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## Lowering High-Normal Phosphate Levels Could Benefit Many, Studies Show

lanev

By Timothy O'Brien

owering serum phosphate levels may benefit three groups currently not often targeted for phosphate-lowering therapies, studies show. New dialysis patients, patients with early chronic kidney disease (CKD), and possibly even healthy individuals with no clinical evidence of cardiovascular or renal disease may all benefit from reducing their high-normal phosphate levels.

Taking phosphorus binders reduced the risk of death by 25 to 30 percent among dialysis patients in a study reported in the January 2009 *Journal of the American Society of Nephrology*. New dialysis patients with only modest or even no increase in their serum phosphate levels were among those who showed improved survival rates.

> Two other reports suggest that high-normal phosphate levels may be tied to a

Knowledge of phosphate crystals such as those shown from a 19th century urological dictionary aided yesterday's practitioners. Advanced understanding of phosphates' role in health may change how today's clinicians practice. Courtey History and Special Collections for the Science, UCLA Louise M. Darling Biomedical Librars marker of increased cardiovascular risk, not only in patients with moderate CKD but also in apparently healthy young adults.

Taken together, these studies suggest that phosphorus may be less of a bystander and more of an active player in kidney and cardiovascular health.

### Phosphate Binders Lower Mortality in New Dialysis Patients

"A growing number of publications have suggested that abnormalities of phosphorus metabolism—specifically phosphorus overload—are risk factors for mortality," said Myles Wolf, MD, of the University of Miami Miller School of Medicine in Miami, Fla. "As a result, many nephrologists believe that lowering serum phosphate levels can improve survival in patients with kidney disease, particularly those on *Continued on page 3* 

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### **Obama Health Plan Would Expand Insurance Coverage**

By Eric Seaborg

"hange" was the mantra of President Barack Obama's campaign, and health care was a main arena he pledged to reform.

"The time has come for affordable, universal health care in America," Obama said when he introduced his health-care initiative at the outset of the campaign. However, most observers agree that his plan would expand the reach of health insurance coverage, but not come close to making it universal. His strategy also includes measures aimed at decreasing costs, improving efficiency, and increasing the focus on chronic diseases.

Some experts believe that the intervening economic crisis will force Obama and his strategists to scale back their plans.

"Big-time health reform is very hard to do and given the budget deficit and

economy, it will be even harder to enact something like Obama proposed during the campaign," said Jonathan Oberlander, PhD, associate professor at the University of North Carolina Chapel Hill School of Medicine and School of Public Health. "So during the first year of an Obama administration there is a strong chance health reform will be incremental: expanding SCHIP (the State Children's Health Insurance Program) will be a priority. After that, the administration will have to decide whether to take a risk on ambitious reform that could well fail."

Oberlander published a side-by-side analysis of the health-care proposals of

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### **Important Treatment Considerations**

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**References: 1.** Delmez J, Block G, Robertson J, et al. A randomized, double-blind, crossover design study of sevelamer hydrochloride and sevelamer carbonate in patients on hemodialysis. *Clin Nephrol.* 2007;68:386-391. **2.** Renvela [package insert]. Cambridge, MA: Genzyme Corp; 2007. **3.** KDOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Guideline 5. Use of phosphate binders in CKD. National Kidney Foundation website. http://www.kidney.org/PROFESSIONALS/kdoqi/guidelines\_bone/Guide5.htm. Accessed September 12, 2008.



### Phosphate Levels

Continued from page 1

dialysis. However, this therapeutic strategy has been largely based on opinion-no studies have been done to compare survival in dialysis patients receiving phosphate binders versus no treatment."

To address this gap, Wolf and his colleagues compared mortality rates in two groups of new dialysis patients: 3555 patients who started on treatment with phosphorus binders during their first 90 days on dialysis and 5055 who did not. "This is the group we wanted to study, because if you wait until they've been on dialysis for a long time, just about everybody will develop a high serum phosphorus level leading most of them to be treated," said Wolf. "With new dialysis patients, many will be treated and many will not-that's because their serum phosphorus levels are not yet markedly elevated."

During the first year on dialysis, patients treated with phosphate binders were at significantly lower risk of death-30 percent-than those not treated. When findings were adjusted for factors that would increase the likelihood of receiving phosphate binders, the protective effect was smaller but still significant at 25 percent.

"The survival benefit was independent of the baseline serum phosphorus level and extended even to patients who didn't have high phosphorus levels at all," said Wolf. "In other words, we found that there may be a beneficial effect in groups that currently are not routinely treated, suggesting that perhaps we should consider treating those patients as well."

### **New Links to Vascular Calcification in CKD**

Meanwhile, two studies in the February Journal of the American Society of Nephrology sought to determine whether the relationship between serum phosphate levels and cardiovascular risk might appear earlier in the course of kidney disease, or perhaps even in people with no evidence of renal or cardiovascular disease.

Both studies examined associations between serum phosphate levels and coronary artery calcification. Electron-beam or multidetector computed tomography was used to measure calcium in the coronary arteries. The coronary artery calcium (CAC) score, calculated using the Agatston method, provides an accurate indicator of atherosclerosis. The CAC score predicts the incidence of future cardiovascular events in dose-response fashion.

Researchers at the University of Washington measured serum phosphate levels and CAC in 439 patients with moderate CKD and no clinical cardiovascular disease, drawn from the Multi-Ethnic Study of Atherosclerosis. Serum phosphate concentrations were within the normal range-2.5 to 4.5 mg/dL-for 95 percent of patients. The goal was to assess the relationship between phosphate and CAC, focusing on high-normal phosphate levels.

"High serum phosphorus levels within the normal range have been associated with cardiovascular events and premature death in people with CKD," said Bryan Kestenbaum, MD, a University of Washington nephrologist. "Experimental work suggests that phosphorus causes toxicity by promoting calcification of blood vessels."

The group of patients with moderate CKD had high rates of vascular and valvular calcification. The overall prevalence of coronary artery calcification was 67 percent. Calcification was found in the descending thoracic aorta in 49 percent of patients, the aortic valve in 25 percent, and the mitral valve in 20 percent.

Coronary artery calcification was significantly related to serum phosphate level. For each 1 mg/dL increase in serum phosphate level, there was a 21 percent increase in coronary artery calcification, after adjusting for demographic factors and estimated kidney function. The same phosphate increment was linked to a 33 percent increase in thoracic aorta calcification, a 25 percent increase in aortic valve calcification, and a 62 percent increase in mitral valve calcification.

The association between high-normal phosphate level and CAC was unchanged after adjusting for cardiovascular risk factors or dietary intake. It was stronger among younger patients and among those with better kidney function.

The link between phosphate and CAC was also unaffected by adjustment for 1,25-dihydroxyvitamin D and serum parathyroid hormone levels, both of which could affect phosphate concentration.

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### **Phosphate Levels**

Continued from page 3

### Phosphates Also Linked to Coronary Artery Calcium in Healthy People

The link between high-normal phosphate levels and vascular calcification may extend to healthy people without kidney disease, according to Robert N. Foley, MB, of the United States Renal Data System and the University of Minnesota.

"Among apparently healthy young adults without kidney problems, there is an association between phosphate levels in the normal range and the occurrence of cardiovascular calcification 15 years later," Foley said.

Foley and his colleagues analyzed the relationship between phosphate levels and atherosclerosis in 3015 healthy young adults, mean age 25 years, from the Coronary Artery Risk Development in Young Adults (CAR-DIA) study. Almost all those studied were free of kidney and cardiovascular disease when they underwent measurement of serum phosphate level as part of their baseline evaluation.

When these individuals were reevaluated 15 years later, coronary artery calcification was rated minimal in 3.2 percent of study participants, mild in 4.8 percent, moderate in 1.1 percent, and severe in 0.5 percent. When other risk factors were not taken into account, higher phosphate levels were associated with a lower rate of coronary artery calcification.

But when the findings were adjusted for other cardiovascular risk factors, the relationship between high-normal phosphate levels and CAC became significant. Higher phosphate levels were linked to African-American race, family history of myocardial infarction, and elevated triglycerides. For healthy adults with the highest phosphate levels (greater than 3.9 mg/dL), the risk of coronary artery calcification was increased by 52 percent, compared with those at the lowest level (3.3 mg/dL or less).

High-normal phosphate levels were also linked to some factors considered protective for cardiovascular disease, including younger age, female sex, lower body mass index, higher highdensity lipoprotein cholesterol, and lower systolic blood pressure.

The relationship between phosphate and cardiovascular risk is complex. "It's really a mixed bag of some good risk factors and some bad, and you have to take that into account when you look at the association between phosphate and CAC," said Foley. "High phosphate seems to go with some of the risk factors that you might call metabolic syndrome or syndrome X, but then it goes against other ones as well."

Such risk factor duality was also uncovered in a recent report from the

## Letters

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Framingham Offspring Study. "In our community-based sample, serum phosphate was positively associated with age, female sex, high-sensitivity C-reactive protein, estimated glomerular filtration rate, and total/high-density lipoprotein cholesterol ratio, but it was inversely related to body mass index and systolic blood pressure," said Vasan S. Ramachandran, MD, of Boston University and the Framingham Heart Study.

So far, it is unknown how these apparently diverse mechanisms work to increase cardiovascular risk in people with high-normal phosphate. "Multiple mechanisms might be operating, partly though metabolic syndrome, or partly through another mechanism tied to phosphate that we don't really understand," Foley said.

## Lowering Phosphate Levels in CKD . . . and Before?

The newly discovered links between serum phosphate and CAC suggest a possible benefit of treatments to lower phosphate levels. While there are about 400,000 dialysis patients in the United States, there are estimated to be more than 15 million patients with less severe CKD.

"These patients are typically not considered for treatment with phosphorus binders, which are approved by the FDA only for use on dialysis," Wolf said. "If further studies could demonstrate a similar survival benefit of binders in patients with pre-dialysis CKD, the results could have a significant impact on public health."

Interventions to lower the cardiovascular risk associated with high phosphate levels already exist. Wolf said current dietary phosphate binders are "perfectly acceptable choices" for use in CKD patients.

Still, it is too early to infer that phosphorus is a cause of poor outcome in the CKD or the general population, said Kamyar Kalantar-Zadeh, MD, PhD, a nephrologist at UCLA David Geffen School of Medicine and Harbor-UCLA Medical Center.

"High-normal serum phosphorus, in addition to reflecting reduced kidney function, may be a surrogate of unhealthy lifestyle including unhealthy diet," he said. "Similarly, the observation that intake of any phosphorus binder in dialysis patients is associated with greater survival compared to no binder could be due to confounding by unknown factors—for example, having received better care or being more compliant with medical care. The ultimate approach to remove unknown confounders is randomization in well designed controlled trials."

Kestenbaum agreed: "It is premature to infer that phosphorus itself is the cause of cardiovascular events and especially premature to infer that lowering phosphorus will beneficially impact health."

The findings in healthy adults also remain to be confirmed. However, even if the relationship isn't a causal one, high-normal phosphate might become an important addition to cardiovascular risk screening.

Said Foley: "Even if you don't have a single mechanism tying it all together, you certainly have a group of people at higher risk, after you take into account their other classic risk factors. At least you have another high-risk group that might benefit from intervention."

### Disclosures:

Prof. Adeney, principal investigator of the University of Washington research, has received consulting fees from Genzyme, Abbott, and Shire, Inc., and has received grant support from Amgen, Inc.

Dr. Wolf has received research support from Shire and Honoraria from Genzyme and Ineos.

Dr. Foley's study was performed as a deliverable under a National Institutes of Health contract. Dr. Foley has received consulting fees from Amgen; other authors have also received consulting fees from Amgen or for work on Amgen-sponsored clinical trials.

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## **Essay and Opinion**

## **ASN Kidney News Debuts**

By Pascale H. Lane

### Who are you?

Welcome to ASN Kidney News, your source for information in the world of nephrology.

ASN Kidney News is a magazine. It is not a scientific journal; JASN and CJASN fill that role for the Society. The newsmagazine will cover ASN news and provide other infor-

mation supporting all aspects of the work of kidney specialists, information that is important but not necessarily appropriate for a peer-reviewed journal. *ASN Kidney News* will also provide a venue to expound upon scientific and clinical advances, with more commentary and speculation than a scientific journal can allow. Since taking on this endeavor, I have been asked a

number of questions by colleagues in the kidney world. Here are *ASN Kidney News* FAQs:

### How will ASN Kidney News be delivered?

The magazine will be a print publication starting in January 2009. The first year it will be mailed every other month. We plan to publish monthly beginning with the January 2010 issue.

### Will ASN Kidney News be available online?

For now, a pdf of *ASN Kidney News* will be available online. Ultimately, a website will supplement rather than duplicate the print publication. Many of our graphics will be available for download. Links to other sources will be considered. Our site will provide a lively forum for discussion of everything kidney!

### What is the relationship between ASN Kidney News and Renal Express?

Renal Express, ASN's electronic newsletter, is undergoing some changes at this time. Its relationship to *ASN Kidney News* will be complementary, but has not been finalized as we go to press.

### Will I still get ASN Kidney Daily?

These email updates will be unaffected by *ASN Kidney News*. Some stories may be expanded and updated in the magazine.

### How can I contact ASN Kidney News?

Magazine staff can be reached by email at kidneynews@asn-online.org.

### Can I contribute to ASN Kidney News?

This magazine belongs to you, the members of the nephrology community. If you have an idea for an article or feature, please contact the magazine staff at kidneynews@ asn-online.org. One beautiful thing about a new publication is that we can mold it to be whatever we want! I am a pediatric nephrologist at the University of Nebraska Medical Center. I have done a bit of everything during my career: patient care, bench and clinical research, education, administration, patient and research advocacy, and editorial work. In short, I've experienced what this magazine will cover! I also deal with kidney disease on another level: Our family cat has stage 3 chronic kidney disease (CKD), a leading cause of death in elderly felines. Who knew there were stages of CKD based on estimated glomerular filtration rate for cats!

ASN Kidney News will include some regular features, and others may be added at your request. The following will appear regularly in most issues:

**Essay and Opinion:** Welcome to the kidney soapbox, where controversies and issues can be addressed. Have a strong opinion? Contact us (kidneynews@asn-online. org) and we may give you an audience.

**Policy Update:** Government regulations affect the care of our patients, the education of our providers, and the funding of our researchers. Conventions for approval of drugs and devices can change as well. Learn about proposed and enacted policies that could alter your world.

**Practice Pointers:** Delivering excellent care to our patients is everyone's goal. Sometimes a study or consensus statement will change the standard of care. Others may have developed processes that will improve your practice. Learn ways to improve kidney health care from experts driving the paradigm shifts.

**Journal View:** Read highlights of cutting-edge biomedical research from the journals of the ASN, as well as other publications. It is impossible for you to read everything in the medical literature, but *ASN Kidney News* can help you hit the highlights.

**Trends in Medical Education:** Not just for program directors, this section will include information about maintenance of certification. Issues in fellow education will be included, with contributions from trainees.

**Industry Spotlight:** Pharmaceutical companies, biomedical supply providers, dialysis units, and even insurance companies employ kidney specialists. Learn more about the issues these people face during the development and delivery of drugs, devices, and clinical care.

The six months we have worked on this inaugural issue have been fast, frightening, and fun. We think you will find this magazine a useful addition to your library. It is a work in progress, and it should be what you, the readers, want and need. Once again, please contact us at kidneynews@asn-online.org with your ideas.

Pascale H. Lane, MD, editor-in-chief of ASN Kidney News, is the Helen Freytag Distinguished Professor of Pediatrics at the University of Nebraska Medical Center.



### Health Plan

Continued from page 1

Obama and Republican presidential nominee John McCain in the New England Journal of Medicine during the campaign.

"I think the U.S. health care system would be in much better shape under the Obama plan than it is today," he told ASN Kidney News. "The Obama plan would substantially expand insurance coverage and provide the uninsured with new public and private insurance options. At the same time, it has significant weaknesses, including the absence of both a realistic financing mechanism to pay for expanded coverage and reliable cost controls.<sup>2</sup>

The heart of the plan is an attempt to make health insurance more accessible and affordable through a combination of a new public insurance option, expansion of the SCHIP, employer mandates, tax credits, and greater regulation of insurance companies.

The provision that could stir the most controversy is the promise to introduce a "public plan" that would compete with private insurance plans, and "offer benefits similar to what every federal employee or member of Congress gets," according to the campaign website.

A National Health Insurance Exchange would be created as a mechanism for businesses and individuals without access to other public programs or employer-based coverage to enroll in the new public plan or an approved private plan. Income-based sliding-scale tax credits will be provided for those who need them.

The plan requires that all children have health-care coverage, with young adults up to age 25 eligible to continue coverage through their parents' plans. Expansion of SCHIP will make it easier for more parents to obtain coverage for their children, and individuals will be offered tax credits for purchasing insurance.

Except for the smallest businesses, employers will be subject to a "play or pay" provision, in which they will be required to "offer meaningful coverage or make a meaningful contribution to the cost of quality health coverage for their employees" by paying a percentage of payroll to help fund the national plan.

Small businesses would be eligible for a refundable tax credit for offering an approved health plan, and the government would provide a "reinsurance" pool, which would provide aid when the catastrophic costs of an employee or two threaten the firm's ability to obtain affordable insurance.

Insurance companies would be required to cover pre-existing conditions as a part of making insurance more portable, so patients will be free to change jobs and change insurers in pursuit of the best coverage at the best price.

A study by The Lewin Group, a Virginia-based health-care consulting firm, projects that full implementation of the plan in 2010 would reduce the ranks of the uninsured by more than 50 percent, from a projected 48.9 million to 26.6 million. The study also projects a decline in the number of people enrolled in private plans, resulting from individuals and small businesses electing to enroll in the public plan.

### **Bringing down costs**

A major objective of the plan is to take on health-care costs broadly, with a willing-ness to spend federal dollars in a way that reduces costs across the board.

The most ambitious step is to spend \$50 billion over five years on the implementation of electronic health information systems and records. The Obama plan quotes a Rand Corporation study that the use of electronic health records could save \$77 billion a year in reduced hospital stays, avoidance of unnecessary testing, better drug use, and other efficiencies. The Congressional Budget Office has rejected the Rand numbers, but The Lewin Group estimates that the \$50 billion investment would lead to savings of \$11 billion per year.

Other cost-cutting measures are much less specific, and include expansion of prevention and disease management programs, for example, by requiring that plans participating in the National Health Insurance Exchange be required to use proven disease management programs.

#### Increasing competition

The plan also promises to "lower costs by taking on anticompetitive actions in the drug and insurance companies." The costcutting actions include:

- allowing Medicare to negotiate with drug companies for cheaper prices by amending the 2003 Medicare Prescription Drug Improvement and Modernization Act.
- allowing the importation of drugs from other developed countries where prices are lower.

- preventing drug companies from blocking generic drugs.
- reducing overpayments in Medicare's private plan alternative, Medicare Advantage, which cost the government an estimated 12 percent more than traditional Medicare.
- increasing competition by introducing the public plan in an industry that has become increasingly dominated by large companies, with two companies controlling a third of the national market.

The plan's architects say that, taken together, these cost-containment measures could save about 8 percent of overall health spending, bringing the average annual cost of insurance down about \$2500.

The Lewin Group estimates that together the measures in the plan could lower costs by about \$50 billion a year.

### **Prevention**

The plan also aims to address the country's "epidemic of chronic disease," including obesity, diabetes, heart disease, asthma, and HIV/AIDS. "Our health-care system has become a disease-care system," the plan says, promising to address "underinvestment in prevention and public health.'

The plan is short on specifics or dollar amounts on how this will be done, but notes that "preventive care only works if Americans take personal responsibility for their health and make the right decisions in their own lives-if they eat the right foods, stay active, and stop smoking.'



#### Federal outlays in \$U.S. billions

- 1 The federal government's 2008 fiscal year began in October 2007 and ended in September 2008. while the figures provided refer to government outlays, most of the figures are from estimates that have been updated toward the end of the fiscal year to reflect actual costs more accurately. Still, actual expenditure amounts reported for programs such as Medicare and Medicaid do typically exceed outlays. 2 Additional "bridge" funds of \$67 billion have also been allocated to the Department of Defense to sustain operations through
  - the first half of 2009.
- Source: Bellasco, Amy. "The Cost of Iraq, Afghanistan, and Other Global War on Terror Operations Since 9/11." Congressional Research Service Report for Congress. October 15, 2008.
- 3 Discretionary Security Funding primarily relates to the Department of Defense and Department of Homeland Security's normal operating budgets. Source: Office of Management and Budget FY 2009 Mid-Session Review. Produced July 28, 2008.
- Source: Office of Management and Budget FY 2009 Mid-Session Review
   Medicare and Medicaid figures from OMB FY2009 Mid-Session Review.
- SCHIP = State Children's Health Insurance Program. Note that the Medicaid expense figure only refers to Medicaid payments covered by the federal government. State governments are required to provide additional funding.
- 6 Source: ONB FY 2009 Mid-Session Review.
   7 Source: Congressional Budget Office Cost Estimate. February 11, 2008.
- 8 This number refers to the amount of federal funds that have already been "tapped" by financial institutions. An additional \$4 trillion of support has been approved for use and may be accessed over the following months and years. \*This chart does not include the Citigroup ballout package, which includes a \$20 billion cash infusion upfront and a federal government guarantee on roughly \$277 billion worth of risky assets. Source: Bloomberg. "Follow the \$7.4 Trillion: Breakdown of the U.S. Government's Rescue Efforts." November 24, 2008.

### **Outlook for passage**

The plan's architects say it would cost the federal government \$50 billion to \$65 billion a year when fully phased in, with the up-front costs "more than covered by allowing the Bush tax cuts to expire for people making more than \$250,000 per year." However, the Congressional Budget Office already factors the expiration of these cuts into federal deficit projections, so many observers question this as a funding mechanism. And congressional Democrats have emphasized "pay as you go" rules, requiring spending increases to be offset by revenue increases or compensatory cuts in other budget items.

The current economic climate is expected to restrict federal revenues available for any new programs, but with health insurance premiums doubling in the past eight years and a troubled economy likely to leave more people uninsured, there will also be pressure to act.

#### **Nephrology angle?**

There appears to be little in the plan directed specifically at nephrology, but Jonathan Himmelfarb, MD, director of the Kidney Research Institute and professor of medicine at the University of Washington in Seattle, said that the field would benefit from more widespread health insurance coverage and lower drug prices.

"Most people with chronic kidney disease are unaware that they have [it]. Many people . . . present to the health-care system with advanced disease which is often at that point irreversible. So if the Obama plan allows more people to achieve healthcare coverage early and receive preventive care, that should be beneficial in terms of kidney disease in general," Himmelfarb said. "Dialysis patients, kidney transplant patients, and people with chronic kidney disease are often on so many medications that they fall into what's called the doughnut hole of Medicare part D coverage, and if costs of prescription drugs come down, this may turn out to be beneficial for some patients with kidney disease by eliminating the hole in coverage that they now experience."

But the "big action" from the standpoint of nephrology in 2009 is likely to stem from legislation that has already passed, the Medicare Improvements for Patients and Providers Act of 2008 (MIPPA).

"MIPPA has a number of very substantial provisions around the bundling of care for end-stage renal disease and dialysis, and provisions around reimbursement for education, for prevention, and stage 4 chronic kidney disease that are very important for nephrology practice. MIPPA leaves a lot of discretion in the hands of the secretary of health and human services, as to how these provisions are going to be implemented," Himmelfarb said.

The Hanover

It is hard to divine what Obama's appointment of former Senate majority leader Tom Daschle as secretary of health and human services bodes for MIPPA, but as for the greater agenda, Oberlander said: "The pick of Daschle is a sign that Obama is serious about comprehensive health reform. Daschle favors ambitious reforms similar to those proposed by the president. And it's a sign they are serious about working well with Congress." Daschle's interest in health-care reform extends to publishing a book on the subject in 2008, Critical: What We Can Do About the American Health-Care Crisis.

## **Journal View**

### Tacrolimus Shows Benefits in Class V Lupus Nephritis

Treatment with the immunosuppressive drug tacrolimus hastens recovery in systemic lupus erythematosus (SLE) patients with pure membranous (class V) nephropathy, according to a preliminary study in *Rheumatology*. C.-C. Szeto, MD, and colleagues of

C.-C. Szeto, MD, and colleagues of the Chinese University of Hong Kong performed an open-label study in 18 patients with SLE and biopsy-confirmed class V lupus nephritis. In addition to a tailing dose of prednisolone, all patients received tacrolimus, 0.1 to 0.2 mg/kg/ dL. After 6 months, patients received maintenance therapy with prednisolone and azathioprine. Outcomes were compared with historical controls treated with cyclophosphamide or azathioprine.

By 12 weeks, proteinuria had decreased by 76.2 percent in the tacrolimus group, compared to 47.1 percent in the historical control group. There were no major differences in remission rates; changes in renal function and SLE disease activity were similar between groups. Lupus flares occurred in 4 of 18 patients in the tacrolimus group versus 11 of 19 in the control group.

The results suggest that tacrolimus may offer a safe and effective alternative to conventional cytotoxic therapy for patients with pure membranous lupus nephropathy, including faster resolution of proteinuria and a lower risk of lupus flare. More study is needed to define the long-term benefit and optimal regimen of tacrolimus [Szeto C-C, Kwan BC-H, Lai FM-M, Tam L-S, Li EK-M, Chow K-M, Gang W and Li PK-T: Tacrolimus for the treatment of systemic lupus erythematosus with pure class V nephritis. *Rheumatology* 2008; 47:1678–1681].

### No Difference in Kidney Transplant Outcomes for Black vs. White Canadians

In contrast to disparities in the outcomes of kidney transplantation for African-American versus white patients in the United States, black and white kidney recipients in Canada have similar outcomes, according to a study in the *Journal of the American Society of Nephrology*.

Led by Karen Yeates, MD, of Queens University, Kingston, Ont., Canada, the researchers assessed the outcomes of 5036 renal transplant recipients in Canada, identified from a national registry. The transplants occurred in a group of 20,243 dialysis patients, of whom 3 percent were black and 97 percent white. Blacks were 41 percent less likely to undergo transplantation than white patients.

However, for transplant recipients, there was no racial difference in the risk of graft failure, after adjustment for comorbidity and socioeconomic status. Mortality after transplantation was 51 percent lower for blacks.

Why are the racial disparities observed in the United States not seen in Canada? Yeates speculates that black transplant recipients in Canada may have better access to post-transplant medical care, including immunosuppressive medications. While urging further study, the researchers write, "[O]ur results raise potentially important questions about whether better access to health services for African-Americans would improve outcomes following kidney transplantation in this population." [Yeates K, Wiebe N, Gill J, Sima C, Schaubel D, Holland D, Hemmelgarn B, and Tonelli M: Similar outcomes among black and white renal allograft recipients. J Am Soc Nephrol 2009; 172–179].

### Lowering Blood Pressure Benefits the Very Elderly

For hypertensive patients 80 years and older, treatment to lower blood pressure yields significant reductions in stroke, heart failure, and death, reports a study in *The New England Journal of Medicine*.

The placebo-controlled Hypertension in the Very Elderly Trial (HYVET) included a worldwide sample of 3845 patients 80 or older with persistent hypertension—systolic blood pressure 160 mm Hg or higher. The active treatment group received sustained-release indapamide, 1.5 mg. Those who did not reach a blood pressure of 150/80 mm Hg were further randomized to receive perindopril, 2 or 4 mg, or placebo.

At a median of 1.8 years, blood pressure was about 15/6 mm Hg lower in the indapamide/perindopril group. Active treatment was associated with a 30 percent reduction in fatal or nonfatal stroke (the primary endpoint), including a 39 percent reduction in fatal stroke. Mortality from all causes was reduced by 21 percent, cardiovascular mortality by 23 percent, and heart failure risk by 64 percent. Patients assigned to active treatment actually had fewer serious adverse events than the placebo group.

It has been unclear whether bloodpressure-lowering treatment is beneficial for patients 80 or older. However, the antihypertensive regimen evaluated in HYVET-sustained-release indapamide, plus perindopril if needed-leads to significant reductions in stroke and mortality. These benefits are achieved at a target blood pressure of 150/80 mm Hg, which was reached in nearly half of HYVET patients [Beckett NS, Peters R, Fletcher ÅE, Staessen JA, Liu L, Dumitrascu D, Stoyanovsky V, Antikainen RL, Nikitin Y, Anderson C, Belhani A, Forette F, Rajkumar C, Thijs L, Banya W and Bulpitt CJ, for the HYVET Study Group: Treatment of hypertension in patients 80 years of age or older. N Engl J Med 2008; 358:1887–1898].

### Hemoglobin Affects Quality of Life in CKD

For CKD patients, higher hemoglobin levels are associated with higher scores on measures of health-related quality of life, according to a report in the *Clinical Journal of the American Society of Nephrology.* 

Led by Frederic O. Finkelstein, MD, of Yale University, the researchers looked at the relationship between hemoglobin and health-related quality of life in 1200 patients with stage 3 to 5 CKD. Patients with higher hemoglobin levels scored higher on several quality-of-life tests, including all physical domains of the Short Form-36 questionnaire.

On a kidney disease-specific assessment, general health score also increased with hemoglobin level. The biggest jumps in quality of life were noted at hemoglobin levels of 11 to 12 g/dL, compared to levels under 11 g/dL. The results may help to inform the ongoing debate over the use of erythropoeisis-stimulating agents (ESAs) to treat anemia in CKD. Many nephrologists believe that ESAs improve quality of life, but previous studies of this issue are not reflected in the current guidelines for ESA use.

The authors hope that an upcoming FDA report on the use of patient-reported outcomes to assess health-related quality of life will help nephrologists address the many outstanding questions on ESA use [Finkelstein F, Story K, Firanek C, Mendelssohn D, Barre P, Takano T, Rodd K and Mujair S: Health-related quality of life and hemoglobin levels in chronic kidney disease patients. *Clin J Am Soc Nephrol* 2009; 4:33–38].

plant evaluation. After referral, mean time to waitlisting was 6.6 months for

patients with inadequate health literacy,

with adequate health literacy. There was

no significant difference in the likelihood

nephrologists' perceptions of the patient's

The reasons for the difference in

ability to keep up with posttransplant

referral rate are unknown, although

compared with 2.1 months for those

of being waitlisted.

### **Health Literacy May Affect Transplantation Chances**

Inadequate health literacy is common in ESRD patients and is linked to a lower rate of referral for transplant evaluation, reports a study in the *Clinical Journal of the American Society of Nephrology*.

Vanessa Grubbs, MD, and colleagues at the University of California, San Francisco, administered a brief test of functional health literacy to 62 black and white patients on maintenance hemodialysis. The results suggested an inadequate level of health literacy—"the capacity to obtain, process, and understand basic health information and services to make appropriate health decisions"—in about one-third of patients. Older adults had lower health literacy scores, as did lower-income and less educated patients.

On adjusted analysis, patients with inadequate health literacy were 78 percent less likely to be referred for trans-

Eplerenone Doesn't Lead to Hyperkalemia in AMI Patients with Heart Failure

In acute myocardial infarction (AMI) survivors with heart failure and left ventricular systolic dysfunction, selective aldosterone blockade with eplerenone reduces mortality while avoiding hyperkalemia, according to a trial reported in *Circulation*.

The "Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study" (EPHESUS) included 6632 post-AMI patients with congestive heart failure and a left ventricular ejection fraction of 40 percent or less. Patients received eplerenone, 25 to 50 mg/dL, or placebo in addition to standard therapy.

The eplerenone group had a 4.4 percent absolute increase in risk of hyperkalemia (more than 5.5 mEq/L) and a 1.6 percent increase in more marked hyperkalemia (6.0 mEq/L or greater). The incidence of hypokalemia (less than 3.5 mEq/L) was decreased by 4.7 percent.

The EPHESUS investigators hope their report will alleviate fears that eplerenone may induce hyperkalemia in post-AMI patients with heart failure. They recomcare could have an impact. Inadequate health literacy "may play a potentially important and modifiable role in equitable access to kidney transplantation," the investigators conclude [Grubbs V, Gregorich S, Perez-Stable S, and Hsu C-y: Health literacy and access to kidney transplantation. *Clin J Am Soc Nephrol* 2009; 4:195–200].

mend adding eplerenone to standard treatment for post-AMI patients who also have heart failure," as called for in current U.S. and European guidelines [Pitt B, Bakris G, Ruilope LM, et al, DiCarlo L and Mukherjee R, on behalf of the EPHESUS Investigators: Serum potassium and clinical outcomes in the eplerenone post–acute myocardial infarction heart failure efficacy and survival study (EPHESUS). *Circulation*, 2008; 118:1643–1650].



## **Trends in Medical Education**

## Helping Nephrologists Become Lifelong Learners

By Ronald J. Falk

Adapted from Ronald J. Falk, et al., Clin J Am Soc Nephrol 3: 1238-1241, 2008. doi: 10.2215/CJN.02980608, September 2008



onsider this: Approximately 80 percent of a nephrologist's learning occurs after nine to 10 years of formal training. The implications of this statement for ASN are huge: The Society must provide high-quality learning opportunities for nephrologists throughout their careers, regardless of career focus, level of experience, or learning style.

ASN accomplishes this goal through several means: Renal Week and its offerings of short courses and clinical nephrology conferences, the annual Board Review Course and Update (BRCU), NephSAP, and through partnering with the American Board of Internal Medicine (ABIM) to help nephrologists complete maintenance of certification (MOC).

But first, how can it be that only 20 percent of a nephrologist's learning occurs during those nine to 10 years of formal training?

Throughout their academic experience and professional careers, nephrologists learn within the context of an educational continuum for internal medicine that has four distinct phases. The first phase is the third-year internal medicine clerkship, which in U.S. medical schools lasts on average 10.5 weeks. Given the breadth and depth of internal medicine, it is not surprising that the exposure of medical students to career options in nephrology is limited.

During the second phase, internal medicine residency programs are required to include a "clinical experience in each of the subspecialties of internal medicine"; however, "it is not necessary that each resident be assigned to a dedicated rotation in every subspecialty" (1). It is during the third phase of learning, the two- to three-year nephrology fellowship, that an in-depth understanding of the broad discipline of the kidney in health and disease unfolds.

The fourth phase is the longest and least structured part of the continuum. Postgraduate education (PGE) or continuing medical education (CME), terms used interchangeably, refer to the educational experiences of a nephrologist during the rest of their 30- to 40-year careers. This is the phase during which nephrologists learn about 80 percent of what they will carry with them throughout their careers. ASN, then, has a responsibility to make every aspect of PGE/CME as high quality as possible for all nephrologists.

### **Renal Week**

The centerpiece of the ASN educational program has always been—and always will be—its prestigious annual meeting, Renal Week. One- and two-day PGE courses take place during the first two days of Renal Week, offering 9.25 to 14.25 CME credits for a single course.

The Clinical Nephrology Conferences are held from 10 a.m. to noon and from 2 to 4 for three days of the conference, and official symposia are offered during breakfasts, lunches, and dinners.

A major long-term goal of ASN is to repackage the excellent programs offered at Renal Week to allow for additional opportunities for learning. Through its website, ASN can disseminate programs based on Renal Week to ASN members and others. Potential learning tools include webinars, audio files, and streaming video. As with sessions offered during Renal Week, these learning tools must provide nephrologists CME credits to maintain state licensure and MOC points to help complete recertification by ABIM.

### **Renal WeekEnds**

Busy nephrologists, with ever-increasing demands on their time, may not have the time to attend Renal Week. Renal WeekEnds provide an opportunity for those who could not attend Renal Week to catch up on what they missed in a distilled version of the meeting that happens over one and a half days. Participants in one Renal WeekEnd earn 12 CME credits.

Renal WeekEnds also appeal to those who attended the annual meeting. Because Renal Week's sessions occur simultaneously, participants simply cannot attend them all. Enter Renal WeekEnds, which offer a way for individuals to catch up on sessions they could not attend at Renal Week.

The time constraints of Renal Week-Ends will drive ASN to create enhanced opportunities for learning at these sessions in the near future. Moving into the digital era, for example, ASN will continue to refine the organization of Renal WeekEnds, which will increase the interaction among participants, speakers, and co-chairs. As with Renal Week, Renal WeekEnds will provide opportunities for learning through downloading digital files from the ASN website.

### **Board Review Course** and Update

The Society's BRCU provides participants a superb update in nephrology as well as preparing them for initial certification or MOC examinations by ABIM. Moving forward, ASN is aware of

the need to focus on those who attend

BRCU for an update. The course's faculty makes a point of separating "Pearls for the Boards" from the evolving and sometimes controversial "Updates." ASN is increasing the quality of content testing material used during BRCU, in order to provide both updates and preparation for ABIM examinations. Likewise the answer key to the BRCU practice exam will be expanded to include a detailed discussion of the rationale supporting the correct answers.

As with other ASN educational materials, BRCU will begin to develop a presence on the Society's website.

## ASN and Maintenance of Certification

Several organizations are responsible for evaluating the quality of nephrologists during the PGE/CME phase of their careers, including ABIM, the Accreditation Council for Continuing Medical Education (ACCME), and the Federa-



tion of State Medical Boards (FSMB). FSMB licenses physicians to practice in their respective states, districts, or territories in the United States. To remain licensed, physicians must pursue CME throughout their careers. ACCME accredits CME providers, such as ASN and most other specialty societies.

ABIM evaluates general internists after their residency training and nephrologists after their fellowship training. General internists and nephrologists must renew their certificates through ABIM's MOC program every 10 years. To complete MOC, a nephrologist must maintain an unencumbered medical license through FSMB; demonstrate self-evaluation of medical knowledge; pass "a secure computer-based, cognitive examination" administered by ABIM; and measure aspects of his or her practice, reflect on these results, and consider how he or she can improve based on this feedback (2).

ASN partners with ABIM to help nephrologists complete two parts of MOC: self-evaluation of medical knowledge and self-evaluation of practice performance.

Nephrologists have largely relied on NephSAP to evaluate their medical knowledge. NephSAP combines challenging questions based on case vignettes and a detailed syllabus that reviews recent publications. Taken together, the vignettes and syllabi are intended to help nephrologists self-assess their strengths and weaknesses in nephrology.

During a two-year period, the editors of NephSAP address 12 distinct topics in nephrology. Eight of these issues, such as chronic kidney disease, are core aspects of nephrology, whereas four issues cover variable topics such as renal imaging. Audio versions of NephSAP launched on ASN's website in October 2008 allow some nephrologists to offset their "windshield time" between dialysis centers and hospitals.

In addition to NephSAP, part 2 of MOC can also be achieved by attending the two-day recertification review course that is part of Renal Week. Advances in internal medicine and nephrology are reviewed using update modules developed by ABIM. Case vignettes followed by questions are reviewed by an expert panel.

To complete part 4 of MOC, nephrologists use ABIM's Practice Improvement Modules (PIMs). According to ABIM, a PIM is a "web-based evaluation and improvement tool focused in a clinical area relevant to the physician's practice, such as diabetes, hypertension, or hospital-based care."

ABIM currently offers PIMs in seven areas, including chronic conditions, prevention, and communication. ASN has started to work with ABIM to develop PIMs in areas of greatest interest to nephrologists, such as chronic kidney disease and dialysis. Ideally, directors of nephrology fellowship training programs will also consider using nephrologyrelevant PIMs as teaching and evaluation tools for fellows.

ASN is committed to helping ABIM develop PIMs and related tools for nephrologists, producing self-assessment materials for nephrologists, and providing nephrologists credit for CME through the Society's educational activities. In addition, ASN will continue to ensure that the organizations responsible for evaluating the quality of PGE/CME think creatively about assessment tools that work in the real world for every nephrologist.

### **Challenges and Opportunities**

The ASN educational enterprise currently includes synchronous (learners and teachers are in the same place at the same time) learning opportunities such as Renal Week, Renal WeekEnds, and BRCU. ASN is also now adding asynchronous (for example, web-based) learning to Renal Week, Renal Week-Ends and BRCU.

ASN is committed to developing as many ways as possible for helping nephrologists earn CME credits and MOC points. At the same time, the Society must develop a strategy for dealing with several challenges. The Society must produce educational material that is relevant for all types of nephrologists, such as those interested in acute kidney injury, dialysis, or transplantation. Each subspecialty within nephrology is well-represented by organizations that meet the needs of that constituency. So ASN's educational offerings must appeal to general nephrologists and every subspecialist within nephrology as well as link the renal community from an educational perspective.

ASN must also address efforts to centralize, and possibly homogenize, the first three phases of the educational continuum (medical school, internal medicine residency, and nephrology fellowship). Today's physicians-in-training must master the six core competencies required by the Accreditation Council for Graduate Medical Education (which accredits residency and fellowship programs) and the American Board of Medical Specialties. Four of these competencies (medical knowledge, patient care, professionalism, and interpersonal skills and communications) are familiar to previous generations of physicians. But competencies for systems-based practice and practice-based learning and improvement are relatively new.

The fourth phase of the educational continuum (PGE/CME) will offer the primary mode for ensuring the competence of nephrologists. ASN must balance the responsibility to help all nephrologists meet the expectations for CME and MOC throughout their careers with the need to appeal educationally to the myriad subspecialists within nephrology.

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Ronald J. Falk, MD, is director of the North Carolina Kidney Center and chief of the Division of Nephrology and Hypertension, University of North Carolina School of Medicine, Chapel Hill, NC.



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## **Renal Week 2008: News and Analysis**

Philadelphia hosted 13,000-plus kidney specialists at ASN's Renal Week November 4–9, 2008. Our eight-page special section reports on top findings from the meeting, which focused on "Translating Basic and Clinical Science into Advances in Prevention and Treatment of Kidney Disease."

Our articles start here, with more extensive coverage by subject area on pages 12–18. Also be sure to see our

update on the policy sessions at Renal Week, which highlighted performance measures, MIPPA, and public health, on pages 24–25.



## Stents best for short-term heart disease survival in kidney patients; bypass surgery best over long term

Drug-eluting stents provide the best one-year survival for patients with kidney disease who also must be treated for heart disease, but bypass surgery provides the best long-term survival, according to a study by Charles Herzog, MD, and Craig Solid, MS, of the Cardiovascular Special Studies Center at the United States Renal Data System (USRDS) in Minneapolis, Minn.

Coronary artery disease and other cardiovascular diseases constitute the single largest cause of death in kidney disease patients on dialysis. Therapies used to treat these patients include heart bypass surgery and stents, or scaffolds placed into narrowed coronary arteries. Many stents used today are drugeluting, slowly releasing drugs that block clots from forming.

Despite the widespread use of these therapies, it is unclear which is best for treating patients with coronary artery disease in patients with kidney disease, so the investigators analyzed information housed in the USRDS to see whether different therapies resulted in different survival outcomes. They found data from 2003 to 2005 on 13,066 dialysis patients undergoing their first coronary revascularization procedure after developing advanced kidney disease. Of these patients, 3665 received coronary bypass surgery, 6164 received drug-eluting stents, and 3237 received non-drug-eluting stents.

The investigators found that drugeluting stents were associated with the best one-year survival, but long-term survival was best in patients receiving bypass surgery. The survival advantage of surgery was increased with greater numbers of arteries bypassed.

"As this study shows, there is no simple answer to which revascularization procedure is best in dialysis patients," Herzog said. "Different patients might view the information, when presented to them by their counseling physician regarding treatment options, in different ways." For example, patients who wish to maximize their chance of better shortterm survival with fewer in-hospital risks might choose drug-eluting stents. Other patients may choose to maximize their long-term survival while risking higher in-hospital complications.

The study, "Long-Term Survival of U.S. Dialysis Patients after Surgical Bypass or Percutaneous Coronary Stent Placement in the Drug-Eluting Stent Era" was presented as part of the Renal Week session on "Effects of Traditional and Nontraditional Risk Factors on Cardiovascular Risk in Chronic Kidney Disease and End Stage Renal Disease."

## Low Potassium Diets Related to High Blood Pressure

Low levels of potassium in the diet may be as important a contributor to high blood pressure as high levels of sodium—especially among African-Americans—researchers have found.

"Lowering salt or sodium in the diet to lower blood pressure is relatively well known, but more publicity on increasing dietary potassium is needed," said lead author Susan Hedayati, MD, at the University of Texas Southwestern Medical Center in Dallas and the Dallas VA Medical Center.

Hedayati and her team studied whether low potassium intake, independent of sodium intake, was associated with increased blood pressure. They analyzed the fasting blood and first-void urine samples and blood pressure of more than 3300 multi-ethnic participants of the Dallas Heart Study, about half of whom were African-Americans.

Results showed that the lower the potassium in the urine, and thus in the diet, the higher the blood pressure. This relationship remained significant even after controlling for cardiovascular risk factors and the



degree of kidney

> function. The effect of potassium on blood pressure was even stronger than the effect of sodium.

Additional research led by Chou-Long Huang, MD, a co-author of this study, suggests that a specific gene, called WNK1, may be responsible for potassium's effects on blood pressure. Hedayati, Huang, and their team are currently testing how low dietary potassium affects blood pressure through the activity of this gene.

"This study highlights the longsuspected beneficial effects of dietary potassium on blood pressure regulation," said Levi Moshe, MD, of the University of Denver's Division of Renal Diseases and Hypertension. "Now, studies to identify the mechanisms involved will be most interesting and important."

The study "Dietary Potassium Deficiency Is Independently Associated with Increased Blood Pressure in a Multi-Ethnic Population-Based Cohort" was presented as part of a free communications session on "Clinical Aspects of Hypertension in Kidney Disease" at Renal Week.

### Preventing End Stage Renal Disease with Combination Drug Treatment in Patients with IgA Nephropathy

A combination of steroids and a blood pressure-lowering drug better prevents end stage renal disease (ESRD) than a blood pressure-lowering drug alone, researchers suggest.

IgA nephropathy (IgAN) is a form of inflammation in the kidneys and is the most common cause of chronic renal failure. Recent studies have shown that steroids improve renal survival and reduce excess protein in the urine in IgAN individuals with moderate protein in the urine and normal renal function. Moreover, long-term use of the blood pressure-lowering ACE inhibitors (ACEi) has been shown to reduce the risk of ESRD in IgAN individuals with excess protein in the urine.

"This new study shows that a definite therapeutic approach has been established for IgAN patients," said Francesco Schena, MD, FASN, professor of nephrology at the University of Bari, in Bari, Italy, and chief of the research group conducting the study. Researchers assessed whether the combination of the oral steroid prednisone and the blood pressure-lowering drug ramipril is more effective in individuals with IgAN than ramipril alone. Forty-eight individuals received the prednisone plus ramipril, while 49 individuals received ramipril only.

Fewer individuals receiving prednisone plus ramipril developed ESRD (2.1 percent) than did individuals receiving only ramipril (16.3 percent), after eight years. Individuals receiving combination treatment also had better renal survival (97.7 percent) than individuals receiving only ramipril (69.9 percent) in the long-term follow-up.

The findings from the study, "Long-Term Prospective Randomized Controlled Multicenter Trial on Steroids Plus Ramipril in Proteinuric IgA Nephropathy," were presented as part of the Renal Week session on latebreaking clinical trials.

### **Renal Week: News and Analysis**

# Improving Kidney Patients'

### Behavioral Therapy Found Effective for Treating Depression in Hemodialysis Patients

Depression is common among individuals on dialysis for kidney disease, but researchers have found that behavioral therapy can significantly improve these patients' quality of life.

Patients undergoing hemodialysis are taxed both physically and mentally, and 20–30 percent become depressed. Many of these



individuals are at increased risk of becoming hospitalized, developing other diseases, and even dying.

Ricardo Sesso, MD, and his colleagues at the Federal University of Sao Paulo, Brazil, set out to determine if psychological therapy might help these individuals. They studied 85 patients with end stage renal disease who were on he-

modialysis and had been diagnosed with depression. Half of the patients underwent three months of weekly 90-minute sessions of cognitive-behavioral therapy that focused on strategies to cope with kidney disease treatment and its effects on daily life. The other half received routine dialysis care without behavioral interventions.

After three months, questionnaires were given to the participants, and the group receiving cognitive-behavioral therapy reported a significant improvement in quality of life compared with the control group. These differences persisted after six months of intervention.

"Cognitive-behavioral therapy is a relatively cheap, harmless, and practical intervention that improves depression, the main psychological problem of dialysis patients," said Sesso.

Others noted that more research is needed to determine therapy's effects on hospitalizations and mortality.

"This is an important study since it represents the first randomized controlled trial of therapy for depression of dialysis patients," said Fred Finkelstein, MD, of the Renal Research Institute in New Haven, Conn. "Whether the improvement in depressive symptoms with cognitive-behavioral therapy translates into improved outcomes for patients in terms of mortality and hospitalizations remains to be determined."

The study, "Effectiveness of a Cognitive-Behavioral Therapy in Hemodialysis Patients with Depression," was part of the session on "Epidemiology, Outcomes, and Clinical Trials in Dialysis."

### Daily Physical Activity Predicts Postdialysis Fatigue

H emodialysis patients who were more physically active had less postdialysis fatigue (PDF) compared with less active patients in a study of patients undergoing maintenance hemodialysis thrice weekly. The amount of physical activity on the day after dialysis was most predictive of PDF, whereas the level of activity on the day of dialysis was not.

The fatigue following dialysis is not well understood but is one of the most debilitating of hemodialysis-related symptoms. It affects a large proportion of patients, may last as short as an hour or more than a day, and may be mild or severe. Up to now, no one has known if physical activity has any effect on PDF, said Patricia Gordon, PhD, RN, adjunct assistant professor in the department of medicine at the University of California, San Francisco. So she and her colleagues performed a retrospective study to investigate the extent to which daily physical activity may be associated with PDF in patients on conventional hemodialysis.

Patients originally participated in the Nandrolone and Exercise Trial, involving men and women undergoing maintenance hemodialysis thrice weekly. Participants were compliant with dialysis and had adequate dialysis delivery. Frequency, severity, and duration of PDF were assessed by questionnaires. Accelerometers, devices that measure motion of the body in three planes, measured physical activity.

The 25 patients (16 male) had a mean age of 54 years, were 56 percent African-American, 32 percent Asian or Pacific Islander, and the rest white. They had been on hemodialysis a mean of 21 months, and the mean hematocrit was 35.1 percent.

Sixteen percent of patients reported that they experienced PDF occasionally; 20 percent, often; and 40 percent, very often. The intensity ranged from none to very severe, with 28 percent rating the intensity as moderate; 24 percent, severe; and 8 percent, very severe. Most PDF lasted a "short" or "moderate" time (combined, 56 percent of responses), but 24 percent of patients said it lasted a "long" or "very long" time.

PDF was significantly associated with less physical activity (P=0.004), more months on dialysis (P=0.02), and lower Kt/V (P=0.03). It was not significantly associated with hematocrit (P=0.11), but there was a trend toward association with lower hematocrit.

The researchers said that 88 percent of the people in the study reported some degree of PDF. The more physically active participants reported less fatigue, and average daily physical activity correlated most strongly with PDF. The level of activity on the day after dialysis predicted PDF whereas the level on dialysis days did not. The investigators speculated that dialysis days may cause some patients to be more active and some less, which could affect their feelings of fatigue.

Gordon said other researchers have studied PDF in conjunction with vari-

ables other than exercise. "Postdialysis fatigue has been associated with ultrafiltration rates, osmolar flux, biocompatible and incompatible membranes," she said. "But when researchers have manipulated those factors, it hasn't really led to a complete amelioration of the symptom."

She said her study suggests that "encouraging patients to be more physically active may decrease their postdialytic complaints because fatigue is very subjective, and it covers a wide range of not feeling well . . . The next step would be to have an intervention to increase physical activity and see then if that ameliorated postdialysis fatigue to any extent."

Gordon noted that some dialysis units have intradialytic exercise programs involving stationary cycling while being treated. Such programs are somewhat difficult to implement and require more staff attention, "but those that are in place, I think are successful," she said.

Gordon presented her results at a poster session titled "Dialysis: Non-Cardiovascular Outcomes and Clinical Trials I."

### **Exercise Improves Function and Quality of Life for ESRD Patients**

By Daniel M. Keller

Exercise may benefit patients with end stage renal disease (ESRD) by improving their functional independence, resistance to disability, and survival of acute stressors.

Exercise is often broken down into endurance exercise, such as walking or running, and resistance exercise. Endurance exercise can be quantified as peak oxygen uptake or aerobic capacity. Resistance exercise is more about strength or muscle power.

Kathy Sietsema, MD, professor of medicine at the David Geffen School of Medicine at the University of California, Los Angeles, and chief of respiratory and critical care medicine at Harbor-UCLA Medical Center in Torrance, Calif., explained that energy production in muscles depends on the body getting oxygen from the atmosphere into the lungs, to the bloodstream, into muscles, and to the mitochondria.

"There are multiple points in this system where patients with renal disease can have impairments, and impairment anywhere along the line can reduce the maximum rate of oxygen uptake or the maximum level of exercise that can be sustained," she said. Sietsema spoke on "Exercise Interventions in ESRD: Can We Improve Function, Quality of Life, or Survival?" at the symposium "Exercise, Physical Function, and Quality of Life in Patients with ESRD."

Oxygen uptake  $(VO_2)$  is measured as mL/min/kg. Maximal  $VO_2$  decreases with age even in healthy people, "so that [when] you get up to the 80s, you might see people with peak  $VO_2$ s around 18 or 20 mL/min/kg," Sietsema said.

Several studies have reported maximal VO, levels in people with end stage renal disease. Epoetin treatment has tended to have an effect on peak VO, in a number of studies, "but it didn't normalize exercise capacity, and it didn't even increase exercise capacity as much as one might expect it to if the sole limitation to exercise function were the anemia or the cardiovascular system," Sietsema said. In a study of 193 ESRD patients from about age 20 to 80 years on hemodialysis, the majority had a peak  $VO_2 < 20 \text{ mL/}$ min/kg across the entire age range. This value is close to that of an 80-year-old healthy but sedentary woman.

The clinical implications are apparent. "Exercise capacity is related to both survival and to function," she said. Among patients with ESRD, 35 percent of patients reported exercising "almost never or never." In a year's follow-up, "the investigators found that mortality rate was considerably higher in those who answered the question that way than in patients who answered it in any other way," Sietsema said, "suggesting that exercise behavior is related to survival in this population."

In another study of 175 high-functioning ESRD patients, those above the median VO<sub>2</sub> value of 17.5 mL/min/ kg had significantly better survival than patients below the median over a period of almost 1600 days.

Neither of the two studies says whether changing exercise behavior would have any effect on survival. Besides exercise capacity, physical functioning was also found to correlate strongly with peak  $VO_2$  among community dwelling elderly adults.

Studies have shown that frailty and disability are dynamic states, and "people move not only to higher levels of disability, but it's also possible to move in the other direction," Sietsema said. Periods of decreased physical activity, such as hospitalization, are among the most common causes of a shift to a lower level of function or increased frailty. "One of the best predictors of the ability to recover independence after a period of disability was the preceding habitual activity level," she said. While this concept may seem self-evident, it provides a scientific basis for the field of rehabilitation.

Exercise interventions can prevent disability. Sietsema cited a study in which patients with osteoarthritis of the knee were assigned to a control group or to aerobic or resistance exercise groups. Over 18 months, about half of the control group lost at least one activity of daily living whereas only about 30 percent of patients in the exercise groups did so (P = 0.03 for resistance exercise group versus control; P = 0.01 for aerobic exercise versus control; and P = 0.006for both exercise groups versus control). "This study is important because it is one of the few that actually demonstrates that an intervention can change the natural history of disability," Sietsema concluded.

In a review of studies of endurance exercise training in ESRD patients, Kirsten Johansen of the San Francisco VA Medical Center showed that the vast majority of the studies demonstrated a significant



the average peak increase in  $\mathrm{VO}_2$  was only 17 percent.

In a small pilot study of intradialytic cycling exercise three times a week, Storer et al. (*Nephrology, Dialysis Transplanta-tion* 2005; 20:1429–1437) showed that this intervention significantly improved "strength, fatigability, and power." An additional finding was an increase in strength, contrary to general findings in healthy people, where strength and endurance training are viewed as very separate processes.

It turns out that increasing peak  $VO_2$  by a small amount (e.g., 17 percent), can increase the endurance exercise time greatly. In daily living, this increase may translate into a patient being able to walk to a bus stop, shop in a warehouse store, or even play golf.

"I think that there are correlations between what we measure in the lab and what people really care about, the activities that people do," Sietsema said. "And there's beginning to be literature that suggests that we can improve these distal endpoints that really matter by the things that we learn from basic exercise physiology."

### Itch Diminishes Hemodialysis Patients' Quality of Life

Uremic pruritis, or itch, can significantly diminish quality of life and interfere with sleep, work, and social interactions for a large proportion of hemodialysis patients, according to findings from two poster presentations at the ASN annual meeting.

Pruritus "is a horrible thing . . . . It's one of the most debilitating facets of the disorder," said Adrienne Ste. Marie, director of project management at Acologix in Hayward, Calif. Moderate to extreme pruritus affects about 40 percent of hemodialysis patients in the United States. Besides diminishing quality of life, it can also shorten lives. The Dialysis Outcome and Practice Patterns Study reported that associated sleep disturbances increased mortality (P <0.0001), so the condition is not just a matter of "itch."

According to lead authors Michael Germain, MD, of Western New England Renal and Transplant Associates in Springfield, Mass., and James Tumlin, MD, of the Chattanooga Kidney Center and the University of Tennessee in Chattanooga, this investigation, the ITCH National Registry, is the first longitudinal observational study of uremic pruritus.

Using multiple instruments of health-related quality of life, the researchers reported on temporal and spatial patterns of itching and on quality of life issues related to pruritus.

The 103 patients in the multicenter study were  $\geq$ 18 years old (mean = 56), on hemodialysis three or more times per week, and had an itch severity >10 mm on a visual analog scale (VAS; 0 = no itching, 100 mm = worst possible). They had had end stage renal disease for a mean of 4.1 years. The study population was two-thirds African-American, reflecting the demographics of the study sites in the southeastern United States.

Participants completed SKIN-DEX-10 and Brief Itch Inventory (BII) surveys. SKINDEX-10 includes questions about occurrence of itching, a mood domain (annoyance, depression, or embarrassment about itching), and a social domain (influence of itching on interactions with people, desire to be with people, and effect on work or enjoyable activities). BII asks about mood and interference with work, sleep, enjoyment of life, and relations with other people. Patients also completed the Beck Depression Index and the Medical Outcomes Survey Sleep Questionnaire.

Despite relatively well-controlled calcium, phosphate, PTH, and Kt/V (mean = 1.69), patients had a high degree of itching, with a median worst nighttime score on the VAS of 60 mm. Both SKINDEX-10 and BII scores reflected lower health-related quality of life, including changes in mood, sleep, and social function with each 10 mm VAS increase of itch intensity. The researchers concluded that even small reductions in itch intensity could improve patients' quality of life.

The same patients also completed surveys of itch patterns using body diagrams. The majority (59 percent) of patients had had pruritus on a daily or nearly daily basis for more than one year, and 41 percent had it this frequently for more than five years. The spatial pattern of pruritus was unique to each patient. Over 12 weeks of follow-up, itch intensity fluctuated for many patients, appeared to be cyclical for some, and rarely disappeared if the initial VAS intensity score was >40 mm.

The investigators concluded that uremic pruritis tends to be unremitting in frequency but may fluctuate in intensity over weeks to months. They also said the spatial pattern suggests a neurogenic process and is not consistent with calcium-phosphate deposition in the skin or other local causes. Ste. Marie added that itch did not correlate with dialysis days.

The poster sessions were titled "Correlation between Uremic Pruritis Intensity and Quality of Life: A Report from the ITCH National Registry" and "Temporal and Spatial Patterns of Uremic Pruritis: A Report from the ITCH National Registry."

**Disclosure:** Ste. Marie's employer, Acologix, has a kappa opioid agonist (TRK-820) in clinical development to treat pruritus.

## CHECH ICON



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### **Quality of Life**

Continued from page 13

### Kidney Stones Tied to Increased Risk of Chronic Kidney Disease

Kidney stones are an important risk factor for chronic kidney disease (CKD), researchers found when they studied the records of all residents of Olmstead County, Minn., over a 20-year span.

Kidney stones are known to lead to CKD in patients with rare genetic diseases, but their role as a risk factor for CKD in the general population had been less clear. Researchers generally thought that complications of kidney stones only rarely cause CKD; however, few long-term studies looked at the question.

John Lieske, MD, and his colleagues at the Mayo Clinic in Rochester, Minn., looked at the clinical records of the Olmstead County residents from 1984 to 2003. In total, 4424 stone formers and 10,995 controls were followed up, on average, for more than eight years. The data came from the Rochester Epidemiology Project, a medical documentation system that includes records from the Mayo Clinic and other community providers in the county.

Individuals diagnosed with kidney stones were significantly more likely to develop CKD, the researchers found. Those who formed kidney stones had a 60 percent greater risk of developing CKD and a 40 percent increased risk of developing end stage renal disease.

"This study strengthens the association of a diagnosis of kidney stones as a risk factor for the development of chronic kidney disease," said Elaine Worcester, MD, professor of medicine in the nephrology section at the University of Chicago. "As yet unknown are the mechanisms by which stones may lead to CKD." Possible factors associated with increased risk of CKD



could be certain stone types, metabolic abnormalities such as severe hyperoxaluria, the need for multiple surgeries for stone removal, or complications such as urinary tract infection or repeated obstruction, Worcester said.

"Patients with kidney stones should be carefully evaluated for CKD and its risk factors, and they should be appropriately treated for any that are identified," Lieske said. "Further studies on potential treatment options are needed, for example, whether treatments to prevent stone recurrence would reduce risk of further CKD progression."

The study, "Kidney Stones Are Associated with an Increased Risk of Developing Chronic Kidney Disease" was part of the Renal Week session on "Chronic Kidney Disease: Its Prediction, Prevention, and Treatment."

### Age, Wasting, and IL-1 Type Raise Risk of Bacterial Infection for Dialysis Patients

O lder age and wasting are risk factors for severe bacterial infections among patients with stage 5 chronic kidney disease (CKD), according to findings from a study by researchers at the Karolinska Instutet in Stockholm. Patients with a central dialysis catheter at the initiation of dialysis were more prone to infection, and patients with a particular single nucleotide polymorphism in the gene for interleukin-1 $\beta$ (IL-1 $\beta$ ) were at markedly increased risk.

Because infectious complications are a major cause of morbidity and mortality in patients with CKD, Olof Heimbürger, MD, PhD, senior physician in the division of renal medicine, and colleagues at the institute investigated risk factors for infection. They presented their findings at the poster session "Dialysis: Non-Cardiovascular Outcomes and Clinical Trials."

CKD patients commonly show signs of chronic inflammation, including elevated acute phase proteins and pro-inflammatory cytokines, one of which is IL-1 $\beta$ . A single base variation, a C/T polymorphism at nucleotide base position +3954 in the IL-1 $\beta$  gene, modulates production of the cytokine. The C/C allotype is linked to lower IL-1 $\beta$  production in monocytes in vitro.

In the study, 360 patients with severe stage 5 CKD were recruited before they started dialysis. About half the patients went on peritoneal dialysis (PD), a third on hemodialysis (HD) with peripheral vascular access, and the remainder on HD using a central dialysis catheter. The endpoint of the study was defined as hospitalization for bacterial infection, with a maximum follow-up period of three years. Patients were eliminated from the study assessment score, SCG >1), inflammation (hsCRP >10 mg/L), and lower serum albumin levels were significantly more frequent in the presence of serious infectious diseases. Glomerular filtration rates did not differ significantly among patients with or without infections .

<sup>44</sup>... we see on one hand that patients on dialysis and in CKD 5 have increased levels of inflammatory cytokines, so they have a kind of constant pro-inflammatory state.... On the other hand, they can't respond in a good way when they are challenged by infection. So they have an overactivated but still blunted immune system.<sup>17</sup>

— Olof Heimbürger

at the time of transplantation or death. The three most common infectious events were PD-related peritonitis (28 percent), respiratory tract infections (21 percent), and septicemia (14 percent). Forty-one percent of the patients had an infectious event leading to hospitalization. Staphylococci were the major causative organisms for both PD-related peritonitis and septicemia.

"The risk of being hospitalized for a bacterial infection was increased in the older patients [>55 years] and in the malnourished patients," Heimbürger reported. These patients were also more likely to have diabetes mellitus (P < 0.005) or cardiovascular disease (P < 0.005). Wasting (subjective global Forty-eight percent of PD patients had an infectious event versus 34 percent of the HD patients. There was no significant difference in the rates of septicemic events between the two groups.

"We found that patients with central dialysis catheters had an increased risk of infection [P < 0.05], and I think we should avoid using central dialysis catheters if possible. Everyone agrees about that, but this is further evidence that this is important," Heimbürger said.

The investigators also found an independent effect of the IL-1 $\beta$  genotype. The 139 patients who were low producers of this pro-inflammatory cytokine, that is, with the C/C

genotype, had a higher risk for serious infectious events compared to patients with the C/T (n=71) or T/T (n=18) genotypes.

"So we see on one hand that patients on dialysis and in CKD 5 have increased levels of inflammatory cytokines, so they have a kind of constant pro-inflammatory state," Heimbürger said. "But, on the other hand, they can't respond in a good way when they are challenged by infection. So they have an overactivated but still blunted immune system."

A multivariate analysis taking into account age, gender, diabetes mellitus, cardiovascular disease, wasting, and the IL-1 $\beta$  +3954 genotype yielded significant approximate odds ratios (OR) for risk of infection: age > 55 years, OR = 2.1; wasting, OR = 2.4; C/C genotype, OR = 1.9.

The investigators did not try to measure IL-1 $\beta$  levels in the blood because the molecule is short-lived and therefore difficult to evaluate. The study was too small to determine if specific types of bacteria were responsible for infections at particular sites.

In light of the finding of increased risk with central dialysis catheters, Heimbürger advised, "We should try to create a fistula, and I know the United States has been far behind Europe, but the United States is shifting very rapidly to have more fistulas, and I think it is the right way to go."

## GLOMERULAR FILTRATION RATE

### Proteinuria Trumps GFR in Predicting Kidney Disease Progression in Type 2 Diabetes

### By Daniel M. Keller

A lbuminuria is a stronger predictor of renal disease progression and cardiovascular (CV) morbidity and mortality than is glomerular filtration rate (GFR), said George Bakris, MD, in his talk at the two-day program "CKD and CVD from the Vascular Viewpoint: Merging Basic and Clinical Sciences to Optimize Treatment" at Renal Week. Bakris stressed the need to monitor and reduce proteinuria to maximize risk reduction and said that blood pressure control is a key element in therapy.

Bakris, professor of medicine and director of the Hypertensive Diseases Unit at the University of Chicago Pritzker School of Medicine, cited a study of 4421 Chinese patients with type 2 diabetes but no macrovascular disease or end stage renal disease at study entry who were followed for a median of 39.4 months (1). Patients were stratified into quartiles of estimated GFR (≥90, 60–89, 30–59, and 15–29 mL/min/1.73 m<sup>2</sup>).

"Even if you have absolutely normal kidney function, if you have albuminuria your risk for cardiovascular events dramatically increased, and if you don't have albuminuria, you're fine," Bakris said.

In the highest estimated GFR quartile, the risk of a CV endpoint (CV death, new admission for angina, myocardial infarction, stroke, revascularization, or heart failure) increased 85 percent if albuminuria was present versus not present.

Similarly, albuminuria was a strong predictor of renal endpoint (reduction in estimated GFR >50 percent, progression to stage 5 estimated GFR, dialysis, or renal death). The hazard ratio for a renal endpoint was 2.62 with albuminuria compared to no albuminuria in the group with the highest estimated GFR (*P*=0.007). Although a lower estimated GFR at the beginning of the study did not predict the likelihood of a renal endpoint, albuminuria did. Albuminuria in the group with the lowest estimated GFR conferred a 90-fold risk of a renal endpoint, compared with no albuminuria in the group with the best estimated GFR.

The findings in the Chinese study were supported by the results of several other trials. The African American Study of Kidney Disease (AASK) involving nondiabetic kidney disease patients (2), the Captopril Trial, the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) Study, and the Irbesartan in Diabetic Nephropathy Trial (IDNT) found an increased time to dialysis associated with a reduction in proteinuria of at least 30 to 35 percent. In the arms of the AASK and IDNT trials that did not achieve a reduction in proteinuria, there was no change in time to dialysis.

When "looking for progression of kidney disease, you're better off looking at changes in proteinuria than you are looking at changes in GFR," Bakris said. In people with advanced kidney disease "unless you have a reduction in proteinuria of 30 to 35 percent with blood pressure reduction, you're not going to get maximal benefit out of slowing kidney disease progression."

Tight control of blood pressure is essential to reducing proteinuria. One factor is sodium intake, and dietary history is a simple and inexpensive way to determine a patient's sodium intake. A 24-hour urinary sodium test may more accurately reveal intake, especially if the patient-reported history does not point to excessive intake.

"Increases in sodium increase oxygen stress, isoprostanes, and as a result, increase proteinuria and blunt the effects of ACE inhibitors and angiotensin receptor blockers (ARBs)," Bakris said. "Sodium intake is very powerful in terms of what it can do if there's a little bit of injury already on board." He explained that sodium intake >4 g/day reduces the antiproteinuric effects of blockade of the renin-angiotensin system. The use of thiazide diuretics only partially restores the effect.

Ambulatory blood pressure monitoring (ABPM) is a good indicator of blood pressure control throughout the day and night. In the AASK study, many of the African-Americans studied did not show a characteristic dip in systolic blood pressure, "which gives you an overall quote 'higher blood pressure load' . . . over a 24-hour period," he said. Obese people and those with sleep apnea may also tend not to dip at night. So some patients may have normal blood pressures in the office but abnormal patterns at night.

Others may have "masked hypertension" with normal office readings but elevated pressures at other times. "Having masked hypertension is as bad as having true hypertension," Bakris said, but a clinician will not detect the problem without doing ABPM. As many as 25 percent of patients may have masked hypertension, which was probably the reason for the inability to stop kidney disease progression in AASK, Bakris said.

To slow the progression of kidney disease, systolic blood pressure needs to be reduced as soon as possible to limit injury to arteries. Multiple drugs are usually necessary, starting with an



ACE inhibitor or an ARB and possibly adding a calcium channel blocker or thiazide diuretic. Updated guidelines of the European Society of Hypertension [Ruilope L et al. *Blood Press*. 2007; 16(2):72-9] and the American Society of Hypertension (ASH Diabetes Consensus Update. *J Clin Hypertens*. Sept. 2008) provide good algorithms for multidrug therapy and treatment monitoring.

Bakris advised having all patients monitor their blood pressures at home once a day. "It makes them an active partner in their own management . . . [and] in many cases it motivates them," he said. Patients may learn what causes their blood pressures to change, and the readings may help the physician change the timing or dose of drugs.

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### **New Equation Provides Better Estimates of CKD Prevalence**

A newly developed equation provides more accurate estimates of glomerular filtration rate (GFR) than do other measures, according to new research. The equation is different from other measures because it was developed on the basis of findings from pooled databases, rather than from a single study.

"Our new estimating equation, developed from pooled databases, is more accurate than the widely used Modification of Diet in Renal Disease (MDRD) Study equation," said Andrew S. Levey, MD, of Tufts Medical Center, one of the study authors and a participant in the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).

The MDRD Study equation, developed from data on approximately 1600 patients in a single study, uses information on age, race, sex, and the level of serum creatinine to estimate GFR. The equation is relatively imprecise and can underestimate GFR, especially at levels that are closer to normal, or higher. As a result, clinical laboratories do not generally report estimated GFR (eGFR) levels greater than or equal to 60 mL/ min/1.73 m<sup>2</sup>.

Measurement of GFR is impractical for routine clinical use. To help improve GFR estimation, the researchers developed a new equation based on pooled databases, initially using data on more than 8000 patients from 10 studies. They then validated the equation by using data on 3896 patients from 16 studies.

The resulting CKD-EPI equation was more accurate than the MDRD Study equation, especially at higher levels of kidney function, when compared against actual GFR measurements. More accurate eGFR is likely to reduce the frequency of false-positive diagnosis of CKD and to refine the classification by stage in patients with CKD.

When applied to a representative sample of 16,000 Americans, the CKD-EPI equation yielded an estimated prevalence of CKD in the general population of 12.2 percent; CKD prevalence estimated with the MDRD equation was 13.3 percent. Among those with CKD, the proportion with stage 1 and 2 CKD was 17 percent and 21 percent, respectively, with the CKD-EPI equation, versus 13 percent and 24 percent, respectively, with the MDRD Study equation.

The investigators suggested that the CKD-EPI equation could replace the MDRD Study equation. They cautioned that GFR estimates are not as accurate as GFR measurements and that the CKD-EPI equation may not be accurate for all populations of patients.

The study, "A New Equation to Estimate GFR from Serum Creatinine Improved Accuracy and Updated Estimates of Prevalence of Chronic Kidney Disease in the United States," was part of the Renal Week session on "Effects of Traditional and Nontraditional Risk Factors on Cardiovascular Risk in Chronic Kidney Disease and End Stage Renal Disease."

## TRANSPLANTATION

### Kidney Donation Holds Few Risks for Women Who May Become Pregnant

Women who want to bear children in the future need not worry about the risks of donating a kidney before pregnancy, researchers have found.

Historically, little information has been available on whether women kidney donors can go on to have healthy pregnancies. Sanjeev Akkina, MD, and his colleagues at the University of Minnesota in Minneapolis looked at the issue by studying 2025 women who donated



kidneys since June 1963. Of these, 965 reported becoming pregnant—822 donors reported 2416 pregnancies before donation and 223 reported 459 pregnancies after donation.

Post-donation pregnancies had a higher incidence of certain health conditions than pre-donation pregnancies, but their incidence was comparable to those seen in the general population.

"A woman who has donated a kidney does not face any additional risks of developing hypertension or diabetes during a future pregnancy or of having a miscarriage or of giving birth prematurely, Akkina said. "We believe this research is important so that future kidney donors are aware of the long-term effects [of donation]," he said.

The study's findings could have a significant clinical impact, according to Milagros Samaniego-Picota, MD, a nephrologist and associate professor at the University of Wisconsin School of Medicine and Public Health in Madison. "There is a paucity of data about outcomes in living kidney donors," she said. "This information will prove useful to nephrologists around the country charged with the task of living donor evaluations and advocacy."

More than half of all living kidney donors are female, and of these, 79 percent are women of childbearing age, said Samaniego-Picota.

The study, "Pregnancy Outcomes after Kidney Donation," was part of the session on "Care Delivery in Kidney Transplantation and the Living Kidney Donor."

### Kidney Transplants Improve Cognitive Performance in Patients with Chronic Kidney Disease

Kidney transplants lead to improved mental performance in people with kidney disease, new research shows.

Individuals with chronic kidney disease often suffer from cognitive impairment, but it is unclear to what extent outside factors such as age and medication play a role.

To investigate the effect of kidney transplantation on the mental performance of individuals with kidney disease, lead author Mark Unruh, MD, and his colleagues at the University of Pittsburgh compared kidney transplantation to dialysis only. They assessed cognitive performance before and after kidney transplantation and dialysis using neuropsychological tests related to language, learning and memory, attention, and other brain processes involved with thought and behavior.

"These findings support the position that kidney transplantation provides optimal replacement of renal function and an opportunity to improve quality of life and rehabilitation in individuals with advanced chronic kidney disease," Unruh said.

The 37 individuals who received kidney transplants in this study significantly improved their overall cognitive performance, specifically performing better on verbal learning and memory and working memory tasks than individuals who received dialysis. The investigators did not find any improvement in individuals not undergoing the surgical procedure. In fact, test scores declined in these individuals over time.

"The findings from this study highlight an important but often overlooked benefit of kidney transplantation and provide further encouraging evidence that the cognitive deficits seen in patients with kidney failure are reversible," said Manjula Tamura, MD, at Stanford University Medical Center's nephrology department.

### Remedies Sought for Inequities in Kidney Transplant Allocation By Tracy Hampton

Wait times for kidney transplants throughout the United States vary widely, so that some individuals can receive a deceased donor's kidney within just one year while others must wait up to a decade. Researchers are investigating the issues related to organ allocation inequities and are searching for ways to remedy them.

"The predominant variable influencing access to kidney transplantation in the United States, even more important than race or insurance status, is geography," said Alan Leichtman, MD, of the University of Michigan in Ann Arbor. "When rates are compared across states, access to living donor transplantation and to waitlisting for deceased donor transplantation each vary twofold, while access to a deceased donor kidney transplant among waitlisted patients varies threefold."

"The predominant variable influencing access to kidney transplantation in the United States, even more important than race or insurance status, is geography."

—Alan Leichtman

A variety of initiatives across the country are striving to change organ allocation practices and may help equalize these rates.

Donor exchange programs, which match an incompatible patient-donor pair with a patient-donor pair of the opposite incompatibility, can help encourage greater access to donated kidneys. In this situation, two patients receive donated organs, but not from the donor who is their own family member or loved one.

"A willing transplant candidate with a willing donor who is incompatible based on blood testing is a missed opportunity," said Ajay Israni, MD, of the Hennepin County Medical Center in Minneapolis. "A paired-exchange program takes advantage of that opportunity and links up incompatible pairs that may, with luck, be compatible after exchanging donors." Israni helped start a program that exchanges paired donor information among nine different centers in the Midwest.

Multi-organ donation, in which patients receive multiple organs—such as a heart, a liver, and a kidney—at one time, can complicate issues of organ allocation. "There are concerns that centers may use one organ to get faster access to another. For example, if you list someone for a liver plus kidney transplant, they will get the kidney much faster than if they were listed for a kidney alone," said Viken Douzdjian, MD, of the Legacy Good Samaritan Hospital in Portland, Ore. Douzdjian added that the regulations for allocating organs for multiple transplants are vague and confusing.

"The rules about listing someone for a combined transplant are very loose compared to single organ transplants. We need minimum listing criteria for multiple organ transplants," he said.

Varying qualities of deceased donors' organs also complicate organ allocation. While receiving an organ from a standard criteria donor (a healthy person who is age 18 to 60 years) is ideal, an increasing number of available organs are from "nonideal" sources. For example, a donated kidney may come from an older donor whose kidney function is not completely normal or from a donor who died from cardiac complications. Often, patients in need of kidney transplants agree to accept organs from these types of donors because it would increase their chance of having a transplant, given the national shortage of kidnevs.

"These trends have resulted in a need to classify deceased donor organs to encapsulate both the physiologic insults and the expected functional quality of the organs—characteristics which may have significant impact on the expected graft and recipient outcomes," said Akinlolu Ojo, MD, PhD, of the University of Michigan in Ann Arbor. Ojo noted that there are ongoing attempts to refine the classification of deceased donor kidneys to better inform the allocation system.

These issues related to organ allocation were discussed during a clinical nephrology conference on "Allocation of Deceased Donor Organs for Renal Transplantation."

### Nephrologists' Perceptions Explain Some of the Demographic Disparities in Transplantation

By Daniel M. Keller

rban and rural physicians involved in kidney transplantation have different perceptions about various aspects of the procedure, including when it should be done in the course of end stage renal disease (ESRD) and for which patients. While several socioeconomic, racial, gender, geographic, and logistical factors have been explored previously to account for differences in transplantation rates, researchers at Pennsylvania State University College of Medicine in Hershey investigated physicians' perceptions about transplantation as another possible explanation for the disparities.

Rural patients in general have a lower rate of being waitlisted or transplanted than their urban counterparts, said Hooman Hajian, MD, MPH, an internal medicine resident at Penn State. Rural African-Americans are less likely to be transplanted than urban blacks or rural or urban whites. Hajian was lead author of a poster session titled "Differences in Perceptions of Transplantation among Urban and Rural Nephrologists in the United States."

To test the hypothesis that provider perceptions and preferences may be important contributors to disparities in transplantation, Hajian conducted a web-based survey of nephrologists and transplant surgeons (International Survey of Physician Opinions on Renal Transplantation). The 52-question survey asked about practice demographics, practice characteristics, level of involvement in kidney transplantation, and various aspects of physicians' perceptions about transplantation. Of the 1375 physicians completing the survey, 399 practice in the United States (292 urban, 107 rural).

"The urban groups by a wide margin favored preemptive transplantation, considered transplantation as a treatment of choice for elderly patients more than 60 years old, and also transplantation as a treatment of choice across all age groups as an overall option," Hajian said. Urban physicians also were more likely to favor research on xenotransplantation and were more likely to be in favor of living anonymous donation and paired donation.

### Urban physicians' preferences in transplantation

- transplantation as treatment of choice for most patients [odds ratio (OR) = 1.77; P<0.05]
- transplantation in patients >60 years old (OR = 1.89; *P*=0.002)
- preemptive transplantation before prolonged dialysis (OR = 3.62; P<0.0001)</li>
- paired organ donation (OR = 5.12; P<0.001)</li>
- living anonymous donation (OR = 2.53; P=0.002)
- research on xenotransplantation (OR = 3.35; *P*<0.005)</li>

Although both urban and rural physicians felt that race and socioeconomic factors were the main contributors to disparities, urban physicians saw age and inner city residence as additional major contributors, while the rural group considered gender and rural residence as contributors to the disparities, Hajian found.

Prior to the study, Hajian thought there might be some difference in perceptions between urban and rural physicians, but the differences were larger than he had expected and covered many aspects of transplantation.

In a related study, Pritika Shrivastava, MD, a nephrology and hypertension fellow at Penn State, surveyed nephrologists to gauge their perceptions on transplantation as the treatment of choice for the majority of patients with ESRD, on preemptive transplants, and on providing the procedure to the elderly. She segmented the data according to whether respondents were transplant or nontransplant (general) nephrologists. Shrivastava presented her findings at a poster session on "Variations in Nephrologists' Perceptions of Patient Suitability for Renal Transplantation."

"We found that transplant nephrologists favored transplant. Preemptive transplant was favored by transplant nephrologists and . . . if the physician was less than 50 years old or . . . in practice less than 10 years," Shrivastava said. "And for the elderly, again, transplant nephrolo-



gists seem to favor it." All differences were statistically significant at the P<0.005 level or better.

Physicians' perceptions about patient age and suitability for kidney transplant were also significantly associated with their own age and proportion of time in practice. "Physicians who were more than 50 years old favored transplant in patients who were more than 60 years old," Shrivastava said. Compared to physicians ≥50 years old, 50 percent more younger physicians opposed transplant in patients >60 years old (OR=1.5; *P*=0.009). Those in clinical practice for less than 50 percent of their time were 30 percent more likely to oppose transplant in older patients compared to nephrologists in clinical practice more than 50 percent of their time.

Shrivastava concluded that nephrologists' demographic and practice characteristics influence their perceptions of patients' suitability for kidney transplantation. Given the differences in perceptions that her study discovered, she acknowledged, "Maybe also it's indicating that patients should go to transplant nephrologists if they want to be considered for transplant."

### Obese Donors Have Good Kidney Function at Six Months and One Year after Kidney Donation; Long-Term Effects Less Clear

Kidney function in obese kidney donors remains strong one year after donation, although long-term effects on renal function are uncertain, said Peter Reese and his colleagues at the University of Pennsylvania-Philadelphia at a Renal Week session.

As transplant centers work to maximize appropriate live donor transplantation, uncertainties remain concerning the potential risks of accepting kidneys from donors with obesity or other risk factors for future kidney disease. Also unclear are risks obese donors may face during and after the surgical procedure.

To shed light on this issue, Reese and his colleagues studied the use of kidneys donated by live obese and non-obese individuals at transplant centers across the United States. Of the 5300 donors studied, nearly 1200 (22.5 percent) were obese. The authors analyzed 2004–2005 registry data from the Organ Procurement and Transplantation Network.

The investigators found that obesity is common among live donors, especially among black and Hispanic donors, who also are more likely to develop kidney disease. Compared with non-obese donors, obese donors also had higher blood pressure prior to kidney donation. Peri-operative outcomes were not worse for obese donors.

To compare the health of obese and non-obese donors after surgery, the investigators measured blood pressure, hypertension status, and kidney function at six months and

one year after the surgery.

Obese donors had slightly higher blood pressure and were more likely to be hypertensive than non-obese donors at follow-up, but they were less likely to have poor kidney function. The study's major limitation was missing data on donor outcomes at followup. Approximately 40 percent of donors had no data on kidney function reported at six months.

Although the study shows that obese individuals have health outcomes after kidney donation similar to those for other donors, the long-term risks are uncertain.

"It is our hope that researchers will pursue longitudinal studies on the health outcomes of obese kidney donors 10 to 20 years after donation," Reese said. "It is important to help clarify these risks because many donors really want to help loved ones. Obese donors should be educated about the limitations in what we know about long-term outcomes after kidney donation. Nonetheless, our data suggest that obesity alone should not be a contraindication to live kidney donation. This finding is important because the prevalence of obesity is increasing."

The study, titled "Peri-Operative Complications and 1-Year Outcomes for Obese Live Kidney Donors" was part of a session on "Care Delivery in Kidney Transplantation and the Living Kidney Donor."

## **ASN News**

## **Ambitious Goals Set for ASN in 2009**

By Thomas M. Coffman



t is my great privilege to serve as president of the American Society of Nephrology (ASN) in 2009. As members of ASN, we owe a debt of gratitude to the previous leaders of the Society who have provided outstanding guidance and stewardship, allowing ASN to reach its current levels of prominence and success.

In particular, Peter S. Aronson, MD, FASN, and William L. Henrich, MD, FASN, deserve special thanks for their leadership during the past two years in helping to steer the Society through several important transitions. For example, new Editors-in-Chief were appointed for the Journal of the American Society of Nephrology (JASN) and the Nephrology Self-Assessment Program (NephSAP). Through this transition, *JASN* remains the highest-rated, most highly cited nephrology publication in the world, while NephSAP continues to set the standard for continuing medical education (CME) and maintenance of certification (MOC) in our subspecialty. We anticipate that the quality and stature of these journals will continue to rise as our new editorial teams hit their stride. In addition, a new organizational structure for ASN educational activities produced the highest quality Renal Week, Renal WeekEnds, and Board Review Course and Update in the recent history of the Society, based upon participant evaluations of these meetings.

ASN has successfully navigated these several recent transitions, and it is my hope that with your help we can accomplish the following "top 10 list" of goals for 2009.

#### Launch ASN Kidney News

With this issue, ASN debuts a newsmagazine aimed at summarizing issues relevant to the nephrology community. To this end, we have hired Pascale H. Lane, MD, FASN, as the founding editor-in-chief and Dawn McCoy as ASN President Thomas M. Coffman, MD, FASN, sets forth society goals in publishing, education, public policy, research, and partnering with other organizations. Coffman is chief of the division of nephrology at Duke University.

managing editor, along with a talented editorial board assembled by Dr. Lane. The editorial team plans to develop articles addressing a range of areas important to health professionals in nephrology. This coverage will span new clinical developments, epidemiologic findings, federal and state policy updates, practice management, industry trends, and opinions from leading nephrologists and other policymakers. ASN *Kidney News* will also expand the Society's reach through circulation to nurses, allied health professionals, and administrative staff who work in our field.

### Publish the Clinical Journal of the American Society of Nephrology (CJASN) monthly

In the short time since its launch, CJASN has established itself as a clinical science journal of outstanding quality, receiving official recognition from Pub Med in 2007. In view of progressive increases in manuscript submissions, CJASN will join *JASN* as a monthly publication beginning in January 2009. Moreover, ASN will uncouple both journals so that Society members, other subscribers, and libraries will start to receive each publication separately (as opposed to receiving one big, unwieldy package). This move will solidify our original vision for CJASN and continue its trajectory as an independent and dynamic publication.

## Implement a new brand identity for ASN

In view of the changes and evolution of our Society during the past decade as well as to help achieve our future goals, ASN is working to develop a new brand identity. This effort consists of surveys, focus groups, and meetings carried out with the assistance of a public relations firm. The objective of these efforts is to heighten the society's image and visibility in order to facilitate, among other things, our ability to advocate on behalf of our membership. The new brand identity will include a new logo and tagline, while maintaining the current color scheme to lend a recognizable 'ASN' feel.

## Enhance and foster growth of the ASN website

As users have no doubt noticed, ASN has made a concerted effort to improve its website (www.asn-online.org), attempting to make it more attractive, easy to use, and more relevant for our membership. Through the efforts of a number of individuals, including a working group led by ASN Councilor Ronald Falk, MD, FASN, and our interim web editor, Jerry Yee, MD, FASN, the website now incorporates new content modules and supports emerging functionality, offering the ability to join ASN, to renew ASN membership online, and to update personal demographic information instantly.

This progress will continue in 2009. Helping members earn CME credits and MOC points through the website will be a particular area of emphasis. The ASN Education Committee created a task force-chaired by David J. Salant, MD-to oversee this process and to develop mechanisms to help members earn points through parts two (self-assessment) and four (practice improvement) of MOC. We plan a number of other enhancements providing educational opportunities, linkage to publications, and on-line self-assessment examinations for NephSAP. Please log in early and often to follow our progress.

### Continue to expand and strengthen the ASN public policy operation

Several years ago, ASN launched a significant effort to augment its activi-

ties in public policy and advocacy. Led by the ASN Public Policy Board and including the Society's committees and advisory groups, ASN now manages a broad policy portfolio. These efforts are focused on helping the Society's members provide high-quality care to patients, conduct groundbreaking medical research, and educate the next generation of nephrologists.

In the first instance, as a member of Kidney Care Partners (KCP), ASN advocated for and shaped the Medicare Improvement for Patients and Providers Act of 2008 (HR 6331) and worked to ensure that the bill included several provisions of importance to the renal community, including increased reimbursement to nephrologists who provide comprehensive education for chronic kidney disease (CKD). ASN and KCP also contributed in a meaningful way to the bill's end stage renal disease (ESRD) reform measures.

ASN is a member of the Ad Hoc Group for Medical Research Funding, which advocates for the National Institutes of Health (NIH), and became a member this year of the executive committee of the Friends of the Department of Veterans Affairs (VA) Medical Care and Health Research. Through these and other independent efforts, we have continued to actively engage leadership at NIH and key members of Congress to advocate for increased funding for research into causes, prevention, and treatment for kidney diseases.

At a nonfederal level, ASN will increase its interaction with the Accreditation Council for Graduate Medical Education (ACGME) and the Residency Review Committee for Internal Medicine (RRC-IM), the American Board of Medical Specialties, the American Board of Internal Medicine (ABIM), and other entities that oversee the quality of the educational continuum. As one recent example of these efforts, the ASN Training Program Directors (TPD) Executive Committee (which is chaired by Donald E. Kohan, MD, PhD) is working with RRC-IM to constructively revise the ACGME requirements for nephrology fellowships. Furthermore, in April 2009, TPDs and the National Board of Medical Examiners will roll out the first national in-training examination for nephrology fellows.

### Empower ASN committees and advisory groups

ASN's network of committees and advisory groups provides a powerful mechanism for harnessing the talent and energy of our diverse membership. These groups span the range of interests and constituencies that characterize our society; in the past year, new groups have been constituted, including the Glomerular Diseases Advisory Group and the ASN Web Presence Working Group, discussed above.

Taken together, our committees and advisory groups serve critical functions to inform our decisions and strategies in policy, education, research, and publications. They provide critical insights and advice to the ASN Council in our efforts to develop and expand services of value to each of the myriad constituencies within ASN. I urge you as members to participate actively in these panels.

## Increase the Society's annual research grant portfolio to \$3,325,000

As a result of Dr. Aronson's able leadership over the past several years, ASN has improved every aspect of its grant program, from the amount of funding to the application process and review procedures. Recognizing the challenges for research funding in the current environment, the ASN leadership has attempted to build a substantive financial corpus that can be used to provide support to key vulnerable areas in kidney research, focusing particularly on young investigators and on providing bridge funding to support more senior investigators during the requisite interruptions in funding that characterize today's funding cycles.

During the next year, when ASN Councilor Joseph V. Bonventre, MD, assumes oversight of the ASN Grants Program, the Society will continue to build on these improvements and increase its efforts to promote the availability of funding. Along with our active grant program, we will continue our strong advocacy on Capitol Hill for expanded funding for kidney research at NIH, VA, and other federal agencies.

### Maintain strong separations between planning and funding of high-quality CME for ASN members

The original objective behind the formation of ASN was to organize an annual meeting to facilitate dissemination of new advances in the science of nephrology. Education has remained a major part of our mission while the educational offerings of the ASN have expanded considerably, now including a variety of high-quality CME programs.

In recent years, like other medical societies that provide CME, ASN has become increasingly dependent on industry support for our core educational missions. While we are grateful for this support, this reliance has raised concerns from Congress, the media, the Accreditation Council for Continuing Medical Education (ACCME, which accredits CME providers, such as ASN), and others about potential influence—both real and perceived—on the objectivity and share common goals and interests. We are much stronger working

together with like-minded organizations than we would be on our own. Thus, we have and will continue to seek out opportunities to partner with other groups to achieve our aims. These alliances include the American Society of Pediatric Nephrology, National Kidney Foundation (NKF), and the Renal Physicians Association—our partners in KCP—with whom we worked to ensure the success of HR 6331. We have also partnered with NKF to coordinate visits of nephrologists and patients

### We are much stronger working together with like-minded organizations than we would be on our own.

integrity of teaching, learning, and practicing medicine. During the summer of 2008, ASN responded to a "formal inquiry" from ACCME that examined the firewall between planning and funding the Society's educational activities. As we expected, ACCME determined that ASN already has appropriate systems for checks and balances in place.

However, this inquiry, along with the steady tightening of ACCME rules and the broader concerns about interactions between physicians and industry, has stimulated the Society to further strengthen its mechanisms for protecting the content of Renal Week, Renal WeekEnds, Board Review Course and Update, and other educational activities (such as web-based material).

At the same time, ASN recognizes the need to maintain meaningful and productive relationships with industry. These partnerships benefit all involved including patients. To help ensure this balance, ASN in 2008 established a committee on corporate relationships chaired by John B. Stokes, III, MD, FASN. I am confident that with the guidance of this committee and by maintaining transparent relationships with our corporate partners and regulatory agencies, we will continue to provide high-quality and relevant CME to our members while avoiding inappropriate external influences on our educational programs.

### Promote positive external relationships with other professional societies

The nephrology community is faced with a number of pressures that affect our ability to deliver patient care, to conduct research, and to educate the next generation of nephrologists. These challenges range from expanding regulations to contracting budgets. Therefore, it is imperative that we have productive and robust relationships with our sister renal societies and the constellation of other professional societies with whom we to Capitol Hill on World Kidney Day. We are working with the American Society of Transplantation (AST) to accredit transplant fellowships across the country. In addition, we provide joint research grant funding with the Alaska Kidney Foundation, AST, the Association of Specialty Professors, and the Halpin Foundation.

Likewise, we have contributed to the International Society of Nephrology (ISN) Commission for the Global Advancement of Nephrology Fellowship program and participated in ISN's Global Outreach Programs and Renal Sister Center Program at Renal Week. For several years, we have sponsored "mini-fellowships" and travel grants for Renal Week with the Sociedad Latinoamericana de Nefrologia e Hipertension (SLANH) as well as helped administer the Women in Nephrology's Professional Development Seminar Travel Grant. In 2008, we provided sponsorship for the American Association of Kidney Patients Medical Excellence Award. During 2009, ASN must strengthen these relationships, continue to be a leading citizen in the renal community, and identify new partners to help achieve our shared missions.

### Develop an outstanding program for Renal Week 2009 in San Diego, CA

Renal Week is the crown jewel of ASN, providing a lively mix of science, education, and camaraderie that attracted more than 13,000 participants last year. Raymond C. Harris, MD, FASN, will serve as chair of the Program Committee for the 2009 meeting. He has assembled an outstanding Program Committee consisting of international experts in basic and clinical sciences who have already begun their work to develop an exciting and ambitious program. Ray will work in collaboration with Mark E. Rosenberg, MD, the education director for Renal Week and chair of the Post-Graduate Education Committee. to assemble a program that will deliver spectacular new science along with exciting and engaging educational opportunities. The program will include some of the world's most outstanding clinical and basic scientists, who will present their latest findings to attendees in a beautiful venue.

In closing, I want to express my sincere gratitude for the remarkable contribution of our members, committees, advisory groups, boards, and staff during 2008. The strength of our Society is truly found in the talent, energy, and dedication of our diverse membership. We have an ambitious agenda for 2009, but I am confident that working together, we can accomplish our shared goal of improving patients' lives through research, education, and clinical care.



Renal Week Attendance 2001–2008

## **Practice Pointers**

## **Guidelines for Anemia Treatment in CKD**



Allen Nissenson

What are the main differences between the most recent Kidney Disease Outcomes Quality Initiative (KDOQI) 2007 update and the previous KDOQI guidelines for anemia management in CKD? What was the basis for these updated changes in recommendations?

The latest set of anemia guidelines was developed through a torturous process. Initially published in May 2006, they were widely criticized when studies such as the Cardiovascular Risk Reduction in Early Anemia Treatment with Epoetin Beta (CREATE) and Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) were published in late 2006 and early 2007. The studies, which appeared in the nephrology, as well as oncology, literature raised safety concerns about treatment of anemia with erythropoiesis-stimulating agents (ESAs).

The guidelines panel met again in the spring of 2007 to consider all of the new evidence, including several new randomized controlled trials (RCTs). After extensive evaluation, analysis, and discussion, the panel's key recommendations included: 1) a clear articulation about the difference between target and achieved hemoglobin and the implications for interpreting the literature; 2) a clinical practice recommendation (insufficient evidence existed for a clinical practice guideline) that target hemoglobin should be 11-12 g/dL; 3) a clinical practice guideline with moderately strong evidence that hemoglobin should not be targeted to  $\geq 13$  g/ dL; and 4) a clinical practice recommendation that patients with ferritin ≥500 ng/mL should not routinely

In this month's issue, ASN Kidney News editorial board member Edgar Lerma interviewed Allen Nissenson, MD, about the new guidelines for treating anemia in chronic kidney disease. Nissenson is currently chief medical officer of DaVita, Inc. He is also emeritus professor of medicine with the David Geffen School of Medicine at UCLA, where he served as associate dean for special projects during the previous three years.

Nissenson has been active in the American Society of Nephrology, National Kidney Foundation, Renal Physicians Association, and American Heart Association. He was founding member, then president, of the National Anemia Action Council from 2001 to 2007, and he continues to be involved with policies and implications of recent changes in the management of anemia and the role of erythropoiesis-stimulating agents on outcomes, morbidity, and mortality.

receive iron. The last recommendation was based on a lack of evidence from RCTs on the beneficial effects of iron above this level of ferritin, although no evidence of harm was apparent from the literature.

### Tell us more about the dilemma regarding target hemoglobin levels and how the CHOIR and CREATE trials played significant roles in this conundrum.

The debate is about the importance of achieved versus targeted hemoglobin. CHOIR, CREATE, and the Normal Hematocrit Cardiac Trial (NHCT) are the key studies that contributed to the debate, but investigations are now beginning to help unravel the science. inflammation, who have the adverse outcomes. Still unclear is whether the underlying inflammation, the high ESA dose, the large amount of iron, or some combination of these drives the increased morbidity and mortality.

### Are there any other ongoing trials that might settle this ongoing dilemma—for example, TREAT, STIMULATE (which looks at the ESA Hematide<sup>™</sup>'s ability to stimulate production of red blood cells), and NEPHRODIAB2?

More data will be helpful, but it is questionable whether these large clinical trials will resolve the dilemma regarding targeted vs. achieved hemoglobin and mortality and morbidity. These trials are likely, however, ant to ESAs seem prudent. Similarly, current CMS reimbursement policies created to incentivize maintaining this same level of hemoglobin are largely reasonable.

Recent policy to have a cutoff of ≥400,000 units per month is more problematic. First, there is an overrepresentation of patients in this category with malnutrition/inflammation and hemoglobinopathies who may need high ESA doses or will receive multiple transfusions. Decisions regarding ESA administration involve tradeoffs and should be made by the nephrologist and the patient, not the payer. Second, if the ESA dose is exceeded, CMS now denies the entire claim for the month including all erythropoietin (EPO), dialysis treatments, and other medications. This sort of administrative approach is overly punitive and clearly not patient-centered.

What are the new CMS guidelines regarding coverage for ESAs that came about as a result of the ongoing debate over their use? Aside from the obvious cost benefits, do you think the CMS guidelines will have a positive or negative impact on patients' overall care, in terms of morbidity and mortality?

Clearly, the CMS guidelines were developed following the concern about safety at higher hemoglobin levels and charges by some that ESAs were being overused for profit. Unfortunately, the new policy has already resulted in a movement of the hemoglobin distribution curve to the left, resulting in fewer patients treated with ESAs with achieved hemoglobin >13 g/dL and more patients with hemoglobin

The decision regarding the optimal hemoglobin target for a particular patient should be made jointly between the nephrologist and patient.

It appears that the studies confirm observational trials showing that patients who achieve a higher hemoglobin level have the best outcomes, while those who don't achieve higher hemoglobin have a poorer outcome.

On the other hand, targeting a higher hemoglobin in a large population will uncover a group of patients who are poor responders to ESAs, have lower achieved hemoglobin, and receive large doses of ESAs and usually parenteral iron as part of the study protocol. It is this latter group of patients, probably with chronic to help resolve the controversy over patient-reported outcomes and quality of life because they are carefully assessing quality of life at various hemoglobin levels.

### What about the new recommendations—such as monitoring of response—regarding administration of ESAs?

Current package insert recommendations for maintaining hemoglobin at 10–12 g/dL and avoiding dose escalation in patients seemingly resist<10 g/dL. Time will tell if this change results in better or worse outcomes.

### What do you think about Medicare coverage of ESAs only for patients at stage 3 or higher chronic kidney disease (CKD)?

This would clearly be an inappropriate policy. The indication for ESAs should be anemia caused by CKD. Although it is not common for anemia of CKD to be present when GFR is >60, it occasionally occurs. This is one of the only situations in which determining the serum EPO level may be useful and appropriate.

### Could you comment on how the updated changes in iron parameters might affect management of concomitant iron deficiency?

The recommendation for use of serum ferritin as a guide to iron administration has been widely misinterpreted. Most people believe the guideline group recommends holding iron if the ferritin is >500 ng/mL. That is not the recommendation, which states that *routine* administration is not recommended at that level. In addition, clinicians should consider the results of the DRIVE (Dialysis Patients' Response to Intravenous Iron with Elevated Ferritin) studies, which may modify their approach to this recommendation.

### How will these new guidelines and updates affect nephrologists' practice? What are the pros and cons?

Unfortunately, the guidelines have rapidly become considered standards of care and do drive clinical practice and publically reported data. They are used as the basis for pay for performance. It is still the obligation of every practitioner to do what is best for each individual patient and take guidelines as just that—tools to assist in decision making.

What does the future of anemia in CKD hold? What new ESA products are on the horizon, e.g., CERA (continuous erythropoietin receptor activator) or HIF (hypoxia-inducible factor)? Are there new pharmacologic adjuvant drugs on the horizon, e.g., L-carnitine or Vitamin C? How far are they from being ready for prime time?

We are about to see an explosion of new products and approaches to anemia management. In addition to enabling us to better understand the pathogenesis and management of anemia, these products may permit achieving whatever target hemoglobin we choose more safely and efficiently. Bio-similar (generic) ESAs, HIF- prolyl hydroxylase inhibitors, EPOmimetics, and gene therapy are all approaches that are currently undergoing phase II and III clinical trials. Agents such as these are likely to be on the market in the next several years.

### When is the ideal time to start ESAs and iron replacement or supplementation therapy?

I believe that the bulk of the evidence shows that no patient should have a hemoglobin <10 g/dL. I start an ESA as this figure is approached. Iron should be administered if transferrin saturation is <20 percent or ferritin <100 ng/mL.

### In this age of evidence-based medicine, please give us your advice regarding the appropriate management of anemia of CKD in light of all of the published RCTS and guidelines.

The key is to maximize benefits while minimizing risks and individualizing care. For the vast majority of patients, maintaining the hemoglobin at 10–12 g/dL will achieve this balance. For some patients, however, the ability to function and quality of life are not optimized until the hemoglobin is higher. The decision regarding the optimal hemoglobin target for a particular patient should be made jointly between the nephrologist and patient. Finally, nephrologists need to focus greater attention on the ESA-resistant patient and not continue to escalate ESA doses if there is not hemoglobin response in these individuals.

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## **Policy Update**

## Performance Measures, MIPPA, and Public Health Headline ASN Policy Sessions

### By Caroline Jennette

### **Clinical Performance Measures**

The growing tide of new metrics for evaluating delivery of care for chronic kidney disease (CKD) and other outpatient services warrants a healthy look at their efficacy, according to speakers at the policy sessions at Renal Week. Even as physicians and other care providers gear up to meet the new requirements, they must also take part in evaluating how well the measures work, speakers said.

Historically, there has been a lack of quality measures for CKD, but as some care services move away from hospitals and toward ambulatory care providers, a plethora of new measures for CKD and other outpatient services are on the horizon.

Quality measures for kidney disease need to be carefully developed and evaluated to be most effective, said Neil Powe, MD, director of the Welch Center for Prevention, Epidemiology and Clinical Research at Johns Hopkins. Future needs for CKD quality measures include demonstrating that measures are related to outcomes, creating more measures for early stages of CKD, and using performance measures to address health-care inequalities. These measures must not only be tested during their application, but also during all stages of development. Powe gave the Christopher Blagg Endowed Lecture at the Public Policy Forum on "Clinical Performance Measures: How Will You Be Measured?'

Louis Diamond, MBChB, medical director of the Medstat Group, spoke about recent trends by government and the private sector to assess physician performance and link performance to relicensure. The "elephant in the room," Diamond said, is "we still don't know how best to assess physician performance." As policymakers and professionals look toward the future, he urged a closer look at the efficacy of using both process and outcome measures and called for national, coordinated efforts-with funding attached—to develop and evaluate guidelines for a robust system of physician performance measures.

Jay Wish, MD, professor of medicine at University Hospitals of Cleveland, explored the future of clinical performance measures, starting with the 1998 "core indicators" for end stage renal disease (ESRD), some of which are still in use, and ending with the 2008 Phase III ESRD guidelines, recently released to coincide with the new ESRD facility conditions for coverage. These Phase III guidelines include 26 new measures, some of which have not been approved by the National Quality Forum [contracted by the Centers for Medicare and Medicaid Services (CMS) to approve ESRD guidelines], including hemodialysis adequacy metrics and anemia management. The new measures move from being solely facility-based to now covering facilities, clinicians, and patients. State surveyors will look at implementation of these new guidelines as they review compliance with the new ESRD conditions for coverage, but it is likely they will not be used as pay-for-

performance measures until the implementation of bundling in 2010. Wish advised the health-care community to "proceed with caution" because not all of the new measures have been validated and process measures are not currently being collected.

### Understanding the Medicare Improvements for Patients and Providers Act of 2008

A "perfect storm" of variables led to passage of the landmark Medicare Improvements for Patients and Providers Act of

## ASN Grant Opportunities

### Alaska Kidney Foundation-ASN Research Grant, Carl W. Gottschalk Research Scholar Grant, and the Norman Siegel Research Scholar Grant

Those applying for the AKF-ASN Research Grant, Carl W. Gottschalk Research Scholar Grant, or Normal Siegel Research Scholar Grant will be automatically considered for any of the three awards.

These career development grants are designed to foster the independent careers of young investigators in biomedical research related to nephrology. Applicants must be within seven years of initial faculty appointment. This grant provides \$100,000 annually for two years. Preference for the Norman Siegel Research Scholar Grant will be given to a pediatric investigator. The AKF-ASN Research Grant is cosponsored by AKF.

Next application deadline: February 6, 2009

### ASN-Association of Specialty Professors Junior Development Grant in Geriatric Nephrology

Cosponsored by ASP, this grant provides \$75,000 annually for two years for researchers interested in careers focusing on the geriatric and gerontological aspects of nephrology.

Next application deadline: February 6, 2009

### ASN-American Society of Transplantation John Merrill Grant in Transplantation

Cosponsored by AST, this grant is designed to foster the independent careers of young investigators in biomedical research related to transplantation. This grant provides \$100,000 annually for two years.

Next application deadline: February 6, 2009



### The Halpin Foundation-ASN Research Grant

Cosponsored by The Halpin Foundation, this career development grant is directed at researchers studying membranous nephropathy. This grant provides \$100,000 annually for two years.

Next application deadline: February 6, 2009

### M. James Scherbenske Grant

This grant is designed as a bridge grant to support only those investigators who have submitted a competitive renewal RO1 application that was not funded. This grant is a one-time award of \$100,000.

Upcoming application deadlines: November 14, 2008; March 13, 2009; June 12, 2009

### Student Scholar Grant

This program is designed to enable selected medical students with an interest in either basic or clinical research to spend time engaged in work on a nephrology-based research project.

Upcoming application deadlines: March 6, 2009 and October 2, 2009

ASN acknowledges the following organizations whose generous support assists the Society in providing funding for new investigators in kidney research:

- Alaska Kidney Foundation
- Association of Specialty Professors
- American Society of Transplantation
- The Halpin Foundation

2008 (MIPPA), said Jonathan Himmelfarb, MD, chair of ASN's Public Policy Council. Himmelfarb, director of the Kidney Research Institute and professor of medicine at the University of Washington in Seattle, spoke at a special session on "Medicare Implications for Nephrology."

A "gathering storm" of unsustainable costs and questionable health-care quality, combined with government unease with "perverse incentives" (read: anemia management) and the convergence of a broad base of powerful advocacy groups including private and academic physicians, patients, and the dialysis industry, created an environment conducive to legislatively based changes to Medicare, Himmelfarb said. The dialysis provisions include an annual update framework for the composite rate starting in 2010 and a bundled system for Medicare reimbursement, which includes a case-mix adjustment and an optional four-year phase-in period, with all dialysis providers compliant by 2012.

Educational provisions are also included in the bill. Starting in January 2010, Medicare will reimburse providers for up to six educational sessions for stage 4 CKD beneficiaries. The purpose of these sessions is to explain all options for renal replacement therapy and to educate patients on how to manage their disease and its co-morbidities. The legislation includes a provision that will award funding to at least three states to implement demonstration projects focused on increasing public awareness, as well as CKD screening and surveillance. These two educational provisions are currently unfunded and will need legislative action to appropriate funds.

While MIPPA has been hailed as a victory for both the renal community and Congress, there is still work to do as the bill now moves from the legislative stage to the implementation process and details are worked out with CMS and the Department of Health and Human Services. Congress has given enormous discretion to these two agencies for the interpretation of the bill, and only time will tell if renal community interests stay aligned, Himmelfarb said.

## 2008 ASN Grant Recipients

Alaska Kidney Foundation-ASN Research Grant Samir M. Parikh, MD

ASN-American Society of Transplantation John Merrill Grant in Transplantation Arjang Djamali, MD, FASN

Arlang Daman, MD, FASIN

ASN-Association of Specialty Professors Junior Development Grant in Geriatric Nephrology

Steven G. Coca, DO Lisa M. Nanovic, DO

### Carl W. Gottschalk Research Scholar Grant

Brian D. Adair, PhD Markus Bitzer, MD Ion Alexandru Bobulescu, MD Marcelo D. Carattino, PhD Tarek M. El-Achkar, MD Sarah Faubel, MD George Jarad, MD Michal Mrug, MD Alexander Staruschenko, PhD Farook Thameem, PhD The Halpin Foundation-ASN Research Grant Elena Torban, PhD

### M. James Scherbenske Grant

Steven C. Borkan, MD He-Ping Ma, MD Stewart H. Lecker, MD, PhD, FASN

New Directions Grant David Pearce, MD, FASN

Norman Siegel Research Scholar Grant Tammy McLoughlin Brady, MD

### **Student Scholar Grant Winners**

Maureen Moen David Hobbs Neha M. Patel Christopher Lawton Leonid Cherkassky

Questions about an ASN grant? Please contact Holly Osborne at (202) 659-0599 or hosborne@asn-online.org.

#### CKD and Public Health

The ASN Public Policy Board Symposium focused on the economic and health burdens of CKD and national efforts to educate, screen, and treat those at risk for or with CKD.

The Chronic Kidney Disease Surveillance Pilot is one such project. A partnership between the Centers for Disease Control (CDC), Johns Hopkins University, and the University of Michigan, the project assesses the prevalence, impact, and resource utilization of CKD. The surveillance project integrates 11 data sources into a comprehensive system that tracks factors associated with CKD, including awareness, risk, and health outcomes.

Among the challenges to creating this type of surveillance project are data procurement, missing data, and comparison across data sources, said Rajiv Saran, MD, associate director of the University of Michigan Kidney Epidemiology and Cost Center. Results from the CDC pilot program have not yet been released, but a copy of the executive summary is available upon request from www.cdc.gov/ diabetes/projects/kidney.htm.

The burden of ESRD, coupled with the risk factors of diabetes, hypertension, and cardiovascular disease, provide a strong rationale for focusing on programs that increase early detection of CKD, said Alan Collins, director of the Chronic Disease Research Group (CDRG). The "Cherish Your Kidneys" program, a partnership between the CDC, the CDRG, and the National Kidney Foundation, targets patients at high risk for kidney disease, screening those older than 50 with self-reported diabetes and/or hypertension.

Andrew Narva, MD, director of the National Kidney Disease Education Program (NKDEP), described the efforts of NKDEP to improve CKD care at both a provider and patient level through education, outreach, and collaboration with other federal agencies. The NK-DEP's community health center CKD pilot project works to improve screening, detection, and management of CKD care for vulnerable populations, typically uninsured or underinsured, who use community health centers.

L. Ebony Bouleware, MD, associate professor of medicine and epidemiology at Johns Hopkins University, noted that expenditures for CKD—both direct and indirect—are on the rise. In her studies on the economic impact of CKD, Bouleware found that annual screenings were not cost-effective unless used with targeted groups. She stressed that targeting patients at greatest risk for *progression* to kidney disease may be the most costeffective practice.

As the burden of kidney disease continues to grow, government agencies and private entities are taking notice and working to create policies that combine cost-cutting and quality measure development for current CKD and ESRD. Agencies are also working on early detection through screening and educational initiatives to catch CKD in the early stages and slow the progression to ESRD. The renal community can help by staying informed and lending a voice to policy development both now and in the future.

ASN Kidney News editorial board member Caroline Jennette, MSW, is with the University of North Carolina Kidney Center in Chapel Hill, NC.

## Coming Soon A bold leap forward in iron therapy for CKD patients



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## **Industry Spotlight**

### ICD-9 Codes Make Way for ICD-10

The ICD-10 billing code system for Medicare and Medicaid programs, though delayed, is on its way. Designed to replace the 27-year-old ICD-9 system, ICD-10 will expand the number of codes available for billing. With every innovation, however, comes a price tag.

Many medical groups, including the American Medical Association, American College of Physicians, and the Medical Group Management Association, solicited Nachimson Advisors to study the impact of ICD-10 coding and asked for an extended deadline for implementation, which currently stands at Oct. 1, 2011.

Cost to convert to ICD-10 for a three-physician practice					
Education	\$ 2,405				
Process analysis	\$ 6,900				
Change to superbills	\$ 2,985				
Information technology costs	\$ 7,500				
Increased documentation costs	\$44,000				
Cash flow disuption	\$19,000				
TOTAL	\$83,290				

Nachimson Advisors estimates the cost of conversion to ICD-10 for a typical three-physician practice at more than \$83,000. For a 100physician practice, the cost of conversion is estimated at more than \$2.7 million.

The high-ticket item is increased documentation costs. Using the new alphanumeric ICD-10 codes will require more extensive documentation, the Nachimson report noted.

According to the proposed rulemaking on ICD-10 codes (for outpatient practices) and ICD-10 PCS codes for inpatient procedures, the new codes are needed because codes in the old system are being exhausted. Many new codes have been added to describe new procedures and diagnoses that reflect changes in medical practice.

ICD-9 was not designed to handle the increased level of detail required to support emerging needs, such as biosurveillance and payfor-performance programs. The old codes also have a lack of detail to describe advanced technology procedures. Since 2002, 138 countries worldwide have adopted ICD-10 reporting. The United States has only adopted ICD-10 codes for reporting mortality.

What are the benefits of the new codes? According to the American Health Information Management Association (AHIMA), once ICD-10 is implemented, "the trend of deteriorating health data will reverse to allow the healthcare industry to accommodate a robust 21st century classification system." Among the data being collected that would improve significantly under ICD-10 are quality measurement, pay-for-performance, medical error reduction, public health reporting, biosurveillance, actuarial premium setting, cost analysis, and service reimbursement, according to AHIMA.

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### Inkjet Technology Leveraged in Home Dialysis Device

A well-known computer printer technology is in line to help dialysis patients at home. Inkjet injection technology from Hewlett Packard (HP) will merge with dialysis devices from Home Dialysis Plus (HD+) in a new dialysis system to be used at night. HP's inkjet technology will be used within HD+'s dialysis machine proportioning system to mix the correct amount of water and concentrated dialysate, as well as the needed salt and electrolyte solution in real time, and to pump the dialysis solution into the dialyzer. Mixing the solution in real time helps to filter toxins over a longer period, HP reported. In addition, HP's memory chip technology will be used to ensure that the correct dialysate prescription is being delivered over time so dialysis can take place while the patient is sleeping.

These technological advances are expected to afford patients a slower and more accurate nocturnal dialysis treatment that is more in tune with the body's natural biological processes and that will dramatically reduce a patient's post-treatment recovery time from hours to minutes.

The technology also is expected to offer a significantly smaller and more convenient option for portable and flexible care of dialysis needs at any location with access to a water source. For health-care providers, the dialysis machine should make it much easier and less expensive to train patients to perform their treatments— with a helper— at home. The cost of implementing the HD+ system is expected to be much lower than the cost of shipping prepackaged dialysate solutions.

Under the agreement, HP will license its intellectual property to HD+ in return for royalty payments. HD+ will develop, manufacture, and sell the product, which the company expects to be available in the United States and other markets by the end of 2010.

### **Reports Highlight Diet and Anemia Management**

Two Nephrology TreatmentTrends<sup>™</sup> publications released late last year analyze the market trends of products that help nephrologists and renal dietitians manage their patients' renal anemia, hyperphosphatemia, and secondary hyperparathyroidism. The reports, issued by BioTrends Research Group, are based on survey results from 204 nephrologists and 201 renal dietitians in the United States.

The reports noted that renal dietitians (RDs) are integral to the management of dialysis patients, reinforcing patient adherence in taking phosphate binders, active Vitamin D, and agents that mimic calcium (calcimimetics).

Nephrologists are split regarding their first-line preference of agent in treating dialysis patients. Approximately half of nephrologists choose a calcium-based binder and half choose a non-calcium based binder, compared with more than two-thirds of RDs who choose to start with a non-calcium based binder. Seventy-three percent of nephrologists prefer to start with calcium-based binders in patients with chronic kidney disease who are not on dialysis.

In the parathyroid hormone modifier market, RDs report a high level of influence in the choice of Vitamin D product used. Nephrologists continue to use oral calcitriol most often.

In the renal anemia market, nephrologists are pursuing new treatment standards, such as lower target hemoglobin levels, lower levels for ESA (erythropoiesis-stimulating agent) initiation, holds, and dose reductions. More than two-thirds do not anticipate making any additional changes to their use of ESAs in chronic kidney disease or dialysis. Bundling will have an impact on ESA use, most likely through shifts to subcutaneous dosing and less aggressive treatment of EPO hypo-responders. New ESAs in development could also shift market dynamics, the report stated.

## New Device Lowers Blood Pressure, Improves Heart Function

Patients with high blood pressure may have a new way to improve their health beyond bypassing the salt shaker and taking blood pressure medications. A national clinical trial is finding that the Minneapolis-based CVRx<sup>®</sup> Rheos <sup>®</sup> System is effective in treating early-stage heart failure.

As part of the multicenter, phase III trial, 18 patients in the United States and Europe had the device implanted. The patients had early-stage heart failure and high blood pressure and were on personalized medication levels deemed to be the best for each patient.

After one year of Rheos therapy, left ventricular mass and left atrial dimension were reduced toward normal levels. In addition, the patients' blood pressure levels were lower.

The system works with a pressure sensor that activates the carotid artery baroreceptors. When these natural receptors are activated, they send signals through neural pathways to the brain that interpret a rise in blood pressure. The brain works to lower this rise in pressure by sending signals to the heart, blood vessels, and kidneys to relax the blood vessels. The brain also restricts production of stress-related hormones. Thus, the heart can increase blood output while continuing with its workload.

The Rheos system has a small pulse generator, implanted under the collar bone; two thin lead wires implanted in the left and right carotid arteries, which are connected to the pulse generator; and an external device used by physicians to noninvasively regulate the activation energy level from the generator to the lead wires.

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- NO mortality benefits with sevelamer when compared to calcium-based phosphate binders in DCOR (Genzyme-sponsored) study.<sup>3</sup>
- NO mortality, morbidity, or hospitalization benefits with sevelamer over calcium-based binders as stated in DCOR secondary analysis.<sup>4</sup>

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- Nearly two decades of proven results

PhosLo is indicated for control of hyperphosphatemia in end-stage renal failure. Patients with higher-than-normal serum calcium levels should be closely monitored and their dose adjusted or terminated to bring levels to normal. PhosLo is contraindicated in patients with hypercalcemia. No other calcium supplements should be given concurrently with PhosLo. Nausea, hypercalcemia and pruritus have been reported during PhosLo therapy.

**CelCaps** (CalciumAcetate) **Dispense as written** 

Do not substitute

Please see brief summary of prescribing information and references below.

For more information on PhosLo, please contact Fresenius Medical Care at 800-323-5188 or visit phoslo.com

REFERENCES: 1. Qunibi WY, Hootkins RE, McDowell LL, et al. Treatment of hyperphosphatemia in her charters 1: dunior W, nousins RL, webowen LL, et al. nearnent of hyperphosphatematin hermodialysis patients: the calcium acetate renagel evaluation (CARE Study), *Kidney Int.* 2004;65:1914-1926. **2.** Qunibi W, Moustafa M, Muenz LR, et al. A 1-year randomized trial of calcium acetate versus sevelamer on progression of coronary artery calcification in hemodialysis patients with comparable lipid control: the calcium acetate renagel evaluation-2 (CARE-2) study. *Am J Kidney Dis.* 2008;51:952-965. **3.** Suki WN, Zabaneh R, Cangiano JL, et al. Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. *Kidney Int.* Aug 29, 2007. **4**. St. Peter WL, Liu J, Weinhandl E, Fan Q. A comparison of sevelamer and calcium-based phosphate binders on mortality, hospitalization, and morbidity in hemodialysis: a secondary analysis of the dialysis clinical outcomes revisited (DCOR) randomized trial using claims data. *Am J* Kidney Dis. 2008;51:445-454. 5. PhosLo<sup>®</sup> [prescribing information]. Fresenius Medical Care, Waltham, MA: January 2007. 6. Mehrotra R, Kopple JD,Wolfson M. Metabolic acidosis in mainte-nance dialysis patients: clinical considerations. *Kidney Int.* 2003;64(suppl 88):S13-S25.

### BRIEF SUMMARY OF PRESCRIBING INFORMATION

CONTRAINDICATIONS: Patients with hypercalcemia. INDICATIONS AND USAGE: For the control of hyperphosphatemia in end-stage renal failure. WARNINGS: Patients with end-stage renal failure may develop hypercalcemia when given calcium with meals. No other calcium supplements should be given concurrently with PhosLo. Progressive hypercalcemia due to overdose of PhosLo may be severe as to require emergency measures. Chronic hypercalcemia may lead to vascular calcification, and other soft-tissue calcification. The serum calcium level should be monitored twice weekly during the early dose adjustment period. The serum calcium times phosphate (Ca x P) product

should not be allowed to exceed 66. Radiographic evaluation of suspect anatomical

should not be allowed to exceed 66. Radiographic evaluation of suspect anatomical region may be helpful in early detection of soft-tissue calcification. **PRECAUTIONS:** Excessive dosage induces hypercalcemia; therefore, early in the treatment during dosage adjustment serum calcium should be determined twice weekly. Should hypercalcemia develop, the dosage should be reduced or the treatment discontinued immediately depending on the severity of hypercalcemia. Do not give to patients on digitalis, because hypercalcemia may precipitate cardiac arrhythmias.Always start PhosLo at low dose and do not increase without careful monitoring of serum calcium.An estimate of daily calcium intake should be made initially and the intake adjusted as needed. Serum phosphorus should also be determined periodically. determined periodically

Information for the Patient: Inform the patient about: 1) compliance with dosage, 2) adherence to diet instructions and avoidance of nonprescription antacids, and 3) symptoms of hypercalcemia. Drug Interactions: PhosLo may decrease the bioavailability of tetracyclines. Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term primed advice have no the hore northermored. animal studies have not been performed.

Pregnancy: Teratogenic Effects: Category C.Animal reproduction studies have not been conducted. It is not known whether PhosLo can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Give to a pregnant woman only if clearly needed.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established Geriatric Use: Of the total number of subjects in clinical studies of PhosLo (n = 91), 25 percent were 65 and over, while 7 percent were 75 and over. No overall differences in

safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be

ruled out. **ADVERSE REACTIONS:** In clinical studies, patients have occasionally experienced nausea during PhosLo therapy. Hypercalcemia may occur during treatment with PhosLo. Mild hypercalcemia (Ca>10.5 mg/dl) may be asymptomatic or manifest itself as constipation, anorexia, nausea and vomiting. More severe hypercalcemia (Ca>12 mg/dl) is associated with confusion, delirium, stupor and coma. Mild hypercalcemia is easily controlled by reducing the PhosLo dose or temporarily discontinuing therapy. Severe hypercalcemia can be treated by acute hemodialysis and discontinuing PhosLo therapy. Decreasing dialysate calcium concentration could reduce the incidence and severity of PhosLo induced hypercalcemia. The long-term effect of PhosLo on the progression of vascular or soft-tissue calcification has not been determined. Isolated cases of pruritus have been reported which may represent alleroir, reactions. cases of pruritus have been reported which may represent allergic reactions. OVERDOSAGE: Administration of PhosLo in excess of appropriate daily dosage can

cause severe hypercalcemia (see ADVERSE REACTIONS)

For more information on PhosLo, please contact Fresenius Medical Care at 800-323-5188. Manufactured for and distributed by: Fresenius Medical Care North America, Waltham, MA 02451

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