valuable diagnostic tool with a proven safety record for the overwhelming majority of patients to whom they are prescribed."

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Journal View

Study Shows High U.S. Rates of Diabetic Retinopathy

More than 25 percent of adults in the United States who have diabetes have diabetic retinopathy, and the rate is even higher for African American patients, reports a study in *The Journal of the American Medical Association*.

The study included a nationally representative sample of 1006 adults aged ≥40 years drawn from the National Health and Nutrition Examination Survey 2005–2008. Diabetes was assessed by self-reported physician diagnosis or glycated hemoglobin (A1c) level of ≥6.5 percent. Retinopathy in both eyes was assessed and graded with the use of digital fundus photographs.

Based on the findings, the prevalence of diabetic retinopathy among adults with diabetes in the United States was estimated at 28.5 percent. For vision-threatening diabetic retinopathy (defined as severe nonproliferative or proliferative diabetic retinopathy or clinically significant macular edema), the estimated prevalence was 4.4 percent.

Diabetic retinopathy was more common in men than in women (31.6 versus 25.7 percent). The prevalence was 38.8 percent in non-Hispanic blacks compared with 26.4 percent in non-Hispanic whites. Rates of vision-threatening diabetic nephropathy were 9.3 and 3.2 percent, respectively.

Factors independently associated with diabetic retinopathy were male sex (odds ratio [OR] 2.07), higher hemoglobin A1c level, duration of diabetes, insulin use, and higher blood pressure (OR 1.03 per mm Hg).

Diabetic retinopathy is a common complication of diabetes that may indicate microcirculatory dysfunction in other organ systems. It also reflects macrovascular complications, and thus may be a useful indicator of the overall impact of diabetes.

This updated analysis draws attention to the high rate of diabetic retinopathy among adults with diabetes in the United States. The risk of this complication, including vision-threatening diabetic retinopathy, is particularly high among African American patients. Improved screening and treatment for diabetic retinopathy may reduce the burden of diabetes-related vision loss. [Zhang X, et al. Prevalence of diabetic retinopathy in the United States, 2005-2008. *JAMA* 2010; 304:649–656].

Gene Variants Affect ESRD Risk in Patients with Diabetes

In Chinese patients with type 2 diabetes, polymorphisms of the protein kinase C-β 1 gene (*PRKCB1*) are independently associated with the risk of developing end stage renal disease (ESRD), according to a study ian *The Journal of the American Medical Association*.

The prospective cohort study included 1172 Chinese patients with type 2 diabetes who were free of kidney disease at baseline. The patients were genotyped for 18 common tag single-nucleotide polymorphisms (SNPs) spanning *PRKCB1*. This gene encodes protein kinase C-β, a molecule involved in cell signaling that has been linked to the development of diabetes-related microvascular complications and cardiomyopathy. The relationship between *PRKCB1* polymorphisms and ESRD risk was assessed under additive, dominant, and recessive genetic models, with adjustment for medications and conventional risk factors.

At a mean follow-up of 7.9 years, the rate of ESRD in this Chinese diabetic population was 7.7 percent. Four common *PRKCB1* SNPs were linked to ESRD.

In a validation cohort of 1049 patients with early-onset diabetes, 14.3 percent developed chronic kidney disease during follow-up. In this group, kidney disease risk was significantly associated with the T allele of rs3760106 and the G allele of rs2575390.

China and Asia are experiencing an epidemic of type 2 diabetes, and Asian patients may be at particularly high risk of diabetic kidney disease. Previous studies have suggested that *PRKCB1* SNPs may contribute to diabetic nephropathy risk.

This study identifies *PRKCB1* gene variants as risk factors for kidney disease in Chinese patients with diabetes. The associations are independent of albuminuria, glycemia, retinopathy, and other risk factors. Further research is needed, possibly including a trial of treatment with ruboxistaurin, a selective protein kinase C-β inhibitor [Ma RCW, et al. Genetic variants of the protein kinase C-β 1 gene and development of end-stage renal disease in patients with type 2 diabetes. *JAMA* 2010; 304: 881–889].

Gene Variants Linked to FSGS Risk in African Americans

Variants in a region of chromosome 22 containing the genes *APOL1* and *MYH9* may contribute to the high rate of focal segmental glomerulosclerosis (FSGS) in African Americans, reports a genome-wide association study in *Kidney International*.

A "dense genome-wide scan" was performed in two small groups of patients with biopsy-confirmed FSGS and no family history: 56 African Americans and 61 European Americans. The analysis used a set of more than one million single-nucleotide polymorphisms included on the Illumina 1M-Duo array, with the goal of seeking common genetic factors with a potentially high magnitude of effect in FSGS cases. The findings were compared with unselected control samples of 1641 European Americans and 1800 African Americans.

No significant associations were found in European Americans with sporadic FSGS. In contrast, FSGS risk in the African American sample was significantly associated with variants in a 60-kg region of chromosome 22 containing part of the *APOL1* and *MYH9* genes.

Risk of FSGS is approximately four times higher in African Americans than in European Americans. The *APOL1* gene—which has undergone recent selective pressure in Africa related to infection with the parasite *Trypanosoma brucei*—was considered a strong candidate gene. Likewise, previous studies have suggested that variation in the *MYH9* gene may contribute to the increased rates of FSGS and nondiabetic end stage renal disease in African American patients.

The *Kidney International* study suggests that a risk allele for FSGS in African Americans may be found within a region of chromosome 22 containing *APOL1* and *MYH9*. The disease-causing variant may be related to an evolutionarily recent "selective sweep" occurring near or at the *MYH9*. locus in the African population. Further study will be needed to establish which variants are causally associated with kidney disease. [Genovese G, et al. A risk allele for focal segmental glomerulosclerosis in African Americans is located within a region containing *APOL1* and *MYH9* *Kidney Int* 2010; 78: 698–704].

Racial Differences in Outcome for Living Kidney Donors

Black and Hispanic living kidney donors experience more medical conditions during long-term follow-up compared with white donors, reports *The New England Journal of Medicine*.

The retrospective analysis included 4650 Americans who had been living kidney donors between 1987 and 2007 and had available follow-up data from a private insurance database. Claims data were analyzed to assess postnephrectomy diagnosis and medical conditions. Long-term health outcomes were compared with the general population, based on the 2005–2006 National Health and Nutrition Examination Survey (NHANES). Postnephrectomy outcomes were also compared in donors of racial/ethnic minorities versus white donors.

Approximately 76 percent of the living kidney donors were white, 13 percent were black, 8 percent were Hispanic, and 2 percent were "other." The median follow-up was 7.7 years. Several postnephrectomy medical problems were more frequent in black living kidney donors than in white donors (adjusted hazard ratios: hypertension, 1.52; diabetes requiring drug treatment, 2.31; chronic kidney disease, 2.32). Similar risk increases were noted for Hispanic living kidney donors. There was no significant racial/ethnic variation in cardiovascular disease diagnoses.

Overall diabetes prevalence among living kidney donors was no higher than in the NHANES general population sample. However, some subgroups had a higher rate of hypertension. The prevalence of end stage renal disease among living kidney donors was <1 percent, but was higher for black donors than for white donors.

There are few data on the long-term medical outcomes of living kidney donors, especially nonwhite donors. This study shows significant racial/ethnic disparities in medical outcomes among living kidney donors, similar to the health disparities in the general population. Although the investigators emphasize that racial and ethnic minority patients should not be discouraged from consideration for living kidney donation, they state: "[T]hese data may increase awareness of variation in long-term outcomes among living donors and of the need for longer in-depth follow-up of demographically diverse living donors." [Lentine KL, et al. Racial variation in medical outcomes among living kidney donors. *N Engl J Med* 2010; 341: 724–732].

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Detective Nephron

Detective Nephron, world-renowned for expert analytical skills, trains budding physician-detectives on the diagnosis and treatment of kidney diseases. L.O. Henle, a budding nephrologist, presents a new case to the master consultant.

Nephron (nervously) My apprentice is late… should be here with a case he has been struggling with.

Henle enters the room looking confused.

Nephron So… what have you got, my friend?

Henle I… have a case for us.

Nephron Why are you confused?

Henle This is a tough one!

Nephron (with ease) Nothing new… pick one abnormal value, and let's take it from there.

Henle A 70-year-old female was seen recently for fatigue and muscle weakness and found to have a serum potassium (K) level of 2.6 mmol/L.

Nephron Good! Hypokalemia is a good start.

Henle (with a curious look) She has known hypertension for the last 10 years. She is not on any diuretics, or any other medications. Did I mention she has had abdominal pain, as well?

Nephron Ahah! This is going to be fun.

Henle Just some more information, if you will allow me, sir…

Nephron (chuckling) No, you've already given me enough.

Henle The medical student couldn't make it today.

Nephron So, it's just you and me, partner.

Henle (smirking) You seem to be in a good mood today. Your coffee must be quite strong!

Nephron Let's go back to your case. Since you evaluated her, what is your biggest worry about her presentation?

Henle Clinically, I was worried about a cardiac arrhythmia, but her electrocardiogram was normal. I was trying to find out whether this abdominal pain was leading to some vomiting episodes. And perhaps her losses are gastrointestinal in origin.

Nephron Maybe she just eats less potassium?

Henle That's not that common. Renal and gastrointestinal losses are more common. Also, a shift is more common from extracellular compartment to intracellular compartment. Things that can do that are insulin, catecholamines, and metabolic alkalosis. She is not diabetic, and she is not in a high catecholamine state (beta adrenergic state). Her urine toxicology screen was negative.

Nephron Great job… let's move on. Why can't she have an insulinoma?

Henle (sarcastically) Of course she could in your world; that's more common than diuretic abuse. However, her sugars are normal, within the 90 to 130 range… so I don't think so.

Nephron You mentioned she had alkalosis?

Henle I'm getting to that point. No, she didn't. But she did have acute kidney injury with a creatinine level of 5.1 mg/dL and BUN level of 89 mg/dL. Her bicarbonate was 23 mmol/L and chloride (Cl) level was 78 mmol/L, with a sodium (Na) level of 134 mmol/L. Her magnesium levels were in normal range.

Nephron As much as I love hyperkalemia without renal injury, I think hypokalemia with renal injury is also fascinating. I strongly urge you to focus on her extracellular fluid status.

Henle I did. Her blood pressure was 80/56 and heart rate was approximately 100 beats per minute. Her hematocrit level is 17 g/dL, suggesting severe volume depletion.

Nephron Are you sure? Go back and check again. It's very important to make sure.

Henle exits, and Detective Nephron decides to make some coffee. Henle returns shortly thereafter.

Nephron You're back.

Henle (excited) Yes, and I have confirmed that she is hypovolemic.

Nephron What are her urine Na and K levels?

Henle Interestingly, they both are low. Her fractional excretion of sodium is <1 percent as well.

Nephron Stop right there. So now you're telling me that the kidney is doing its job correctly. This does not seem like a kidney problem to me.

Henle Correct.

Nephron So what is it?

Henle Well… if I just take her hypokalemia, and since it's not her intake, there are no medications, we ruled out shifts (hormones, alkalosis, adrenergic states), we are then left with increased urine K losses or gastrointestinal (GI) or skin K losses. Again, I confirmed no diuretic use. Given her hypertension, she could have Liddle's syndrome, but that's rare. She could have Conn's syndrome, but her urine K level would be high in that setting. She is not getting amphoterecin B, which would cause it. I doubt we would have another case of adrenocorticotropic

hormone–producing tumor like last time, given she is not alkalotic. However, I think we need to hydrate her first with NaCl and K repletion, then readdress her laboratory data and see if she has any hidden disorders. Her arterial blood gas showed….

Nephron That's enough… I don't need an arterial blood gas measurement or any more laboratory data. To me, this seems to be a GI loss. We're looking in the wrong organ.

Henle leaves to look for other clues.

Nephron Hmm… I doubt this is a kidney problem. The kidney is in prerenal success here. There is appropriate metabolic acidosis, and I think that her acid base status might resolve with hydration… then let's see if we're left with hypokalemia.

Henle returns two days later, looking even more puzzled.

Henle You were right, sir: her kidney function is now normal, but her K level is still within the 2.6 to 3.0 mmol/L range.

Nephron Does she have diarrhea or vomiting?

Henle Neither… that's the confusing part. She does have some intermittently mucus-like loose stools on further questioning, in addition to mild abdominal pain.

Nephron Image her abdomen and ask for a colonoscopy. Something is causing a GI loss in her lower GI tract. Usually with hypokalemia, there are two ways it can proceed: an upper GI problem causing vomiting and subsequent metabolic alkalosis and renal loss of potassium, or metabolic acidosis, a non-gap type due to loose stools and GI losses of potassium.

Henle So… when she first presented, her arterial blood gas showed a pH of 7.38 and a pCO_2 of 38. She had an anion gap of 33 from severe renal failure and lactic acidosis. She had anion gap metabolic acidosis and a metabolic alkalosis. After her renal function normalized, she has diarrhea and a non-anion gap metabolic acidosis.

Nephron, Regardless of those specifics, she has shown you that it's not her kidneys.

Henle Her computed tomography scan of the abdomen showed a rectal mass.

Nephron Aha! You are hiding the right information from me, my friend. Please have her get a colonoscopy soon… she likely has a villous adenoma. Also, have her get an upper GI evaluation including a barium swallow. She might have polyps everywhere!

Henle Sure will!

Henle returns to the office a few days later.

Nephron What do you have for me, my friend?

Henle She had an aggressive tubulo-villous adenoma. She also had multiple polyps in her lower GI tract, but her upper GI tract was spared.

Nephron (confidently) She has McKittrick-Wheelock syndrome.

Henle (surprised) What?

Nephron This eponymous syndrome was first described in 1954. Patients usually have aggressive villous adenomatous polyps in the sigmo-rectal area with diarrhea, dehydration, electrolyte depletion, and acute renal injury. The condition results from elevated adenylate cyclase, cAMP, and prostaglandin E2 levels in the mucosa, which inhibit Na absorption and increase water and Cl secretion. Villous adenomas are usually reported to be 7 to 18 cm and are situated primarily in the rectum. Distal location and large size limit the colon's ability to reabsorb. Usually, patients present with typically watery mucinous tumors. Initially, fluid/electrolyte losses are easily compensated for by increased PO intake and renal regulation. Patients may deny GI disturbances and can be found to pass mucus from the rectum. Sometimes, they present with severe cases like this one, with volume depletion, hypokalemia, and either metabolic alkalosis or acidosis.

Henle Her cancer is being surgically removed, and all her polyps are slowly being removed.

Nephron Remember, this patient presented with hypokalemia. We often assume that just because there is an electrolyte problem, it's the kidney's fault… but this is not the case the majority of the time. Here a systematic approach led us to pursue a GI route, and a prompt diagnosis was made. Well done, apprentice! From an initial diagnosis of hypokalemia, you eventually made a diagnosis of a life-threatening cancer. Always be a good detective. Observe, think, read, and apply. If it doesn't cross your mind, you will never diagnose it. Great case, Henle. Now let's go get some real coffee.

This case was submitted by Mohini Alexander, MD, at New York Downtown Hospital, Weill Cornell Medical Center, New York, NY

Detective Nephron was developed by Kenar Jhaveri, MD, FASN, assistant professor of medicine at Hofstra Medical School and an attending nephrologist at North Shore University and Long Island Jewish Medical Center in Great Neck, NY. The column was inspired by Muthukumar Thangamani, MD, and Alan Weinstein, MD, both of Cornell University, and Mitch Halperin, MD, of the University of Toronto. Send correspondence regarding this section to kjhaveri@nshs.edu or kdj200@gmail.com

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