ASN® THE AMERICAN SOCIETY OF NEPHROLOGY

KidneyNews

December 2009 | Vol. 1, Number 6

An Official Publication of the American Society of Nephrology

Fatigue may be Life-Threatening for Some Dialysis Patients

By Tracy Hampton

Most patients—from 60 to 97 percent—undergoing dialysis experience profound fatigue.

Undergoing dialysis may not be a physically strenuous activity, but dialysis patients with end stage renal disease experience profound levels of fatigue. While physicians may be aware that fatigue is a debilitating symptom experienced by patients undergoing dialysis, there is only limited information on its prevalence and its association with patient outcomes.

A recent study sheds light on the incidence and effects of fatigue in incident hemodialysis and peritoneal dialysis patients (Jhamb M, et al. *Clin J Am Soc Nephrol* 2009; 4:1779–1786). The results show that fatigue is an important—and sometimes overlooked—problem for patients beginning maintenance dialysis, and it may indicate an underlying inflammatory burden and an increased risk of dying.

Can Fatigue Be Fatal?

Although fatigue has been reported to affect from 60 percent to 97 percent of chronic dialysis patients, it may be the last thing on nephrologists' minds as they monitor and treat patients' other potentially life-threatening complications. Concerns about kidney failure, malnutrition, increased risks of cardiovascular disease and death, and other dangers are more pressing among kidney specialists. However, some have suspected that fatigue may not be as innocuous as once thought.

"It is my experience that patients have different interactions with dialysis and that substantial numbers of patients are washed out after treatments," said Mark Unruh, MD, of the University of Pittsburgh Medical Center. "Profound fatigue may not

Continued on page 3

Reimbursements May Drop for Some Dialysis Facilities under Bundled Payments

Researchers Voice Concern about High-Poverty Areas of South

By Timothy O'Brien

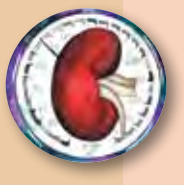
When it comes to the financial impact of the proposed ESRD bundled payment system, all dialysis centers may not be created equal. A study presented at Renal Week 2009 suggested that dialysis units with certain characteristics and in some regions—including some of the most impoverished regions in the United States—could see disproportionate cuts in Medicare payments under the new system.

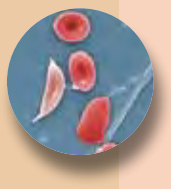
Under a bundled payment system, Medicare makes a single reimbursement for all the hospital and physician care for kidney disease, rather than separate payments for the facility and physicians.

"Based on facility-level analysis, it appears there may be unanticipated geographic variation in facility reimbursement payments," according to lead author Sumit Mohan, MD, of Columbia University. The findings raise concerns that some dialysis centers—and the patients they serve—may be at risk under the Centers for Medicare & Medicaid Services' (CMS) proposed Medicare bundle.

Continued on page 4

Inside





genzyme
Renal

Before you start, stop.

Because the benefits should accumulate. Not the risks.

Renvela® (sevelamer carbonate) tablets or for oral suspension is an effective first-line monotherapy for controlling serum phosphorus in dialysis patients — without calcium or metal[1] accumulation. Renvela is the ***only*** phosphate binder available in both tablet and powder dosing options.

NEW

New Renvela powder.
See demo at renvela.com.

Important Treatment Considerations

Renvela® (sevelamer carbonate) is indicated for the control of serum phosphorus in patients with chronic kidney disease (CKD) on dialysis • Renvela is contraindicated in patients with bowel obstruction • Caution should be exercised in patients with dysphagia, swallowing disorders, severe gastrointestinal (GI) motility disorders including severe constipation, or major GI tract surgery • Uncommon cases of bowel obstruction and perforation have been reported • Serum bicarbonate and chloride levels should be monitored • Vitamins D, E, K (coagulation parameters), and folic acid levels should be monitored • The most frequently occurring adverse reactions in a short-term study with sevelamer carbonate tablets were nausea and vomiting • In a short-term study of sevelamer carbonate powder dosed three times daily, adverse events were similar to those reported for sevelamer carbonate tablets • In long-term studies with sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, the most common adverse events included: vomiting, nausea, diarrhea, dyspepsia, abdominal pain, flatulence, and constipation • Cases of fecal impaction and, less commonly, ileus, bowel obstruction, and bowel perforation have been reported • Drug-drug interactions may occur with some medications and should be taken into consideration when instructing patients how to take Renvela • Patients should be informed to take Renvela with meals and to adhere to their prescribed diets

Please see Brief Summary of Prescribing Information on adjacent page.

Reference: 1. Renvela [package insert]. Cambridge, MA: Genzyme Corp; 2009.

Renvela®
sevelamer carbonate

Right from the start℠

Fatigue

Continued from page 1

only interfere with daily activities, but it may also influence adherence to the medical regimen." If true, this could have serious consequences for patients' health.

Unruh and his colleagues set out to determine the effects of fatigue on dialysis patients by examining the correlates of self-reported fatigue at initiation of dialysis and after one year. They assessed the extent to which fatigue was associated with health-related quality of life and survival in 917 dialysis patients.

Patients in the study were a subpopulation of participants in the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Study, a national prospective cohort study of incident hemodialysis and peritoneal dialysis patients that enrolled patients from 1995 to 1998. Unruh's study (which followed patients through 2004) included participants who completed the CHOICE Health Experience Questionnaire (CHEQ), which includes SF-36 vitality scale questions that measure the continuum of fatigue. Predictors of fatigue—including sociodemographic and psychosocial factors, dialysis-related factors, biochemical variables (such as inflammatory markers), comorbidities, and medications—were used as covariates.

The researchers found that the average vitality score of these end stage renal disease patients was similar to that of patients with clinical depression. A low vitality score was independently associated with white race, higher Index of Coexistent Disease score, higher body mass index, physical exercise, antidepressant use, and higher C-reactive protein (CRP) levels. A lower vitality score was strongly associated with lower SF-36 physical functioning, mental health, bodily pain scores, and decreased sleep quality (all p <0.001) at baseline.

Also, among surviving participants in the study, higher serum creatinine at baseline was associated with preserved vitality at one year (Adjusted Odds Ratio 0.84; 95 percent Confidence Interval 0.72–0.98, p = 0.03). Patients with the highest baseline vitality scores experienced longer survival [hazard ratio 0.75; 95 percent confidence interval 0.58–0.96, p =0.03].

The researchers also analyzed the effect of change in vitality over one year on survival. The median survival for those with a decline in vitality at one year was 3 years, compared with 3.8 years for those with stable or improved vitality. Also, compared with patients who reported stable or improved vitality at one year, patients who reported a decline in vitality had a 41 percent increased risk of death (HR 1.41; 95 percent confidence interval 1.06–1.89, p = 0.02) after adjusting for age, sex, race, use of antidepressants, dialysis modality, albumin, creatinine, and other factors.

The investigators speculate that the existence of a pathogenic inflammatory factor common to fatigue and decreased survival may explain these findings.

Fighting Fatigue

Kidney researchers not involved with this study noted that the link between low vitality scores and an increased risk of premature death could be important, but it must be verified with additional studies. "In an epidemiological study such as this, causality cannot be proven," said Srinivasan Beddhu, MD, associate professor of medicine at the University of Utah Health Sciences Center in Salt Lake City. "But this is a very important first step, and interventions that improve sleep quality or increased physical activity might improve vitality scores and survival."

They also noted that the observed differences in survival among different types of patients on dialysis are intriguing. "A very interesting finding is that nonwhite race was associated with higher adjusted vitality scores," said Alan Kliger, MD, clinical professor of medicine at Yale University School of Medicine in New Haven and past president of the Renal Physicians Association. "African Americans report more vitality and less loss of vitality than non-African Americans, so race appears to impact adaptation to dialysis. It's not surprising that sociologic and economic factors impact adaptation to disease, but this finding deserves further study."

Fatigue is clearly important to patients. Most—94 percent—of the dialysis patients surveyed would accept more frequent hemodialysis if it would increase their energy. Certain steps can

Continued on page 5

ASN The American Society of Nephrology
Kidney News

ASN Kidney News is published by the American Society of Nephrology
1725 I Street NW, Suite 510, Washington, DC 20006. Phone: 202-659-0599

www.asn-online.org

Postmaster: Please send address changes to *ASN Kidney News*, c/o Customer Service, American Society of Nephrology 1725 I Street NW, Suite 510, Washington DC 20006.

Publications mail agreement No. 40624074. Return undeliverable Canadian addresses to PO Box 503, RPO West Beaver Creek, Richmond Hill ON L4B 4R6

ASN Kidney News (ISSN print 1943-8044 and online 1943-8052) is an official publication of the American Society of Nephrology, 1725 I Street NW, Suite 510, Washington DC 20006, and is published bimonthly. Application to mail as Periodicals Postage Pending at Washington, DC, and at additional mailing offices. Subscription rates: $12 per year. To order, please email bhenkel@asn-online.org. Subscription prices subject to change. Annual ASN membership dues include $12 for *ASN Kidney News* subscription.

Reimbursements

Continued from page 1

Variations by Dialysis Center Ownership

Mohan, along with co-authors William McClellan, MD (Emory University School of Medicine) and Rich Mutell, MBA, MA (Amgen), retrospectively analyzed data from all U.S. dialysis centers, drawn from CMS and other federal sources. Their goal was to identify the geographical characteristics of dialysis centers at risk of reduced payments under the proposed bundled payment system.

Their initial study looked at the impact of the model developed by the Kidney Epidemiology and Cost Center (KECC) at the University of Michigan, commissioned by CMS. KECC estimated that, based on ownership characteristics, some types of dialysis facilities would be more likely to see reduced reimbursements—specifically, large dialysis organizations (LDOs), defined as corporations owning 100 or more freestanding dialysis units located in more than one state, and hospital-based dialysis units. "We used the KECC estimates for our model, which found about a 0.9 percent reduction for the LDOs and an average 1.6 percent reduction for hospital-based dialysis units," said Mohan.

The prospect of reduced payments to hospital-based dialysis units raised special concerns because these centers tend to be a safety net for patients who might otherwise face difficulties accessing dialysis services, according to Mohan. "They tend to have a larger percentage of uninsured patients or they tend to be geographically isolated units."

However, when the researchers reran the analysis using the preliminary estimates issued in September by CMS using a slightly different payment model, a different picture emerged. Under the revised CMS plan, LDOs take an even bigger hit. "It's now a 3.7 percent reduction for the LDOs, i.e., the three largest chains in the country," said Mohan. Meanwhile, the CMS proposal seems to reverse the projected drop in reimbursements forecast under the original KECC model. "The hospital-based units actually gained somewhere in the range of 3.7 to 4.0 percent."

Unanticipated Geographic Variation Raises Concerns

Geography appears to be another factor affecting the likelihood of reduced reimbursements under the ESRD payment bundle. "Our facility-level analysis suggested considerable geographic variation in the impact of the bundled payments on facilities across the country, with adversely impacted facilities being predominantly in the South," said Mohan. Their original analysis based on the KECC model suggested that dialysis centers located in the South and Southeast—virtually all of ESRD Network regions 5, 6, 7, and 8—were at risk of receiving lower reimbursements.

Why was the South so hard hit? The Congressional mandate to CMS included the requirement to use some type of geographical weightage, Mutell explained. "Our first analysis based on KECC facility characteristics used census region for that geographic weightage. That is why we saw such stark results in certain geographic areas. It was when we modeled the CMS data using a wage index refined to a lower level of geography—specifically, the Core-Based Statistical Area (CSBA)—that we saw the similarities between low wage index areas and poverty."

"The areas that have a low wage index are relatively poor and are also the areas that have facilities that get hit with lower reimbursement rates," said Mohan. "If you actually look at the wage index map, it almost superimposes on a poverty map. And most of the poverty in the United States is in the South and Southeast."

This echoes concerns about reduced access to pre-ESRD care in the same areas. Previous research led by McClellan—published earlier this year in *Journal of the American Society of Nephrology* (2009; 20:1078–1085)—found geographic clusters of suboptimal care for patients with advanced chronic kidney disease in the South and Southeast. The result was that patients in these areas were less likely to receive recommended pre-ESRD care, which in turn led to poorer survival after starting dialysis.

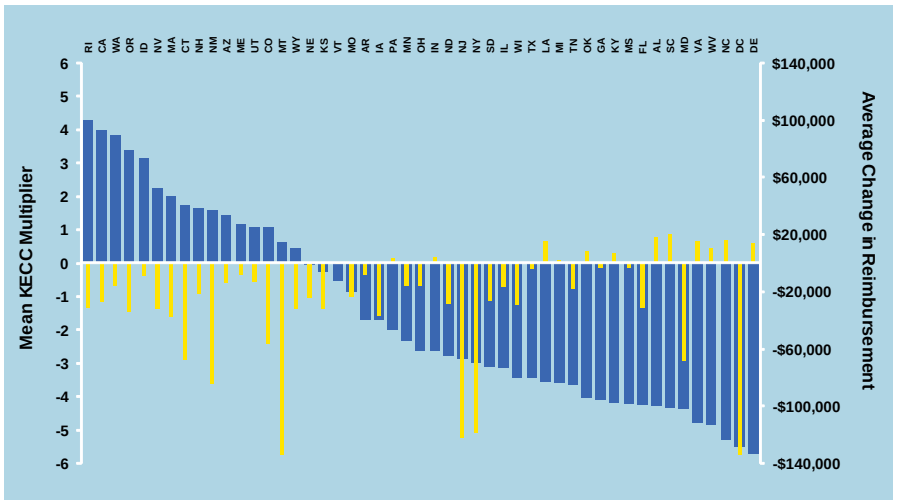
McClellan emphasized that the disproportionate effects on impoverished regions and patients are unintended consequences of both the original KECC model and the subsequent CMS proposal. "This is just a consequence of the tools that they had to use to come up with a case-mix adjustment rate that met their revenue adjustment goals," he said.

Reduced Reimbursement for High-Quality Care?

The quality of dialysis care provided in high-poverty areas has emerged as another interesting piece of the puzzle. "When we compared dialysis facilities most likely to see lower reimbursements, we found they performed better than the rest of the country on CMS's quality measures for adequacy and achieving hemoglobin concentrations above 10 g/dL," said Mohan. "And yet, under the CMS proposal, those are the facilities that you're going to take money away from, disproportionately."

Prompted by these findings, one of McClellan's students, Eiichiro Kanda, MD, matched data from the previous study on pre-ESRD care to the new data on facility characteristics of care. "As we found previously, the care prior to going to the dialysis center was heavily influenced by the poverty of the community, and that tended to cluster in high-poverty areas," said McClellan. "However, once patients got into that dialysis center, their care was no longer influenced by the area of poverty." (Kanda also presented his research at Renal Week 2009.)

Thus poverty in the surrounding



How will dialysis centers in your state fare under the ESRD bundle? For most states, drops in reimbursements are likely under the latest CMS proposal. Blue bars reflect the original model, based on the Kidney Epidemiology and Cost Center (KECC) analysis; yellow bars reflect the latest bundle proposal by the Centers for Medicare & Medicaid Services (CMS).The multiplier reflects the case-mix adjustment used in the KECC analysis.

community is much less likely to affect the center-to-center variability in care, as opposed to pre-ESRD care. "CMS has done a pretty good job at removing some of the impact of poverty after patients get into the system," said McClellan.

Call for a More Sophisticated Approach

McClellan added, "Quite apart from the pros and cons of establishing rates and bundling services as cost containment measures, we would hope that the geographic consequences, particularly as they impact disadvantaged populations—the very populations CMS is committed to bringing more equitable health care—would be examined in a more sophisticated manner than they have been to this date."

Some of the ownership and geographic variations go hand in hand, reflecting differences in the way dialysis services are provided in different parts of the country. "The genesis of all this work was simply putting all the dialysis facilities on the map and seeing where they clustered geographically," said Mutell. "When we did that, we saw in the North how it's dominated almost by hospitals, while other areas of the country are pockets where the medium dialysis organizations operate."

A more nuanced approach to reimbursement would consider local differences in dialysis care, according to Mutell. "The point of looking at the impact of location is that when you try to apply something universally across the board and don't take into account these rather unique regional and geographical characteristics, it could lead to some of these unanticipated consequences that we're seeing."

The researchers found some other important differences in their updated analysis of the proposed CMS bundle, compared to the original analysis based on the KECC model. "When the original KECC analysis was done, the geographic factor that was supplied to us was at the census region level, where we saw some of those bigger swings," said Mutell. "In the follow-up analysis, we're looking at a more granular wage index area."

The updated analysis showed differences in how the states were ordered in terms of their percentage of dialysis centers at risk of reduced reimbursements—including a less consistently negative impact on the states in the South and Southeast. "More states now have a net statewide loss," Mohan said. "The average reimbursement per state will be lower, and far fewer states will show a gain. But what states are in what category has switched around quite a bit."

Other effects of the CMS proposal include eliminating disincentives to peritoneal dialysis and home dialysis. Several other critical issues remain to be worked out, such as the impact of policies regarding Medicare Part D drugs.

Mohan and colleagues believe their findings have important implications for the final CMS bundle. At press time, the researchers were working to prepare a summary of their findings before the scheduled end of the CMS comment period in mid-December.

The aggregation of high-poverty areas in the Southeast deserves special consideration in designing the final bundle plan, McClellan said. "If government policies for health care reimbursement shortchange those poor communities, then it may have consequences that we'd rather avoid—especially since, as seems to be the case, some of the things that have been done in the U.S. dialysis system may actually be benefiting those populations.

"The system is capable of getting beyond the poverty issues and poor education to providing decent care for everybody, which I think is a goal that everybody, no matter where they fall on the health care reform debate, would strive for, and that's equitable, equal high-quality care—for everybody."

The researchers don't claim to have "the truth or the answer" to the best ESRD payment bundle, McClellan added. "What we're doing is holding a mirror up to this process and letting CMS see it as we see it. And asking them, Is this picture accurate, and does it depict what you really want to see from your policy initiatives? And if we get them thinking about it, it will really be a major accomplishment."

Fatigue

Continued from page 3

be taken to counteract fatigue in dialysis patients.

"Physicians should screen dialysis patients for fatigue that interferes with quality of life and daily activities," Unruh said. "In addition, they should ascertain if there are addressable causes of fatigue in the patient such as sleep disorders, mood disorders, hypothyroidism, and polypharmacy."

A better understanding of the interactions between factors such as type of dialysis, sleep, depression, and cytokine production may help clinicians develop interventions to improve survival and quality of life among dialysis patients, Unruh said.

"The authors identify several potential avenues for intervention, including increased levels of physical activity," said Nancy Kutner, PhD, director of the United States Renal Data System's Rehabilitation and Quality of Life Special Studies Center and professor in the department of rehabilitation medicine at Emory University in Atlanta. "And although the etiology of fatigue is likely multifactorial, addressing depression may be a valuable intervention at least in a subset of patients."

In addition, "clinicians and patients might speculate about inflammation, which correlates with both fatigue and survival." Kliger said. "Could techniques that reduce both fatigue and survival improve both?"

Clinical trials are in the works to address many of the unanswered questions about dialysis and fatigue. An ancillary study in the Frequent Hemodialysis Network Trial [supported by the National Institutes of Health (*Kidney Int* 2007; 71(4):349–359)] is examining the impact of dialysis on sleep and fatigue.

ASN News

ASN: What's in a Name (or a Logo)?

Members of the American Society of Nephrology (ASN) dedicate countless hours and myriad talents to improving the lives of millions of patients worldwide who live with kidney disease. Since the society's inception in 1966, ASN leaders and staff have supported this dedication by advancing professional education, advocating for research support, and promoting ever higher standards of care for patients.

In 2008, ASN leaders hired a leading health care communications firm, GYMR, to survey members, staff, external partners, and other stakeholders to better understand how the society is perceived by kidney professionals. Responses to a 52-question survey and numerous interviews were very consistent: ASN was considered the premier professional society supporting intellectually rigorous kidney education and research, was regarded as a successful and highly credible organization, and was known for holding the world's most essential meeting focused on kidney disease (ASN Renal Week). Many respondents, however, were unaware of how active a role ASN plays in addressing current concerns in kidney disease and policy.

Society leaders recognized that if ASN were to continue to build on its work advancing health care and science, the society must more accurately reflect the strength and energy members and leaders bring to improving all aspects of kidney health. To better highlight ASN's role in promoting improvements in clinical care, research, education, and health care policy, ASN leaders began to evaluate how the society presents its goals, agendas, and achievements. ASN contracted with a leading design firm, Informatics, to develop a new logo and visual identity. Leaders agreed that the logo and identity should embody ASN's active role in the kidney community.

The society tagline, "*Leading the fight against kidney disease*," introduced in 2009, recognizes the effort, passion, and results ASN members bring to addressing health care challenges. Staff and leaders continue to highlight the dynamic role ASN and its members play in educating professionals, shaping policy, extending key partnerships, and advocating for the best in kidney care. As part of this ongoing effort, ASN will introduce a new logo on January 1, 2010, that reflects the creativity, strength, and dedication that has always marked the achievements of ASN and its members.

This logo will serve as a tangible symbol of ASN's commitment to leading the fight against kidney disease as well as to improving lives through kidney care, research, and education.

CHECK IRON

References: 1. Hsu C-Y, McCulloch CE, Curhan GC. Iron status and hemoglobin level in chronic renal insufficiency. *J Am Soc Nephrol.* 2002;13(11):2783-2786. **2.** KDOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. http://www.kidney.org/professionals/kdoqi/guidelines_ckd/p6_comp_g8.htm. Accessed March 12, 2008. **3.** National Kidney Foundation. KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. *Am J Kidney Dis.* 2006;47(5 suppl 3):S11-S145.

1.888.880.AMAG

EARLY AND OFTEN

- More than 50% of anemic CKD patients have iron deficiency[1]
- KDOQI™ guidelines recommend monitoring TSAT, ferritin, and hemoglobin as early as CKD Stage 3[2,3]
- Regular monitoring of TSAT and ferritin along with hemoglobin is a critical part of optimal anemia management

www.IDanemia.com

AMAG PHARMACEUTICALS

Get it write

Proven results

- **PhosLo® (calcium acetate) achieved K/DOQI target levels** for mean serum phosphorus and Ca x P product within 3 weeks in 8-week CARE study.[1]
- **NO significant difference in the progression of coronary artery calcification** following equivalent lipid control in the PhosLo and sevelamer treated groups in CARE-2 study.[2]
- **NO mortality benefits with sevelamer** when compared to calcium-based phosphate binders in DCOR (Genzyme-sponsored) study.[3]
- **NO mortality, morbidity, or hospitalization benefits with sevelamer** over calcium-based binders as stated in DCOR secondary analysis.[4]

Proven consistency

- Well tolerated with limited GI side effects[5]
- Not associated with metabolic acidosis[6]
- 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.

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

PhosLo® GelCaps (CalciumAcetate) 667 mg

Dispense as written

REFERENCES: 1. Qunibi WY, Hootkins RE, McDowell LL, et al. Treatment of hyperphosphatemia in hemodialysis 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, Han 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® (prescribing information). Fresenius Medical Care, Waltham, MA. January 2007. 6. Mehrotra R, Kopple JD,Wolfson M. Metabolic acidosis in maintenance 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 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.

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 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 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

100907-01 12/2008

Fresenius Medical Care

Renal Week 2009: News and Analysis

Basic Research with Clinical Applications to Kidney Care Featured in State-of-Art Lectures

If Nobel laureate Roger Tsien, PhD, succeeds in translating into clinical application the fluorescent protein technology for which he and two other scientists won the 2008 Nobel Prize in Chemistry, vivid shades of blue and green will stain tumors in vivo to guide surgeons to the borders and help them avoid crucial nerves during operations on cancer patients.

Tsien, one of four internationally acclaimed scientists invited to present state-of-the-art lectures during ASN Renal Week, is a Howard Hughes Medical Institute investigator and professor of pharmacology at the University of California at San Diego.

By genetically modifying the molecules that enable jellyfish and corals to glow, Tsien succeeded in creating fluorescent-colored protein tags, which now allow scientists throughout the world to peer inside living cells and track where and when specific genes are expressed. These tags, whose colors span the rainbow, have revolutionized the field of cell biology. Tsien hopes that this technology will also advance the diagnosis and treatment of cancer.

His first translational research goal: an intraoperative molecular fluorescence guidance technology to help surgeons see tumor borders, spot residual malignancy, and avoid nerves. While the liver is the target of Tsien's animal research to develop this technique, its application could include the kidney.

His lecture was titled "Breeding and Building Molecules for Whole-Animal and Clinical Imaging."

San Diego hosted more than 12,000 kidney specialists at the American Society of Nephrology's Renal Week 2009.

See our special coverage starting here.

Podocytes a focus of research

The role of Nck proteins in the development and maintenance of the kidney's podocytes was among the topics that Tony Pawson, MD, highlighted in his state-of-the-art lecture, "Signal Transduction Mechanisms in the Kidney."

A distinguished investigator at the Samuel Lunenfeld Research Institute at Mount Sinai Hospital in Toronto and professor in the department of molecular genetics at the University of Toronto, Pawson told the audience that his research addresses the following questions: how are complex biological structures formed, and how is signal transduction organized in space and time?

Among his laboratory's achievements is the discovery that nephrin-dependent actin reorganization is mediated by the Nck (non-catalytic region of tyrosine kinase adaptor protein) family of Src homology 2 (SH2)/SH3 cytoskeletal adaptor proteins. Nephrin is located at the glomerular slit membrane and is essential to renal function.

Using an inducible transgenic strategy to delete Nck expression in adult mouse podocytes, Pawson's lab found that that the loss of Nck protein expression rapidly led to proteinuria, glomerulosclerosis, and altered morphology of foot processes. Podocyte injury also reduced phosphorylation of nephrin in adult kidneys.

Nck likely acts in conjunction with other slit diaphragm proteins to sculpt the architecture of podocytes, Pawson said. He added that Nck is so important to maintaining podocyte morphology that its absence leads to a "corruption of the foot processes" of podocytes. In addition to suggesting that Nck is required to maintain adult podocytes, Pawson's research demonstrated that phosphotyrosine-based interactions with nephrin may occur in foot processes of resting, mature podocytes.

The podocytes of mice were also a focus of a state-of-the-art lecture by Karl Tryggvason, MD, PhD.

Mice in which the gene Rhpn1 has been knocked out develop proteinuria and focal segmental glomerulosclerosis.

"This is a novel podocyte-associated gene," he said, referring to Rhpn1 and adding that his lab is now studying the gene and its expression in human disease.

Tryggvason, a professor of medical chemistry at the Karolinska Institute in Stockholm and a member of the Nobel Assembly for physiology or medicine, isolated the defective gene in congenital nephrotic syndrome, leading to the discovery of the novel protein, nephrin.

While most of his talk focused on his laboratory's research studies, Tryggvason's presentation, titled "Toward New Understanding and Therapies in Glomerular Diseases," also tackled the state of renal disease research. "Kidney diseases are underserved when it comes to drug development, mainly due to poor understanding of the molecular and pathological mechanisms" of the diseases, he said.

Now in clinical trials are 1891 drugs for cancer and 305 drugs for diabetes but only 80 drugs for chronic renal diseases and diabetic nephropathy, he said, adding that renal disease drug development primarily emphasizes chronic kidney disease, not the early stages of disease.

The science of renal disease needs more hypothesis-driven research, more risky projects, an unbiased approach as well as innovation, Tryggvason said.

In his state-of-the-art lecture, Bruce Beutler, MD, described the forward genetics approach used by his laboratory at the Scripps Research Institute in La Jolla, Calif., to determine how the body senses microbes.

"The genetic approach is unbiased and produces surprises, unlike hypothesis driven research," said Beutler. The genetics strategy "makes no assumptions about how the system operates, induces mutations at random, screens phenotypes of interest, and positionally clones the causative mutations."

The mouse is the Beutler lab's genetic tool of choice. Using the germline mutagen ethylnitrosourea, his lab has produced 100 million mutations, 1 million of which are heterozygous coding changes. A total of 288 phenotypes are now under study through screens that examine development, behavior, and metabolism, as well as immune activities.

Beutler's lab has identified 33 mutations in 21 genes that affect signaling by TLRs (toll like receptors), which he previously showed to be the key sensors mammals use to perceive infection. The TLRs ignite the immune response within minutes of infection, but paradoxically, can cause much of the morbidity associated with infections.

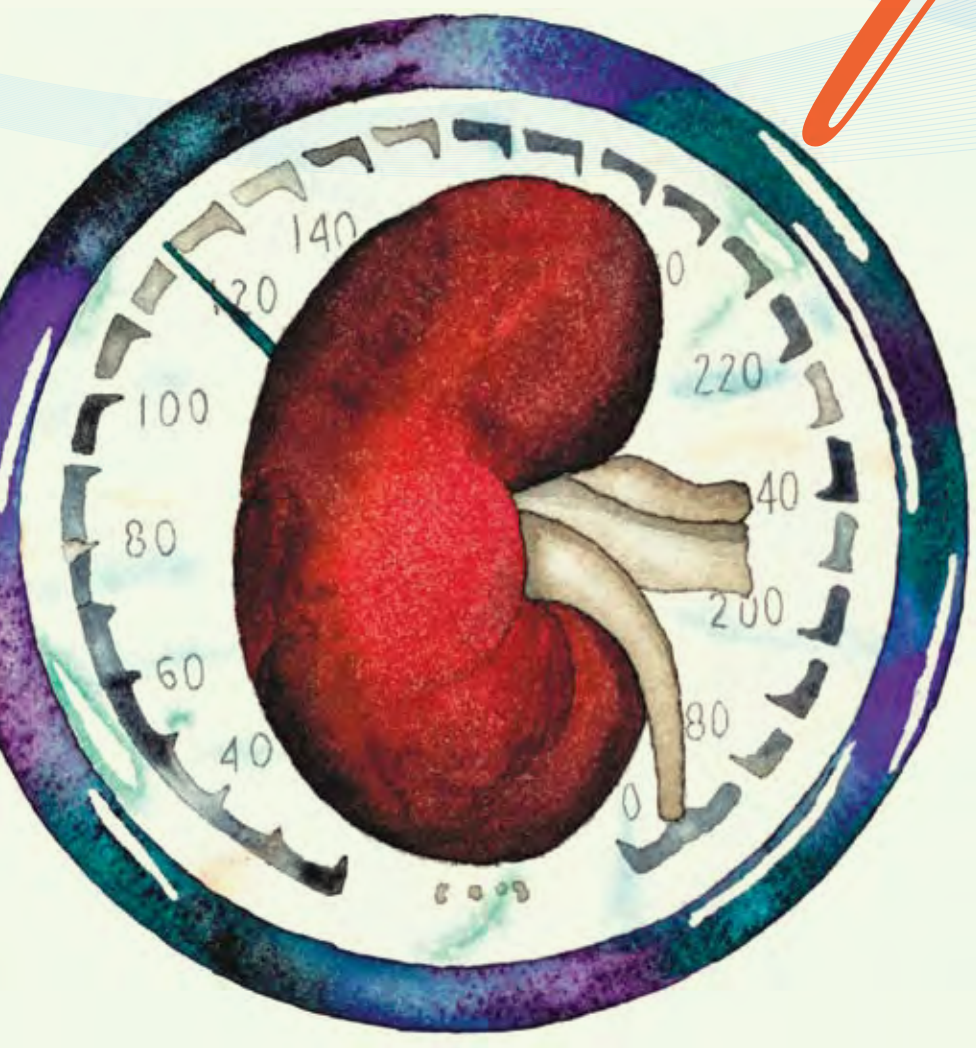
TLR's discovery was based on Beutler's positional cloning of the mutation (Lpsd) that prevented mice from sensing bacterial lipopolysaccharide. The lab has since discovered many of the essential proteins active in TLR signal transduction. As the gatekeepers of the most powerful inflammatory responses known, TLRs likely play a role in a wide range of diseases, not just infections, he said.

Early in his research career, Beutler isolated tumor necrosis factor (TNF) and revealed its role as an additional mediator of immune system-generated inflammation. His recombinant inhibitors of TNF are now widely use as Enbrel in the treatment of rheumatoid arthritis, psoriasis, ankylosing spondylitis, juvenile rheumatoid arthritis, and other autoimmune disorders.

Beutler, professor and chair of the department of genetics at the Scripps Research Institute, titled his state-of-the-art presentation "Genetic Insights into the Innate Immune System."

> **"Kidney diseases are underserved when it comes to drug development, mainly due to poor understanding of the molecular and pathological mechanisms"**
>
> **–Karl Tryggvason**

Dialysis



Insurers Unlikely to Pay for Life-Prolonging Treatments for Dialysis Patients

Keeping kidney disease patients alive on dialysis is so expensive that new therapies allowing patients to live longer would be rejected by groups that pay for medical care, according to a study at Renal Week.

"Our study examines a controversial area," said Philip McFarlane, MD, of the University of Toronto, Canada. "It is likely that new treatments that improve patient survival on hemodialysis will challenge the societal perceptions of how much we are collectively willing to pay to improve a person's survival."

To determine the economic impact of treatments that prolong the lives of hemodialysis patients, McFarlane and co-author David Mendelssohn, MD, of the University of Toronto, Canada, created a decision analysis model that simulated the states of hemodialysis, transplantation, and death and accounted for expected growth in incidence and inflation. Their model showed that even if treatments cost nothing, a modest 22 percent improvement in survival would generate over $5 million of additional costs over 10 years for a small dialysis program that started with 100 hemodialysis patients. For a larger group starting with 7500 hemodialysis patients (for example, Ontario, Canada), this modest improvement in survival would cost an additional $400 million over 10 years.

"These results will require the nephrology community, including those agencies that pay for dialysis care, to examine these issues," said McFarlane. "This may lead to a new priority to reduce the cost of treating people with kidney failure, either through improved efficiencies, greater emphasis on less costly treatments that replace kidney function, or through the development of new methods of replacing kidney function that are less costly than existing methods."

The authors reported no financial disclosures. The study, "Can We Afford to Improve Survival in Patients Receiving Hemodialysis?" was presented as part of a Renal Week session on Clinical Aspects of Chronic Kidney Disease: Prognosis and Complications II.

A More Paradoxical "Obesity Paradox": Skinny Dialysis Patients at Increased Risk for Death

The "obesity paradox" became more paradoxical as a result of a poster presentation at ASN Renal Week, with results indicating that hemodialysis (HD) patients with very low body fat are at increased risk of death—even when compared to HD patients with the highest levels of body fat.

Previous large-scale epidemiological studies have documented that a high body mass index is incrementally associated with better survival in patients with chronic kidney disease (CKD) undergoing maintenance hemodialysis.

"The higher the body fat, the greater the survival," Kamyar Kalantar-Zadeh, PhD, of the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, said about the study of 671 dialysis patients at eight California dialysis centers.

"Our study indicates that body fat may be protective in dialysis patients," he said. "The results add to the increasing number of reports about the 'obesity paradox' or 'reverse epidemiology' in patients with CKD and other chronic diseases."

After measuring the patients' body fat by using near-infrared interactance technology, Kalantar-Zadeh and colleagues divided the patients into five a priori selected body fat percentage groups. A total of 89 patients had a body fat of at least 40 percent. A body fat of 30 to 39 percent characterized 210 patients. The 10 to 19 percent body fat group included 156 patients. A total of 34 patients had a body fat of less than 10 percent.

The scientists subsequently monitored the mortality rate among the 671 patients over a five-year period (2001–2005). The death rate was 2.5 to 3 times higher among the 34 patients with less than 10 percent body fat than in the most numerous group of patients (210) whose body fat percentage was 20 to 29.

The increased risk of death for patients with very low body fat remained after adjustments for age, sex, race, other illnesses, and key laboratory results for albumin, hemoglobin, phosphorus, total iron binding capacity, ferritin, calcium, and creatinine.

Additional analyses using continuous values of body fat (rather than categories) confirmed a direct, linear relationship between body fat and mortality risk.

The patients were 53.6 ±15.0 years old. Most (52 percent) were men, 30 percent were African American, and 54 percent were diabetic. The mean body fat percentage for the entire group was 27.0 ± 10.5 percent, study co-author Debbie Benner, MS, RD, said at the ASN press briefing about the study.

Nephrologist T. Alp Ikizler, MD, who was moderator of the briefing and was not involved in the study, noted that the results suggest that physicians should be cautious about prescribing weight loss to dialysis patients and emphasize to their patients the health importance of consuming high-quality food. Ikizler is the Catherine McLaughlin Hakim chair in Medicine at Vanderbilt University School of Medicine.

Although more research is needed, the results suggest that the obesity paradox may be explained by an increased risk of death for patients with very low body fat, compared to those with average—or even very high—body fat.

Like other epidemiological studies, the investigation presented at ASN had observational findings only. "In addition, we estimated body fat by measuring the subcutaneous fat of the upper arm, which may be different from the intra-abdominal fat," Kalantar-Zadeh pointed out.

A National Institutes of Health grant funded the study, whose authors also included Youngmee Kim; Claudia Luna; Amanda Luna; Allen Nissenson, MD; Debbie Benner; and Csaba Kovesdy, MD.

The study was titled "Association of Body Fat and Survival in Hemodialysis Patients."

U.S. Sees Jump in Survival for Patients on Peritoneal Dialysis

The past few years have witnessed "substantial improvements" in survival among American patients on peritoneal dialysis (PD) relative to those on hemodialysis, according to new research.

That's a shift from the results of previous U.S. studies, which have tended to show better survival with hemodialysis. "This is a significant contribution to the ongoing debate over hemodialysis versus peritoneal dialysis," said Peter Blake, MD, of the University of London, Ontario, Canada.

"It is a little unexpected in that it shows PD doing relatively better than in previous U.S. studies," Blake said. "It brings U.S. findings more into line with those in Canada and Europe."

Led by Austin G. Stack, MD, MSc, a consultant nephrologist and epidemiologist at the Regional Kidney Centre, Letterkenny General Hospital, Ireland, the researchers analyzed trends in mortality for U.S. hemodialysis and peritoneal dialysis patients across three consecutive time periods: 1995–98, 1999–2001, and 2002–04. The analysis included national data on more than 1 million patients who started dialysis between 1995 and 2004, with follow-up to 2006.

In 2002–04, the risk of death for patients on peritoneal dialysis was significantly lower than for hemodialysis patients, the researchers found.

"In fact, peritoneal dialysis patients experienced a 29 percent lower risk of death at ages under 50 and 18 percent lower at age 50 to 70, compared with patients assigned to hemodialysis," said Stack. "There was no difference in mortality between peritoneal dialysis and hemodialysis for patients over 70 years."

Overall mortality for peritoneal dialysis patients decreased by a significant 21 percent from the period 1995–98 to 2002–04, adjusting for differences in case mix. Mortality among hemodialysis patients decreased by only 5 percent between the two calendar periods.

"This is very good news for people who support the use of peritoneal dialysis, in the sense that it's not only less costly but it's equally effective…and perhaps more cost-effective when it's used in the right patient," Blake said.

So why would the survival rate for those on peritoneal dialysis have changed so much in a 10-year period?

"It could involve the development of better practices and newer products and solutions," Blake said. "Another factor could be the use of cycler machines at nighttime, which has become widespread. It's also possible that, as the use of peritoneal dialysis has fallen in the United States, the patient population is a little bit more selected than it was before." Of course, he said, the researchers adjusted their analysis for case mix factors.

Stack cited other likely contributing factors, including reduction in peritonitis episodes, better volume control, the emergence of non-glucose containing solutions, and better pre-dialysis care. "The next challenge will be to tease out which of these, if not all, contributed to these improvements in peritoneal dialysis survival."

The study, "Substantial Improvement in Peritoneal Dialysis Survival Compared with Hemodialysis in the United States. A Longitudinal Trend Analysis: 1995–2006," was part of the Renal Week session on Improving Survival and Decreasing Morbidity of Dialysis.

Travel Is Linked to Increased Complications in Dialysis Patients

For kidney disease patients on dialysis, international travel can contribute to serious health complications. The findings from the study, "Holiday Travel in Hemodialysis Patients is Associated with Increased Infection, Loss of Vascular Access, and Anemia," were presented at Renal Week.

Claire Edwards and Neill Duncan of the Imperial College Kidney and Transplant Institute in London led a team of nurses and other clinicians that prospectively collected health information on patients from satellite units at their medical center who traveled at some point between April 2008 and March 2009. They studied 69 patients, aged 63.6 ± 12.9 years, of diverse ethnic background who traveled on vacation to Europe, the Middle East, India, the United States, Africa, the Pacific Rim, and South Asia.

The researchers noted that during travel, one patient died, and two damaged or lost their fistulas or grafts. (One had revision of his arteriovenous fistula while away, necessitating a temporary central venous catheter, and one required ligation of an infected ulcerated arteriovenous fistula upon return.) A total of 14 units of blood were transfused within one week of return in seven patients, and several patients acquired bloodstream infections. There was a significant decrease in mean hemoglobin from 12.3 ± 0.9 to 11.9 ± 1.0 g/dL ($p < 0.05$).

These findings indicate that travel is associated with significantly increased infection rates, loss of vascular access, and anemia in dialysis patients, Edwards said. "We have now measured the risk of travel for our patients, allowing us to give them good counsel," said Edwards. "This study empowers patients with information in order for them to make choices about their lifestyle."

The study was presented as part of a session on Dialysis: Epidemiology, Outcomes, and Clinical Trials: Non-Cardiovascular.

Sickle Cell Trait Is More Common in African Americans on Dialysis

The prevalence of sickle cell trait is higher—perhaps twice as high—in African Americans on dialysis, compared to the general African American population, suggests a new study from North Carolina.

Although confirmation is needed, "the high prevalence of sickle cell trait and hemoglobin C trait in the African American ESRD population raises questions both about the potential contribution to renal disease and the effect on the course of patients once they reach ESRD," said lead researcher Vimal K. Derebail, MD, of the University of North Carolina, Chapel Hill.

Derebail and colleagues analyzed the results of hemoglobin phenotyping in African American adults with end stage renal disease (ESRD) from four dialysis units. The rate of hemoglobinopathies was compared with that in African Americans in the general population, based on newborn screening data from three North Carolina counties in which the four dialysis units were located.

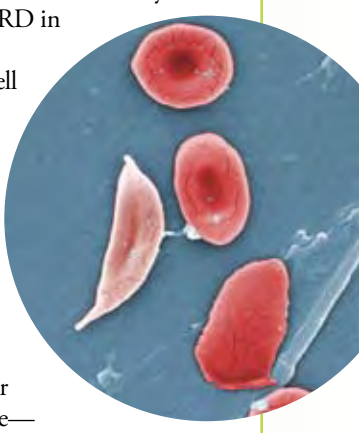
In 188 ESRD patients with available data, the prevalence of sickle cell trait was 14.9 percent—roughly double the 7.1 percent rate in the newborn screening population. The adult dialysis patients also had a higher rate of hemoglobin C trait: 4.8 versus 1.9 percent.

Sickle cell trait has been linked to several different abnormalities of the kidney, and thus might be expected to be more common among African Americans with ESRD. The new results suggest that this is indeed the case—sickle cell trait is found in one in seven of a sample of African American dialysis patients.

Although the findings are preliminary, Derebail said he believes the high rate of hemoglobinopathies could have important implications for African Americans with ESRD. "These less stable hemoglobins could contribute to resistance to treatment of anemia, which is more common in African Americans," he said. "Additionally, sickle cell trait may be a risk factor for venous thrombosis and as such could affect the longevity of arteriovenous fistulas and grafts used for hemodialysis.

"If sickle cell trait is truly associated with these problems, identification of trait carriers could alter patient management and perhaps lead to changes in treatment protocols for anemia and more intense monitoring for vascular access thrombosis."

The results are worthy of confirmation, said Graham Serjeant, MD, chairman of the Sickle Cell Trust in Jamaica. "Presumably many of these patients may have had renal biopsies during the course of their renal investigation. It would be of interest to know whether there was a specific pathology in AS [heterozygous] individuals with ESRD," he said. "The well-recognized renal changes in sickle cell trait affect predominantly the medulla and tubular function. There is currently no evidence of an increase in glomerular involvement, which would be the expected mechanism usually accounting for ESRD in patients with homozygous sickle cell (SS) diseases.



"The significant increase in the prevalence of the hemoglobin C trait—for which there is currently no evidence of tubular or other renal damage—sounds a note of caution in that some aspect of patient selection may have favored subjects with increased frequencies of both AS and AC genotypes," Serjeant said.

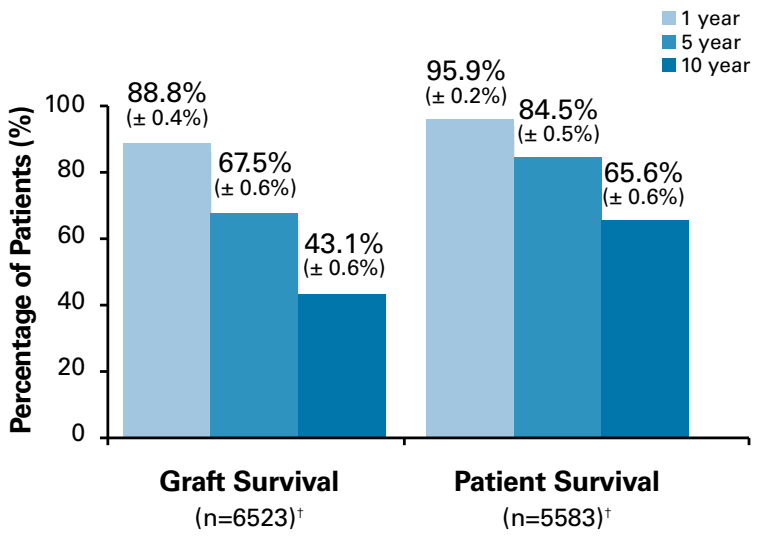
The study, "High Prevalence of Sickle Cell Trait in African-Americans with End-Stage Renal Disease," was part of the session on "CKD: Disparities in Risk, Access, and Outcomes."

Identifying key clinical challenges in

Key clinical challenges post-renal transplant

Data suggest that although considerable progress has been achieved in outcomes, such as acute rejection rates, these improvements are disproportionate to the gradual improvements made in posttransplant outcomes, such as graft and patient survival (Figure 1).[1-3]

Figure 1. Adjusted renal allograft and patient survival for deceased non-ECD donor type.*[2]

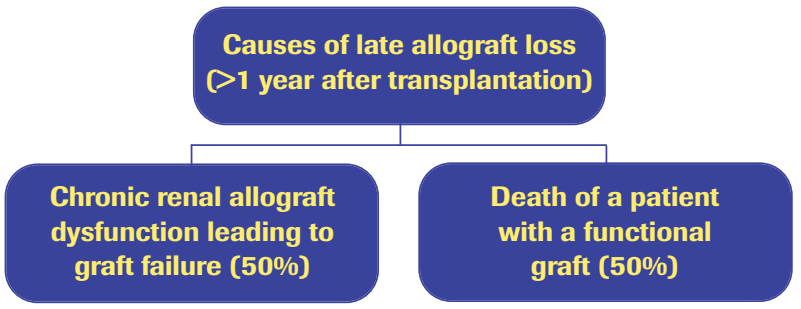


*Data from *OPTN/SRTR 2007 Annual Report*.
†Patients may have had more than 1 renal transplant.
Transplant year=1996.
Non-ECD donor type includes SCDs and DCDs.
Numbers expressed as percent (standard error).

Multiple factors may compromise posttransplant outcomes[4]

Chronic renal allograft dysfunction leading to graft failure and death with a functioning graft have been identified as the predominant causes of graft loss after 1-year posttransplant (Figure 2).[1]

Figure 2. Causes of late allograft loss.[1]



Adapted from Pascual et al. *NEJM* 2002.

El-Zoghby et al conducted a longitudinal cohort analysis of 1317 renal transplants performed between January 1996 and July 2006 to identify the causes of renal allograft failure. A mean follow-up of 50.3±32.6 months revealed 25% of grafts were lost (n=330). Of these, 41.8% (n=138) were due to death with function, 11.8% (n=39) due to permanent absence of renal function starting immediately after transplant, and 46.3% (n=153) due to other causes. Some of these other causes include glomerular disease (37%; n=56), fibrosis/atrophy (31%; n=47), medical/surgical conditions (16%; n=25), and acute rejection (12%; n=18).[4]

CAN: The leading cause of renal allograft failure[1]

There are multiple causes of chronic allograft nephropathy (CAN) occurring after 1 year posttransplant, including both immunologic and nonimmunologic risk factors. Immunologic factors can include episodes of acute rejection, histocompatibility differences, and suboptimal immunosuppression. Some nonimmunologic factors include donor age, graft quality, hypertension, and hyperlipidemia.[1]

Histopathologic findings from kidney allografts with CAN reveal features such as interstitial fibrosis, tubular atrophy, fibrous intimal thickening in the arteries, and variable glomerular lesions.[1,5,6] These histologic changes may result in clinical manifestations, such as a progressive and irreversible decline in renal function, as evidenced by increased serum creatinine or a decline in glomerular filtration rate (GFR), low-grade proteinuria, and hypertension.[1,6-8]

References:

1. Pascual M, Theruvath T, Kawai T, Tolkoff-Rubin N, Cosimi AB. Strategies to improve long-term outcomes after renal transplantation. *N Engl J Med*. 2002;346(8):580-590. **2.** The Organ Procurement and Transplant Network. *OPTN/SRTR 2007 Annual Report*. Transplant data, as of May 1, 2007. Available at: http://www.ustransplant.org/annual_reports/current. Accessed October 31, 2008. **3.** Hariharan S, McBride MA, Cherikh WS, Tolleris CB, Bresnahan BA, Johnson CP. Post-transplant renal function in the first year predicts long-term kidney transplant survival. *Kidney Int*. 2002;62(1):311-318. **4.** El-Zoghby ZM, Stegall MD, Lager DJ, et al. Identifying specific causes of kidney allograft loss. *Am J Transplant*. 2009;9(3):527-535. **5.** Halloran PF, Melk A, Barth C. Rethinking chronic allograft nephropathy: the concept of accelerated senescence. *J Am Soc Nephrol*. 1999;10(1):167-181. **6.** Racusen LC, Solez K, Colvin RB, et al. The Banff 97 working classification of renal allograft pathology. *Kidney Int*. 1999;55(2):713-723. **7.** Aull MJ. Chronic allograft nephropathy: pathogenesis and management of an important posttransplant complication. *Prog Transplant*. 2004;14(2):82-88. **8.** Krieger NR, Becker BN, Heisey DM, et al. Chronic allograft nephropathy uniformly affects recipients of cadaveric, nonidentical living-related, and living-unrelated grafts. *Transplantation*. 2003;75(10):1677-1682. **9.** Meier-Kriesche HU, Baliga R, Kaplan B. Decreased renal function is a strong risk factor for cardiovascular death after renal transplantation. *Transplantation*. 2003;75(8):1291-1295. **10.** Opelz G, Döhler B; Collaborative Transplant Study. Improved long-term outcomes after renal transplantation associated with blood pressure control. *Am J Transplant*. 2005;5(11):2725-2731. **11.** Dimény E, Wahlberg J, Lithell H, Fellström B. Hyperlipidaemia in renal transplantation—risk factor for long-term graft outcome. *Eur J Clin Invest*. 1995;25(8):574-583. **12.** Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ. Diabetes mellitus after kidney transplantation in the United States. *Am J Transplant*. 2003;3(2):178-185. **13.** Bodziak KA, Hricik DE. New-onset diabetes mellitus after solid organ transplantation. *Transpl Int*. 2009;22(5):519-530.

renal transplantation

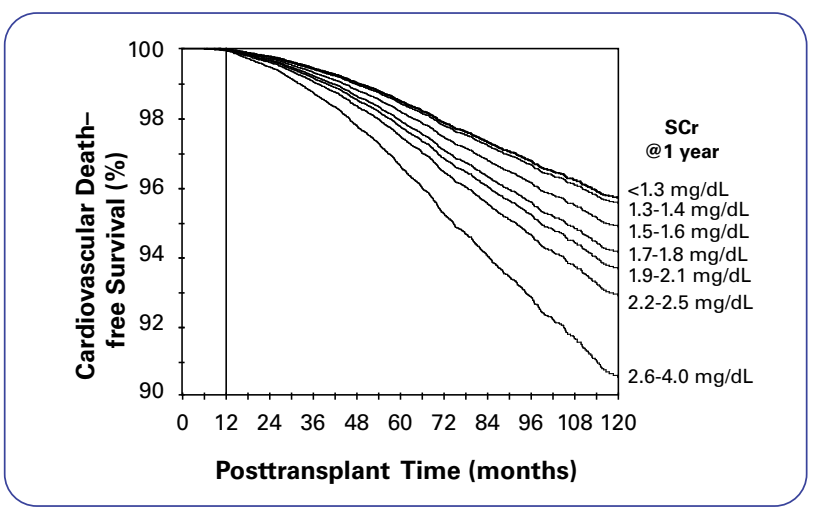
CV disease is the leading cause of death with a functioning graft posttransplant[9]

To investigate the role of renal function in determining the risk of CV death, Meier-Kriesche et al retrospectively studied 58,900 adult renal transplant recipients who received a primary renal transplant between 1988 and 1998 and who had graft survival of at least 1 year.[9]

Of the 5963 patients who died beyond 1 year posttransplant with a functioning graft, 30.1% (n=1797) died due to CV causes. Additional causes of death with a functioning graft included infectious complications, malignancy-related complications, and other, which were responsible for 11.7% (n=698), 10.1% (n=603), and 48.1% (n=2865) of deaths, respectively.[9]

As seen in Figure 3, the risk of CV death significantly increased with serum creatinine levels ≥1.7 mg/dL at 1 year posttransplant (*P*<.001).[9]

Figure 3. Cardiovascular death–free survival by serum creatinine level at 1 year posttransplant.[9]



Reprinted with permission of Wolters Kluwer Health.

Posttransplant CV and metabolic risk factors may be associated with poor posttransplant outcomes[10-12]

Posttransplant CV/metabolic risk factors

Hypertension[10]

Opelz et al:
Patients with higher systolic blood pressure (>140 mm Hg) at 1 and 3 years resulted in an increased risk of graft failure and death (both *P*<.001).

Opelz et al retrospectively analyzed data from 24,404 adult, de novo, renal transplant recipients who received deceased donor kidneys to examine the relationship between blood pressure control and graft and patient survival up to 10 years.

Hyperlipidemia[11]

Dimény et al:
Patients with serum cholesterol ≥6.9 mmol L^{-1} at 6 months posttransplant (n=37) had poorer renal allograft function (serum creatinine >160 µmol L^{-1}) at 2 years than those with lower cholesterol levels (<6.9 mmol L^{-1}, n=69).

In a follow-up study to their prospective trial, Dimény et al evaluated 151 renal allograft transplant patients from 1 center in Sweden, who received transplants between 1989 and 1991, to further assess the effect of hyperlipidemia on posttransplant outcomes.

Diabetes mellitus[12]

Kasiske et al:
Patients with posttransplant diabetes mellitus (PTDM) had an increased risk for renal allograft failure (relative risk: 1.63), death (relative risk: 1.87), and death-censored graft failure (relative risk: 1.46) (all *P*<.0001).

To evaluate the incidence and clinical impact of PTDM, Kasiske et al conducted a retrospective analysis of 11,659 renal transplant patients who were Medicare recipients and received first renal transplants from 1996 to 2000.

Signaling the future: Focusing on clinical challenges to help improve posttransplant outcomes[1,7,13]

Continued management of factors contributing to graft dysfunction leading to failure or death with function is important to improve posttransplant outcomes. Clinical strategies that help slow the progression of CAN and reduce the incidence of CV and metabolic risk factors should be considered.[1,7,13]

Bristol-Myers Squibb

721US09AB04102 09/09

Kidney DONATION & TRANSPLANTATION

African Americans Have Higher Morbidity After Donating Kidneys than Whites

African Americans who have been living kidney donors (LKDs) experience hypertension, diabetes, and chronic kidney disease at higher rates than white LKDs, a new study suggests.

The data do not imply a direct effect of donor nephrectomy on long-term health risks. Rather, they suggest that going through the LKD screening and selection process does not entirely avoid the higher rates of certain disease outcomes—especially hypertension, diabetes, and chronic kidney disease—associated with African American race.

"These results reinforce the view that many of us have, that kidney donation may be low risk for many, but is never safe," commented Robert W. Steiner, MD, director of transplant nephrology at the University of California, San Diego. "The lifetime risks for ESRD are greater for blacks, and this includes blacks who have donated kidneys."

Led by Krista L. Lentine, MD, of Saint Louis University, the study included information on 4650 prior LKDs, derived from a linkage of Organ Procurement and Transplantation Network (OPTN) identifiers to a private insurance claims database, which was used to determine the prevalence of various medical outcomes in the years after donor nephrectomy. A zip code-based index of socioeconomic status was incorporated using census data.

Fifty-five percent of the donors were women. Racial/ethnic status was white for 76 percent of donors, African American for 13 percent, and Hispanic for 8 percent. Mean age at the time of donation was 37; average time since nephrectomy was eight years.

African American LKDs had higher rates of several postdonation medical conditions. The likelihood of hypertension was 51 percent higher in African Americans after donation compared to whites. African American LKDs were more than twice as likely to require drug treatment for diabetes mellitus and to be diagnosed with chronic kidney disease, compared to white donors. The data also suggested higher rates of diabetes and chronic kidney disease in Hispanics compared to whites after kidney donation.

African American and Hispanic LKDs had lower socioeconomic status than their white counterparts. However, socioeconomic status was not significantly related to any study outcome.

Across racial groups, the prevalences of hypertension and diabetes in prior LKDs were lower than those reported in recent National Health and Nutrition Examination Survey data. But relative patterns according to race in prior LKDs were similar to patterns in the general population.

"For the sake of donors, those of us in the transplant profession have long aspired to safe donation," said Steiner. "However, we have also recognized the need to emphasize the unknowns—including risk of kidney disease—to all donors."

The overall risks of perioperative and long-term morbidity and mortality seem low, Steiner said, but it has been challenging to collect detailed information on long-term outcomes after donor nephrectomy, especially among racially diverse LKDs. The new study included 1102 nonwhite prior LKDs—one of the largest samples of nonwhite LKDs described to date.

"The message is not to discourage any group from stepping forward for potential donor evaluation, but to increase awareness of variation in long-term outcomes after kidney donation and the need to individualize counseling," said Lentine. "The 'strictness' of LKD selection has inherent tensions with increasing the organ supply, but the transplant community is obligated to consider health of LKDs as the priority."

There is still a lot to learn, according to Lentine. For example, the study had some important limitations related to the use of billing claims as outcome measures.

"And we need more studies to define the importance of postdonation diabetes and hypertension risk in nonwhite LKDs—even when not present at evaluation screening—on health outcomes such as ESRD, heart disease, and survival," he said. "Longer OPTN-mandated donor follow-up is an important policy advance, but current barriers to compliance, such as cost and inconvenience, warrant novel approaches to defining long-term donor outcomes.

"As a profession, our task is to fully recognize that all donors engage in a risk-taking decision," Steiner added. "In this sense, our mandate is to 'do harm (or risk harm) ethically,' because nothing else is possible here. Only when we quantify risk and use it to inform and select our donors, will we have matured in our approach to acceptable donor selection."

The study, "Variation in Post-Donation Comorbidity among Prior Living Kidney Donors," was part of the Renal Week session on Clinical Transplantation: Outcomes.

Group Discussions about Kidney Transplantation Increase Loved Ones' Willingness to Donate

Group education sessions inform chronic kidney disease (CKD) patients' family and friends about becoming kidney donors and increase the likelihood that they will consider becoming candidates, according to a study at Renal Week.

"Given the organ shortage, living donation is an increasingly important source of donor organs, but it is often overlooked because potential donors lack adequate information, and patients are reluctant to initiate discussion about the subject," said Marinus van den Dorpel, MD, PhD, of Maasstadziekenhuis, Rotterdam, the Netherlands.

Lead author van den Dorpel and his colleagues developed a group education format that addresses both of these issues. "We invited relatives and friends to attend a meeting, preferably at the patient's home, to get information about the disease, its impact on life, the prognosis, and how they could help the patient," said van den Dorpel. An experienced hospital social worker and a trained nurse practitioner provided information on the differences between dialysis and kidney transplantation and explained the risks and benefits of living kidney donation for recipients and donors.

In all 10 groups that participated, the CKD patients, relatives, and friends felt improved mutual understanding and bonding. In addition, all patients were relieved after the health care providers initiated discussion about living kidney donation. After a follow-up period of three months, potential kidney donors came forward from all the groups.

"Group education of families, relatives, and friends of patients with CKD synchronizes information and leads to better family bonding," the authors concluded. "This may enhance willingness to consider living kidney donation, thereby offering great potential benefit to patients."

The study, "Group Education of Families and Friends of CKD Patients: The Impact on Living Kidney Donation," was presented as part of a Renal Week session on Transplantation: Epidemiology, Outcomes, Clinical Trials, and Health Services Research.

Lupus Patients Who Receive Kidney Transplants Rarely Develop Lupus Nephritis

Recurrent lupus nephritis is uncommon in lupus patients who receive a kidney transplant, but the condition often leads to allograft failure with an increased risk of death after transplantation. That was the finding of a study presented recently at Renal Week.

Studies have provided conflicting results about the incidence and severity of the inflammatory condition lupus nephritis in patients with a history of lupus who have received a kidney transplant. To study the issue, Gabriel Contreras, MD, of the University of Miami, and his colleagues analyzed data from the United Network for Organ Sharing to determine the frequency of lupus nephritis in kidney transplant recipients and the risk this condition has for patients. Their analysis included 6850 patients with a history of lupus who received kidney transplants between 1987 and 2006.

The researchers found that lupus nephritis occurred in 2.44 percent of individuals in the study and that it led to a fourfold increased risk of kidney transplant failure. Also, death occurred in approximately 16 percent of affected transplant recipients.

"Lupus recurring in the kidney transplant as an event is less important than rejection in determining the absolute risk of kidney transplant failure because rejection is a much more frequent event, occurring in 26 percent of the recipients," said Contreras.

The investigators discovered that African Americans [odds ratio (OR) = 1.71; 95 percent confidence interval (CI) = 1.25–2.34) and young women (OR = 1.69; 95 percent CI = 1.05–2.75) were at higher risk for developing lupus nephritis in their transplanted kidney, but receiving a kidney transplant before or after starting dialysis did not affect one's risk. The type of kidney transplant (deceased or living donor) also had no effect on a patient's risk of developing lupus nephritis.

The study, "Recurrence of Lupus Nephritis Following Kidney Transplantation," was presented as part of a Renal Week session on Transplantation: Epidemiology, Outcomes, Clinical Trials, and Health Services Research.

Earlier Isn't Better for Preemptive Kidney Transplants

Among patients who receive a kidney transplant before they need to go on dialysis, better preserved native kidney function does not offer any additional survival advantage for the patient or the kidney transplant, according to a study presented at Renal Week.

Kidney disease patients who receive a preemptive transplant before they require dialysis tend to live longer and have better kidney graft function than patients who require dialysis before a transplant. To determine whether better kidney function among preemptive transplant recipients might further improve patients' long-term health, Basit Javaid, MD, of the Stanford University School of Medicine, and his colleagues mined data from the United Network for Organ Sharing (UNOS) and assessed all preemptive kidney transplant recipients who received their first kidney transplant between October 1987 and February 2009. These 25,748 preemptive kidney transplant recipients were divided into two groups: higher kidney function and lower kidney function at the time of transplant, based on estimated glomerular filtration rates.

"The study findings were expected to impact current practice patterns and perhaps the organ allocation criteria," said Javaid. "Superior outcomes among patients with higher residual native kidney function would have supported consideration for kidney transplantation earlier on in the course of chronic kidney disease when the native kidney function is better preserved."

Patients with higher native kidney function required less dialysis within the first week of transplant [odds ratio (OR) = 0.65; 95% confidence interval (CI) = 0.43–0.65; $p < 0.01$] and were less often treated for acute rejection in the first six months of transplantation [OR = 0.66; 95% CI = 0.59–0.74; $p < 0.01$]. But patient and kidney transplant survival rates were similar in the two groups.

Because patient and organ survival rates were not affected by kidney function level, patients and transplant experts anticipating a preemptive kidney transplant can wait for clinical indications to emerge before considering a transplant, Javaid said.

The authors noted that in a subgroup analysis, higher residual native kidney function among patients with polycystic kidney disease was associated with a lower risk of graft failure.

The authors reported no financial disclosures. Study co-authors include Marc Melcher, MD, Jin-Yon Kim, MD, Julie Yabu, MD, Jane Tan, MD, John Scandling, MD, and Stephan Busque, MD, all of the Stanford University School of Medicine.

The study, "Preemptive Kidney Transplant: Wouldn't Earlier Be Even Better?" was presented as part of a Renal Week session on Transplantation: Epidemiology, Outcomes, Clinical Trials, and Health Services Research.

Recent MDs are Better at Referring Patients For Preemptive Kidney Transplants than Veteran Doctors

Compared with doctors who have been practicing for many years, recent medical school graduates are more likely to refer kidney disease patients for preemptive kidney transplants, according to a study presented at Renal Week.

"For patients with irreversible chronic kidney disease (CKD), preemptive kidney transplantation improves patient survival, graft survival, quality of life, and incurs lower costs," said Daniela Ladner, MD, of Northwestern University, Feinberg School of Medicine, in Chicago. "However, little is known about the characteristics of patients who undergo preemptive kidney transplantation especially regarding their referring physicians."

To investigate, Ladner and her colleagues analyzed data from all adult patients who received a living donor kidney transplant at their institution between March 2007 and May 2009. A total of 529 transplantations were performed; 274 were preemptive, while 255 were performed after dialysis was initiated.

Referring physicians with less time since graduation were more likely to refer their kidney disease patients in time for preemptive transplantation ($p < 0.01$). This suggests that recent medical training has incorporated better timing of kidney transplantation. Referring doctors who are further from graduation may provide better care if they learn more about the benefits of preemptive transplantation, the authors said.

The authors report no financial disclosures. Study co-authors include Vadim Lyuksemburg, Raymond Chang, Olivia Ross, Juan Carlos Caicedo, MD, Anton Skaro, MD, PhD, John Friedewald, MD, Michael Abecassis, MD, and Jane Holl, MD, all of Northwestern University.

Artificially Sweetened Sodas Save Calories but not Kidneys

A "significant, twofold increased odds" for a fast decline of kidney function is linked to drinking two or more servings of artificially sweetened soda each day, according to a study presented at ASN Renal Week. Interestingly, a reduction in kidney function was not detected in members of the study population who consumed sugar-sweetened sodas.

According to the industry journal *Beverage Digest*, Americans consumed an average of 760 eight-ounce servings of soda in 2008.

The findings came from an analysis of health data on over 3000 women participating in the Nurses' Health Study by Julie Lin, MD, FASN, and Gary Curhan, MD, FASN, of Brigham and Women's Hospital.

The association between intake of artificially sweetened beverages and kidney function persisted even after Lin and Curhan accounted for age, caloric intake, obesity, high blood pressure, diabetes, cigarette smoking, physical activity, and cardiovascular disease.

Other studies have questioned the health effects of soda consumption. In 2007, Boston University scientists found that the risk for developing metabolic syndrome is 44 percent higher in people who daily consume one or more cans of diet soda and sugar-sweetened beverage. These findings came from an analysis of the Framingham Heart Study data on over 6000 people who filled out food questionnaires and were followed for an average of four years to gauge the health impact of their soft drink consumption habits. The study, funded by the National Institutes of Health and the American Diabetes Association, was published in the American Heart Association's journal *Circulation*.

In addition, Lin and Curhan noted that an association between sugar-sweetened soda and urinary protein was shown in a previous analysis of the nationally representative NHANES III population. However, information on kidney function change was not available then.

"There are currently limited data on the role of diet in kidney disease," Lin said. "While more study is needed, our research suggests that higher intake of artificially sweetened soda is associated with greater rate of decline in kidney function."

Because the participants in the study were older Caucasian women, the findings may not be directly applicable to men or people of other ethnicities, noted the scientists. They presented the paper, titled "Associations of Sweetened Beverages with Kidney Function Decline," during a free communication session.

Stem Cells Could Prevent AKI after Cardiac Surgery in High-Risk Patients

Allogeneic mesenchymal stem cells (MSC) could provide an effective new approach to reducing the rate of postoperative acute kidney injury (AKI) in high-risk patients, preliminary research suggests.

Led by Christof Westenfelder, MD, of the University of Utah, Salt Lake City, the researchers performed a phase I clinical trial with allogeneic MSC for the prevention of AKI in 15 patients undergoing coronary artery bypass grafting, with or without valve surgery. All patients had risk factors for AKI: kidney disease or other chronic disease, age older than 65, or bypass time longer than two hours.

All patients received allogeneic MSC according to the dose-escalation design. This form of stem cell therapy has been shown to preserve kidney function three months after ischemia-reperfusion AKI in rats via paracrine actions. In the new trial, there were no apparent adverse effects of MSC administration.

The treatment reduced patients' postoperative length of stay and hospital readmission rate by about half, compared to closely matched historical controls. At discharge, all patients treated with MSC had normal kidney function—in contrast, about 20 percent of control patients had AKI. Renal function remained normal through six months' of follow-up in MSC-treated patients. Kidney function declined progressively in the historical controls.

Allogeneic MSC shows promising safety and efficacy in preventing AKI and subsequent declines in renal function among cardiac surgical patients at high risk, the researchers said.

"Acute kidney injury is a common complication with high morbidity and mortality rates for which no specific therapy is currently available," Westenfelder said. "It is also increasingly recognized as the cause of progressive chronic kidney disease, eventually requiring dialysis therapy or a kidney transplant. New therapies for both the prevention and treatment of AKI are urgently needed."

Based on their phase I results, Westenfelder's group is planning a phase II multicenter study of MSC for AKI prevention.

"This would be an innovative approach for the prevention of AKI and has tremendous potential," said Anupam Agarwal, MD, of the University of Alabama at Birmingham.

The study, "Administration of Allogeneic Mesenchymal Stem Cells in Open Heart Surgery Patients is Safe and Prevents Post-operative AKI and CKD, and Reduces Length of Stay and Readmission Rates: Results of Phase I Trial," was part of a Renal Week session on Pathophysiology of Kidney Disease: Acute Kidney Injury.

Sodium and Carotene Affect eGFR

Lower dietary sodium and higher carotene intake may reduce a woman's estimated glomerular filtration rate (eGFR), according to work by Julie Lin, MD, FASN, and Gary Curhan, MD, FASN, of Brigham and Women's Hospital.

In their poster presentation, "Associations of Diet with Kidney Function Decline," the scientists did not report significant associations for other nutrients.

The study examined the influence of individual dietary nutrients on eGFR decline in over 3000 women with well-preserved kidney function at baseline between 1989 and 2000. The study participants were women in the Nurses' Health Study, including 730 nurses with diabetes.

"In women with well-preserved kidney function, higher dietary sodium intake was associated with greater kidney function decline, which is consistent with experimental animal data that high sodium intake promotes progressive kidney decline," Lin and Curhan reported.

In addition to sodium and carotene, nutrients targeted by the scientists included dietary protein (total, animal, vegetable, low-fat dairy, high-fat dairy, total dairy, and nondairy); dietary fat (total, saturated, trans, mono-saturated, polyunsaturated, animal and vegetable); cholesterol; dietary fiber (total, soluble, and insoluble); anti-oxidant vitamins (vitamins A, C, and E); vitamin D; folate; fructose; and potassium.

Cumulative average energy-adjusted nutrient intake was derived from the participants' 1984, 1986, and 1990 answers on the Food Frequency Questionnaires, the most common dietary assessment tool used in large epidemiologic studies of diet and health.

Primary outcome was > 30 percent decline in eGFR as estimated by the four-variable MDRD equation.

In the study population, the median age was 67 years, 97 percent were Caucasian, 54 percent had hypertension, 24 percent were diabetic, and median eGFR was 85 mL/min/1.73 m^2 in 1989. A total of 380 women (11.5 percent of the study population) experienced an eGFR decline of more than 30 percent.

New Renal Week symposium honors Steven C. Hebert, who broke open black box of tubule cells

Steven C. Hebert, MD, the board-certified nephrologist and physician-scientist responsible for "breaking open the black box of tubule cells," was honored at an ASN symposium featuring four former colleagues, who described recent studies that build upon Hebert's pioneering research on the thick ascending limb's function and dysfunction in kidney disease.

Serving as moderators of the inaugural Steven C. Hebert Memorial Symposium were Gerhard H. Giebisch, MD, professor emeritus of cellular and molecular physiology at Yale and Robert S. Hoover, MD, assistant professor of medicine at the University of Chicago. Support for the session was provided by an educational grant from Amgen.

Speakers reported recent insights into the role of different NCKK2 isoforms, the regulation of the membrane transport protein NKCC2's function by the WNK protein kinases and reactive oxygen species, and the role of the potassium channel ROMK in solute reabsorption. WNKs (with-no-lysine [K]) play a role in blood pressure control, and ROMK (renal outer medullary potassium) transports potassium out of cells.

The speakers were:

- Jürgen B. Schnermann, MD, chief of the Kidney Disease Branch at the National Institute of Diabetes and Digestive and Kidney Diseases.
- Gerardo Gamba, MD, PhD, professor of medicine at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán and Instituto de Investigaciones Biomédicas, National University of Mexico.
- Pablo A. Ortiz, PhD, associate professor at Henry Ford Hospital's division of hypertension and vascular research in Detroit.
- Tong Wang, MD, professor and director of Integrated Kidney Function Core at Yale.

For the treatment of iron deficiency anemia in adult patients with CKD...

A new IV iron therapy has emerged...

AMAG PHARMACEUTICALS

NEW

Feraheme™ (ferumoxytol) Injection

For Intravenous (IV) use

- 510-mg undiluted IV push that may be delivered in under 1 minute[1]
  — Deliver at a rate of up to 1 mL/sec (30 mg/sec)[1]
  — Second dose should be delivered 3 to 8 days after the first dose[1]
- Proven safety and efficacy across all stages of CKD[1]

Feraheme™
ferumoxytol injection

Important Safety Information

Feraheme is indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease. *Feraheme* is contraindicated in patients with evidence of iron overload, known hypersensitivity to *Feraheme* or any of its components, and patients with anemia not caused by iron deficiency.

In clinical studies, serious hypersensitivity reactions were reported in 0.2% (3/1,726) of subjects receiving *Feraheme*. Other adverse reactions potentially associated with hypersensitivity (e.g., pruritus, rash, urticaria or wheezing) were reported in 3.7% (63/1,726) of subjects. Patients should be observed for signs and symptoms of hypersensitivity for at least 30 minutes following *Feraheme* injection and the drug should only be administered when personnel and therapies are readily available for the treatment of hypersensitivity reactions. 1.9% (33/1,726) of *Feraheme*-treated subjects experienced hypotension. Please monitor for signs and symptoms of hypotension following each *Feraheme* injection. Excessive therapy with parenteral iron can lead to excess storage of iron with the possibility of iatrogenic hemosiderosis. Patients should be regularly monitored for hematologic response during parenteral iron therapy, noting that lab assays may overestimate serum iron and transferrin bound iron values in the 24 hours following administration of *Feraheme*. As a superparamagnetic iron oxide, *Feraheme* may transiently affect magnetic resonance diagnostic imaging studies for up to 3 months following the last *Feraheme* dose. *Feraheme* will not affect X-ray, CT, PET, SPECT, ultrasound, or nuclear imaging.

In clinical trials, the most commonly occurring adverse reactions in *Feraheme* treated patients versus oral iron treated patients reported in ≥ 2% of chronic kidney disease patients were diarrhea (4.0% vs. 8.2%), nausea (3.1% vs. 7.5%), dizziness (2.6% vs. 1.8%), hypotension (2.5% vs. 0.4%), constipation (2.1% vs. 5.7%) and peripheral edema (2.0% vs. 3.2%). In clinical trials, adverse reactions leading to treatment discontinuation and occurring in 2 or more *Feraheme*-treated patients included hypotension, infusion site swelling, increased serum ferritin level, chest pain, diarrhea, dizziness, ecchymosis, pruritus, chronic renal failure, and urticaria.

Reference: 1. Feraheme™ Prescribing Information.

Please see reverse for brief summary of full Prescribing Information.

(877) 411-2510
www.feraheme.com

KDIGO Controversies Conference

Reaches Consensus on Definition, Classification, and Prognosis of Chronic Kidney Disease

Over the past few years, controversy over the definition and classification of chronic kidney disease (CKD) has played out in the editorial pages of nephrology journals. Although the debate occurred primarily among nephrologists, the controversy has implications for the care of CKD across all disciplines of medicine. A recently reached consensus on revisions to the classification of CKD based on prognosis may help to quell the controversy. The revisions do not change the definition of CKD.

The revisions arose from a Controversies Conference on "Chronic Kidney Disease: Definition, Classification and Prognosis" sponsored by Kidney Disease Improving Global Outcomes (KDIGO). KDIGO is an international nonprofit organization whose purpose is to improve the care and outcomes of kidney disease patients worldwide by promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines.

Before the conference, held in October, widespread agreement existed that kidney failure (stage 5 CKD) is a life-threatening condition, with increasing prevalence around the world, high cost, and poor outcomes. In the United States, the prevalence of kidney failure treated by dialysis and transplantation is approximately 0.2 percent of the population (500,000 people), with an annual cost of $35 billion. Kidney disease is silent in its early stages, but can be detected by commonly available laboratory tests, such as serum creatinine to estimate glomerular filtration rate (GFR) and urinary albumin-to-creatinine ratio (ACR) as a marker of kidney damage. Earlier detection and treatment could potentially reduce disease complications and the risk of developing kidney failure.

The controversies aired at the conference centered on the current definition and classification of kidney disease, proposed by the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) in 2002 and subsequently adopted, with minor modifications, by KDIGO in 2005. The guidelines define CKD as either GFR <60 mL/min/1.73 m^2 (less than half of the normal level in young adults) or kidney damage for >3 months, regardless of cause of disease. A urine albumin-to-creatinine ratio >30 mg/g is defined as a marker of kidney damage.

In people with CKD, the disease is

further classified by the level of GFR (known as stages). Population surveys of estimated GFR and urinary ACR identify between 11 and 12 percent of the U.S. adult population as having CKD using this definition (23 million people). The prevalence of CKD is as high as 40 percent among people over 70, primarily because of the large number of people with GFR 30–59 mL/min/1.73 m^2 (CKD stage 3), many of whom do not have elevated ACR. The prognosis of earlier stages of CKD is highly variable, with more people dying of cardiovascular disease (CVD) than kidney failure.

Based on similar findings around the world, the International Society of Nephrology and International Federation of Kidney Foundations adopted the message for World Kidney Day in 2008 that "CKD is common, harmful, and treatable." One of the purposes of the KDIGO conference was to identify absolute and relative risks of complications of CKD, including all-cause mortality, CVD mortality, kidney failure, acute kidney injury, and progressive kidney disease.

Overdiagnosis of CKD a concern

The main concern about the current definition and classification was the possibility of overdiagnosis of CKD and overuse of resources in the investigation and management of CKD, without appropriate modifications for variations in prognosis. Specific issues raised were the appropriateness of the GFR thresholds, albuminuria thresholds, and absence of age modifications—since lower GFR levels and higher albumin excretion rates are commonly observed in the apparently "healthy" elderly.

Underlying these controversies was concern regarding the methods for assessing eGFR and albuminuria, and discomfort with the term "disease" for labeling a large number of people, mostly elderly, with lower levels of GFR and albuminuria.

In response to this debate, the KDIGO Board of Directors convened the Controversies Conference to review and possibly suggest revisions to the definition and classification of CKD, in light of current knowledge regarding its prognosis, with the goal of improving patient outcomes. KDIGO appointed a Planning Committee chaired by Andrew Levey, MD (U.S.), and co-chaired by Meguid El Nahas, MD (U.K.), Paul de Jong, MD (NL), and Josef Coresh, MD, PhD (U.S.). The KDIGO Controversies Conference was tasked with addressing five questions:

1) What are the key outcomes of CKD?
2) What progress has been made in CKD testing (eGFR and albuminuria)?
3) What are the key factors determining prognosis of CKD (e.g., eGFR, albuminuria)?
4) Should the current CKD classification (based on eGFR) be modified to include additional factors associated with prognosis?
5) Should the current CKD definition be modified?

The planning committee invited representatives of studies to contribute data on outcomes of CKD in clinical or research populations in which eGFR and albuminuria had been determined at baseline. Outcomes considered included all-cause mortality, CVD mortality, kidney failure treated by dialysis or transplantation (end stage renal disease), acute kidney injury, and decline in eGFR (progressive CKD). An analytical committee provided a uniform analysis plan for systematic evaluation of the data for each cohort and performed meta-analyses of results provided by the studies.

Altogether, more than 50 cohorts submitted data and participated in the conference. Meta-analyses on 1.5 million study participants on a range of outcomes were performed and reviewed. A databook consisting of 1704 pages of cohort data and 464 pages of results of meta-analyses was distributed to all conference participants.

> **The debate reflects…a paradigm shift…from kidney failure as a life-threatening illness to earlier stages of kidney disease as the target for prevention, detection, evaluation, and management.**
> **—Andrew Levey**

The conference consisted of plenary sessions during which KDIGO Co-Chairs Bertram Kasiske, MD (U.S.), and Kai-Uwe Eckardt, MD (Germany), members of the Planning Committee, Richard Glassock, MD (U.S.), a noted critic of the current definition and classification, and other experts on CKD outlined the background and objectives of the conference. Following plenary sessions, conference participants broke out into smaller groups for in-depth discussions of data and a proposal for revisions, and then reconvened in a plenary session for expression of viewpoints on a number of subjects, including a nonbinding vote on questions prepared by the organizers.

The data reviewed showed a strong, consistent gradation in risk for all outcomes of CKD according to the level of estimated GFR and urine ACR across a wide range of study populations. Interestingly, the gradation was linear for all levels of albumin excretion and nonlinear for GFR. In general, increased risk for CKD was noted below a level of GFR around 60 mL/min/1.73 m^2 and at urinary ACR at all levels above 10 mg/g (the lowest value examined). The risk for cardiovascular mortality and kidney disease outcomes tended to be elevated at a higher eGFR than all-cause mortality. In addition, risk varied according to the cause of kidney disease and other factors, such as age, CVD risk factors, diabetes, hypertension, smoking, hypercholesterolemia, and history of CVD.

A strong consensus reached by those present was that the current classification did not adequately describe the severity of CKD, and that predicting prognosis could be improved by the following modifications to the classification:

1) Emphasize classification by cause, if known, in addition to stage.
2) Add albuminuria stages, in addition to GFR stages (ACR < 30 mg/g, 30–300 mg/g, and >300 mg/g).
3) Subdivide CKD stage 3 into two stages (GFR 30–44 and 45–59 mL/min/1.73 m^2).

Consensus also emerged that it would be premature to change the current definition of CKD based on levels of GFR or presence of kidney damage. The following recommendations were also adopted by those present:

1) Make no change to the definition based on GFR (<60 mL/min/1.73 m^2), regardless of age or sex.
2) Make no change to the level of albuminuria defined as a marker of kidney damage (urine ACR >30 mg/g).

These recommendations need to be codified by a guidelines development group that would include a broader array of disciplines.

The immense and unique database provided by the meta-analyses described at the Controversies Conference will supply a valuable resource upon which to base new guidelines for the diagnosis, classification, and prognosis of CKD.

For the time being, CKD prevalence estimates will remain unchanged, and will continue to include a large fraction of the elderly population. However, a modified classification that includes cause of disease (if known) and albuminuria stages, in addition to GFR stages, will relate better to prognosis than the staging based solely on GFR. This may be particularly helpful in the great majority of elderly individuals with reduced GFR—albuminuria staging may better define their risk for mortality and kidney disease outcomes. Improved information on prognosis can be helpful for a large number of management decisions, including decisions on who to refer to nephrologists.

As a consequence of this landmark meeting—designed to assess the controversies but not to develop new guidelines—it is anticipated that revision of the 2002 KDOQI clinical practice guidelines on definition and classification of CKD will be undertaken by KDIGO in the near future.

After the meeting, Glassock commented: "The Controversies Conference was truly a historical event that will propel this entire field to a new level. The openness of the debate, the rigor of the questions and answers, and the immensity of the data and its analysis was truly remarkable. While much work remains to be done on refining the classification, diagnosis, and prognosis of CKD, there is no doubt that the end product will have as its origins the findings and discussions that were in evidence at the London meeting."

In summarizing the outcome of the conference, Levey said, "The debate reflects a tension in our field caused by the paradigm shift about the basic perspective on CKD—from kidney failure as a life-threatening illness to earlier stages of kidney disease as the target for prevention, detection, evaluation, and management. While change is always difficult, especially for those in its midst, the debate has been healthy, and the discussions and consensus should enable us to move on and work across disciplines to improve outcomes for our patients."

A report from the conference was presented at the American Society of Nephrology annual meeting in San Diego and will be published in *Kidney International.*

Identifying predictive markers in

Better predictors of posttransplant outcomes may be needed[1-4]

Data demonstrated that although posttransplant outcomes have gradually improved over time, these improvements are disproportionate to the considerable progress achieved in other outcomes, such as acute rejection.[1-4] These findings suggest that acute rejection may not be considered the most reliable predictor of posttransplant outcomes.[4]

Alternative short-term surrogate markers, such as renal function, histologic findings, and immunologic markers, are being assessed in an effort to address the need for reliable predictors of posttransplant outcomes in renal transplantation.[4,5]

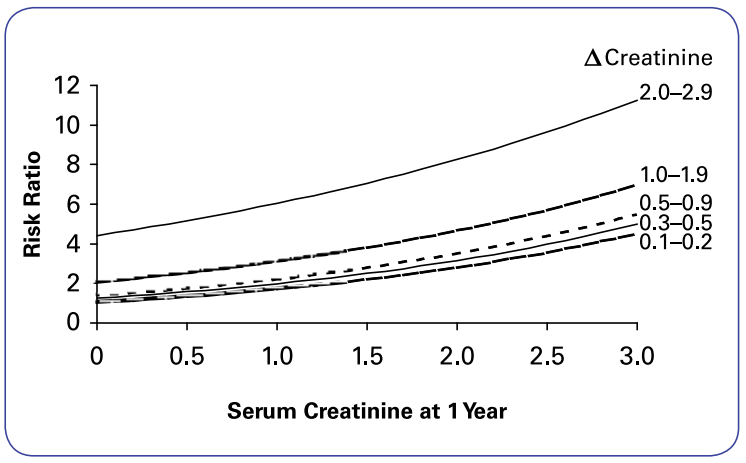
Is renal function a better predictor of posttransplant outcomes?

Studies demonstrated that renal function has emerged as a better marker than acute rejection in predicting posttransplant outcomes.[3,6,7] In addition, research has shown that preservation of renal function is important for graft survival.[3,8]

In a retrospective study of 105,742 de novo or repeat adult renal transplants from living or deceased donors performed between 1988 and 1998, Hariharan et al examined renal function in the first year posttransplant as a variable in determining renal graft survival. Results demonstrated a statistically significant link between renal function and graft survival: elevations in 1-year serum creatinine and change in serum creatinine from 6 to 12 months increase the relative hazard for graft failure (Figure 1).[3]

When assessing the impact of posttransplant variables on outcomes, 1-year serum creatinine and change in serum creatinine from 6 to 12 months had a significant effect ($P<.0001$) on graft failure. Acute rejection within 1 year, however, did not reach significance ($P=.8853$).[3]

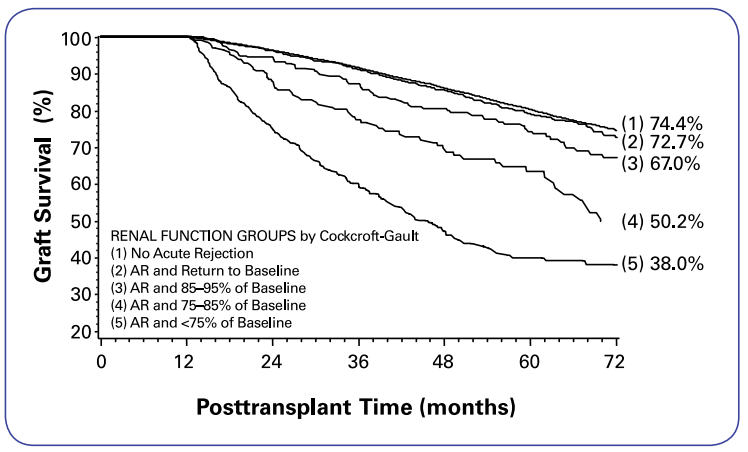
Figure 1. Relative hazard for graft failure according to 1-year creatinine and Δ creatinine values.[3]



Reprinted by permission from Macmillan Publishers Ltd: *Kidney International*, copyright 2002.[3]

To evaluate the impact of renal function on posttransplant graft survival in the absence or presence of acute rejection, Meier-Kriesche et al retrospectively studied 38,426 de novo adult renal transplants performed between 1995 and 2001. This study reported that only those acute rejection episodes that impair renal function negatively affect graft survival. Three- and 6-year graft survival rates were comparable among patients who had an acute rejection episode with renal function returning to baseline and those who had no acute rejection episodes (Figure 2). The data showed that in the presence of acute rejection episodes, renal function is the better predictor of posttransplant outcomes.[8]

Figure 2. Kaplan-Meier graph of overall graft survival by acute rejection/GFR grouping levels.[8]



Reproduced with permission of Blackwell Publishing Ltd.[8]

renal transplantation

Utilizing GFR to evaluate renal function[5,9]

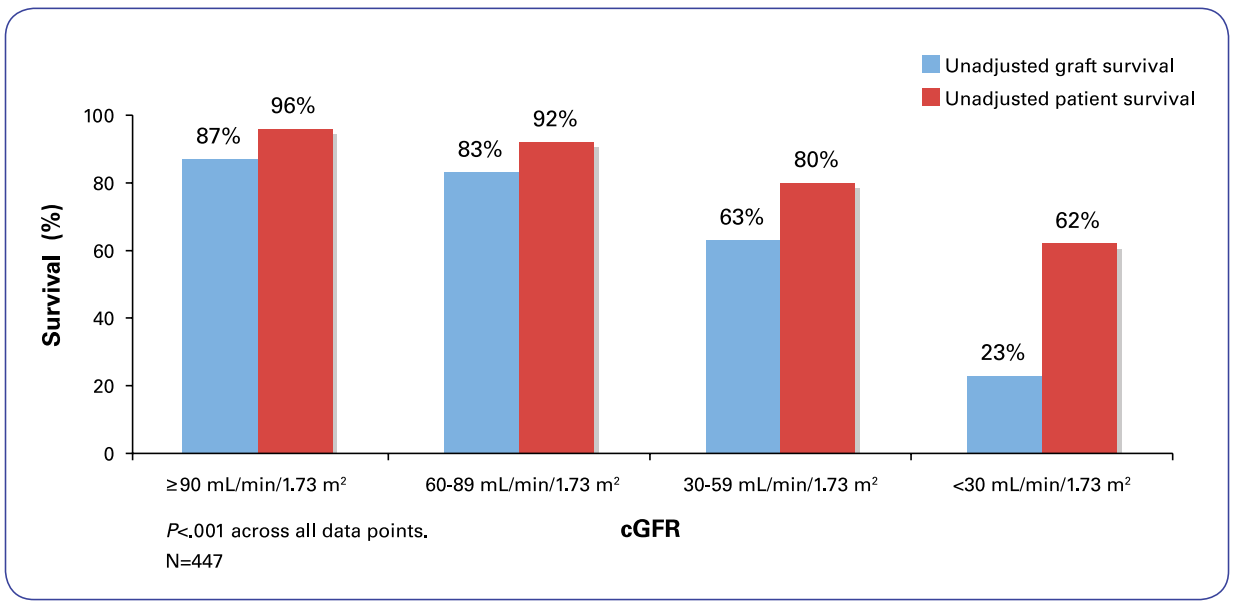
Glomerular filtration rate (GFR), measured through clearance assays, may be a more accurate method of estimating renal function versus serum creatinine by avoiding the dependence on age, gender, race, and body weight.[5]

In a retrospective study of 447 renal transplant recipients who received organs from deceased donors between 1980 and 1994, Marcén et al examined whether calculated GFR (using the MDRD equation) at 12 months posttransplant was predictive of 10-year graft and patient survival. As seen in Figure 3, results from this study are consistent with the findings from Hariharan et al, 2002, demonstrating renal function, as measured by cGFR, to be an important marker of posttransplant outcomes.[9]

Signaling the future: Using renal function as one of the key predictive markers for posttransplant outcomes[4,7,9]

Research findings have demonstrated that renal function may be a key predictor of posttransplant outcomes.[7,9] Renal function, as assessed by GFR, may help clinicians better evaluate posttransplant success.[4,7,9]

Figure 3. 10-year graft and patient survival by cGFR levels at 12 months posttransplant.[9]



References:
1. Pascual M, Theruvath T, Kawai T, Tolkoff-Rubin N, Cosimi AB. Strategies to improve long-term outcomes after renal transplantation. *N Engl J Med*. 2002;346(8):580-590. **2.** The Organ Procurement and Transplant Network. *OPTN/SRTR 2007 Annual Report*. Transplant data, as of May 1, 2007. Available at: http://www.ustransplant.org/annual_reports/current. Accessed October 31, 2008. **3.** Hariharan S, McBride MA, Cherikh WS, Tolleris CB, Bresnahan BA, Johnson CP. Post-transplant renal function in the first year predicts long-term kidney transplant survival. *Kidney Int*. 2002;62(1):311-318. **4.** Hariharan S, McBride MA, Cohen EP. Evolution of endpoints for renal transplant outcome. *Am J Transplant*. 2003;3(8):933-941. **5.** Hariharan S, Kasiske B, Matas A, Cohen A, Harmon W, Rabb H. Surrogate markers for long-term renal allograft survival. *Am J Transplant*. 2004;4(7):1179-1183. **6.** Meier-Kriesche HU, Baliga R, Kaplan B. Decreased renal function is a strong risk factor for cardiovascular death after renal transplantation. *Transplantation*. 2003;75(8):1291-1295. **7.** Salvadori M, Rosati A, Bock A, et al. Estimated one-year glomerular filtration rate is the best predictor of long-term graft function following renal transplant. *Transplantation*. 2006;81(2):202-206. **8.** Meier-Kriesche HU, Schold JD, Srinivas TR, Kaplan B. Lack of improvement in renal allograft survival despite a marked decrease in acute rejection rates over the most recent era. *Am J Transplant*. 2004;4(3):378-383. **9.** Marcén R, Pascual J, Tenorio M, et al. Chronic kidney disease in renal transplant recipients. *Transplant Proc*. 2005;37(9):3718-3720.

Bristol-Myers Squibb

721US09AB00509

09/09

Policy Update

Conflicts of Interest: Managing Bias and Creating Transparency

By Caroline Jennette

The 2009 Renal Week Public Policy Sessions got off to a provocative start with a forum on conflicts of interest in medicine.

Allen Detsky, MD, PhD, an economist and general internist at Mount Sinai Hospital in Toronto, Canada, argued that physicians sitting on clinical practice guideline (CPG) committees may be influenced—both consciously and subconsciously—by relationships they have with pharmaceutical companies.

In a survey of 100 physicians who served on CPG committees, Detsky and his colleagues found that the majority (87 percent) had relationships with pharmaceutical companies and that the average number of companies physicians had relationships with was 10. While most of these physicians did not feel that their own relationships with industry created bias, 17 percent accused their colleagues of having conflicts of interest (1). Detsky recommended mentoring junior faculty to stay free of industry influence as a means to become "bias-free" experts on CPG committees.

The degree to which the pharmaceutical industry has inserted itself into academic and professional societies also concerns Detsky, and he used the ASN exhibition hall as an example, where the carpeted and bright displays of the drug companies stand in stark contrast to the cramped poster area. However, he acknowledged that the relationship between pharmaceutical companies and professional societies is often one of necessity, as the revenue generated from industry helps keep professional meetings operational and keeps their staff employed.

An article published this year in the *Journal of the American Medical Association* lays out a new standard for professional medical associations (PMA) and their relationships with the medical industry (2). The recommendations include a ban on pharmaceutical and medical device industry funding except for journal advertising and exhibit hall fees as well as a ban on industry support for research and/or fellowships sponsored by PMAs. The American Society of Nephrology has produced its own policy on managing conflicts of interest that also addresses limiting industry influence and ensuring that educational activities stay free of industry bias and control (3).

Bernard Lo, MD, continued the conversation on conflicts of interest with the Christopher R. Blagg Endowed Lectureship. Lo, director of the University of San Francisco's Program in Medical Ethics, also chairs the Institute of Medicine's (IOM) Committee on Conflict of Interest in Medical Research, Education, and Practice.

The IOM Committee defines conflict of interest as "a set of circumstances that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest." An example is the subconscious effect that bias can have on practitioners that creates unintended and often negative consequences, Lo said. Although the importance of collaboration between academia and industry could be increased at the front end to develop new compounds for drugs or devices, collaborations at the back end with industry-sponsored clinical trials can create multiple conflicts of interest.

Lo discussed a sampling of recommendations from the IOM Committee on Conflicts of Interest report, published in April 2009 (4). Committee recommendations include:

- Creating a standardized, universal disclosure to decrease the variability between institutions and make the disclosure process easier and less time consuming;
- Establishing a consensus development process to develop continuing medical education that is free of industry influence;
- Creating clinical practice guidelines with no direct funding (general funds acceptable) and with full transparency of guideline members; and
- Requiring governing bodies of institutions engaged in medical research, medical education, patient care, or practice guideline development to establish their own standing committees on institutional conflicts of interest.

Lo noted that health care reform initiatives in both the Senate and the House carry provisions similar to the Physician Payment Sunshine Act 2009 (House Bill 3138/Senate Bill 301), which was introduced earlier this year. These provisions require the makers of drugs, medical devices, and medical supplies to report all payments made to physicians above a certain threshold on a publicly accessible website and highlight the political and public interest in exposing possible conflicts of interest.

Rounding out the Thursday session was Dr. Robert Califf, a cardiologist who heads up the Duke Translational Medicine Institute. Califf made the case that there can be substantial biases in the reporting of clinical trials, but with the caveat that "good people are motivated by the circumstances in which they find themselves." Bias is part of human nature and is here to stay, Califf said. He emphasized the importance of acknowledging that bias and including it with open discussion when presenting clinical trial results. Bias can play a detrimental role in all stages of the clinical trial process, from formulating the question and choosing the research design to answer that question, to who has access to the data and who is doing the manuscript review.

Califf ended his talk with a discussion of new regulations created by the Food and Drug Administration Amendments Act of 2007 (PL110-85, Sec. 85). As of December 2007, all clinical trials were mandated to submit clinical trial data and results to the national ClinicalTrials.gov registry (5). As of September 2009, study investigators must also submit all adverse events to the registry or pay a fine of up to $10,000 a day. These regulatory actions spurred by PL 110-85 may help take some of the bias out of data reporting, but Califf urges academia to work on the relationships it has with industry and to get over the "we are good, they are bad" mentality.

References

1. Choudhry NK, Stelfox HT, Detsky AS. Relationships between authors of clinical practice guidelines and the pharmaceutical industry. *J Am Med Assoc* 2002; 287(5):612–7.
2. Rothman DJ, McDonald WJ, Berkowitz CD, Chimonas SC, DeAngelis CD, Hale RW, Nissen SE, Osborn JE, Scully Jr JH, Thomson GE, Wofsky D. Professional Medical Associations and Their Relationships With Industry: A Proposal for Controlling Conflict of Interest. *J Am Med Assoc* 2009; 301(13):1367–1372.
3. View online here: http://www.asn-online.org/coi/.
4. Read the full IOM report online here: http://books.nap.edu/openbook.php?record_id=12598
5. For more information on the clinical trial reporting guidelines, visit: http://prsinfo.clinicaltrials.gov/fdaaa.html.
6. To read more on Enthoven's position: http://www.huffingtonpost.com/charles-kolb/our-health-future-the-bus_b_336723.html

Health Care Delivery: Lessons from Cleveland, Kaiser, and Canada

A Renal Week public policy symposium used current health care models to illustrate how care delivery systems can be used to provide more cohesive care to consumers.

Randall Cebul, MD, general internist and director of the Case Western Reserve University Center for Health Care Research and Policy, described the current health system in most of the nation as fragmented, with physicians having limited accountability and health care consumers frequently changing doctors and health care plans due to unemployment and lack of insurance portability. This fragmentation of care creates what Cebul terms "insurance churn," a system where insurance companies have little incentive to invest in preventive care and chronic disease management due to the transitory nature of insurance coverage.

The Better Health of Greater Cleveland program was presented as an example of a collaborative care model that works to avoid fragmentation of care by creating a system where health care institutions are accountable through public reporting of clinical outcomes stratified by disease condition, type of insurance, and provider type. The Cleveland program started in 2007, and outcome data have been mixed thus far in terms of results, but this system of open reporting and accountability is expected to increase good health outcomes for patients with chronic diseases. Along with this collaborative care model, Cebul provided several other remedies to fragmentation, including increasing pay for performance incentives, using the patient-centered medical home model, and capitation of payments to providers.

The opposite of fragmentation of care, according to Alain Enthoven, PhD, a health economist with Kaiser Permanente, is the integrated care model, for which Kaiser is a prime example. The goal of an integrated delivery system is to create a streamlined, one-stop shop for health care consumers through patient-centered, integrated care, a continuity of care not found in typical American health care, according to Enthoven. Physicians benefit from a culture of teamwork characterized by an alignment of incentives through capitation, salaried pay, shared practice guidelines, and physician leadership through self-governed group practices. Enthoven decried current health reform efforts to include a public option, stating that integrated delivery systems like Kaiser may be pushed out of the insurance market. He recommended instead that insurance companies need the freedom to compete on their own merit by increasing quality and decreasing costs of care (6).

Adeera Levin, MD, described how "necessity drives innovation" in a fixed system and explained chronic kidney disease and end stage renal disease care through the lens of Canada's single payer system. The Canadian government distributes funds to 10 provinces that create their own budgets and may add supplemental funding. Citizens with conditions deemed medically necessary can receive medical care and never see a bill. Although there is variability among provinces, the universal tenet of nephrology care is "equitable care across all stages of the kidney disease continuum, regardless of age or employment."

The British Columbia Renal Agency, directed by Levin, who is herself a practicing nephrologist, created a "kidney care service delivery framework" that has become a model of care delivery for several other provinces. Health care is delivered within an integrated system combining clinical care based on best practice models, fiscal accountability, and a systemwide information management system. Allied health professionals provide multidisciplinary care for early stage chronic kidney disease (CKD) management, with nephrology care added on as patients get closer to end stage renal disease. Preliminary data from Levin's cohort have been overwhelmingly positive: Patients seen longer in the early stages of CKD have increased survival once they start on dialysis, patients with an eGFR of <15 maintained kidney function for a median of 18 months before needing dialysis, and despite growth in their CKD population, dialysis incidence in British Columbia decreased from 5 percent to 3 percent, saving $3.2 million to be used elsewhere in the system.

While the collaborative care, integrated care, and single payer models all have their weaknesses, using successful elements and learning from their mistakes can help policymakers as they continue to craft changes to the current system of health care delivery.

Journal View

Antibiotics Yield Modest Decrease in Recurrent UTIs in Children

For children with risk factors for recurrent urinary tract infections (UTIs), long-term antibiotic prophylaxis has a small but significant preventive benefit, concludes a randomized trial in *The New England Journal of Medicine*.

The Australian multicenter trial included 576 children with at least one symptomatic UTI. The median age was 14 months; about two-thirds of patients were girls. Vesicoureteral reflux was present in 42 percent, grade III or higher in more than half of cases. Rates of microbiologically confirmed UTIs were compared for children assigned to prophylactic antibiotics (trimethoprim 2 mg/dL plus sulfamethoxazole 10 mg/kg) versus placebo.

Over 12 months, 13 percent of children in the antibiotic group had recurrent UTIs, compared to 19 percent of the placebo group. The number needed to treat to prevent one UTI was 14. The reduction in absolute risk was about the same—six to eight percentage points—across subgroups defined by age, sex, reflux status, or number of previous UTIs.

Large numbers of children receive long-term antibiotics with the goal of preventing recurrent UTIs and resultant kidney damage. However, in the absence of randomized trial data, this practice has been questioned.

The new results show a modest effect of trimethoprim-sulfamethoxazole in reducing the risk of symptomatic UTIs in predisposed children. The benefit appears greatest in the first six months; children whose index infection is resistant to trimethoprim-sulfamethoxazole may not benefit [Craig JC, Simpson JM, Williams GJ, Lowe A, Reynolds GJ, McTaggart SJ, Hodson EM, Carapetis JR, Cranswick NE, Smith G, Irwig LM, Caldwell PHY, Hamilton S, Roy LP, for the Prevention of Recurrent Urinary Tract Infection in Children with Vesicoureteric Reflux and Normal Renal Tracts (PRIVENT) Investigators. Antibiotic prophylaxis and recurrent urinary tract infection in children. *N Engl J Med* 2009; 361:1748–1759].

Serum Amyloid P: A New Inhibitor of Renal Fibrosis?

Serum amyloid P (SAP)—a known inhibitor of pulmonary and cardiac fibrosis—may also have antifibrotic effects in the kidneys, according to a study published in *Science Translational Medicine.*

In experiments in two models of renal fibrosis in mice, administration of human SAP (hSAP) was associated with dose-dependent reductions in fibrosis. Although fibroblasts were still present in similar numbers, hSAP treatment was associated with down-regulation of fibrotic collagen gene transcription and collagen protein deposition. Further experiments suggested that hSAP selectively localized to the injured kidneys, mainly associated with apoptotic and necrotic cells. In humans, more severe kidney disease was associated with lower plasma concentrations of hSAP.

In the kidneys, fibrosis depends on inflammatory monocytes and macrophages, rather than fibroblasts. The antifibrotic effect of hSAP appeared to occur via monocyte/macrophage binding and suppression, dependent on interleukin-19 and regulated binding to Fcy receptors.

There is an urgent need for new treatments directed against chronic inflammation with fibrosis. A natural soluble pattern recognition receptor, SAP has been shown to recognize danger-associated molecular patterns (DAMPs) on the membranes of apoptotic cells and promote Fcy receptor-dependent phagocytosis.

The new results suggest that SAP acts as a natural inhibitor of fibrosis in response to inflammatory kidney injury. A recombinant form of hSAP is undergoing initial studies in humans [Castaño AP, Lin S-L, Surowy T, Nowlin BT, Turlapati SA, Patel T, Singh A, Li S, Lupher ML Jr, Duffield JS. Serum amyloid P inhibits fibrosis through Fcy R-dependent monocyte-macrophage regulation in vivo. *Sci Transl Med*. 2009; 1:5–13].

Erythropoietins Linked to Increased Mortality in Kidney Transplant Patients

Especially when high hemoglobin levels are achieved, the use of erythropoietins in kidney transplant recipients may lead to an increased risk of death, reports a study in the *British Medical Journal*.

The retrospective analysis included Austrian registry data on 1794 patients who survived at least three months after kidney transplantation between 1992 and 2004. The use of erythropoietins increased from 12 percent in 1992 to 28 percent in 2001.

Unadjusted Kaplan-Meier analysis suggested lower 10-year survival in patients treated with erythropoietin: 57 versus 78 percent. With adjustment for confounding factors, hemoglobin levels of greater than 125 g/L tended to be associated with increased mortality—but only in patients receiving erythropoietins. This difference became significant at hemoglobin levels of 147 g/L or higher: hazard ratio 3.0 for erythropoietin-treated patients.

There is continued uncertainty over just how high hemoglobin levels can be safely increased with erythropoietin. Previous studies have suggested increased mortality among eythropoietin-treated patients with chronic kidney disease and end stage renal disease.

This registry study suggests a possible increase in mortality among kidney transplant patients receiving erythropoietins to raise hemoglobin levels, especially above 140 g/L. Although no causal association can be proved, the authors advise against giving erythropoietins to kidney transplant recipients with hemoglobin levels over 125 g/L [Heinze G, Kainz A, Hörl A, Oberbauer R: Mortality in renal transplant recipients given erythropoietins to increase haemoglobin concentration: cohort study. *Brit Med J* 2009; 339:4018].

Index to Advertisers

Practice Pointers

Renal Week Planning Demystified

ASN Kidney News editorial board member Edgar Lerma interviewed Ray Harris, MD, FASN, chair of the 2009 ASN Program Committee, which developed the program for Renal Week 2009. Harris is professor of medicine and director of the nephrology department at Vanderbilt University in Nashville, Tenn.

Ray Harris

What are the responsibilities of the ASN Program Committee and how many times a year does it meet?

There are three meetings during the course of the year. The first meeting is held immediately after the ASN annual meeting has concluded, the second is held in mid-January, and the third is held in mid-July. The initial meeting lasts one afternoon, and the other two meetings are held over a weekend.

The program committee is chosen to reflect the diversity of research and clinical interests of the ASN membership. Each program committee member develops themes and speakers for symposia and oversees the abstract categories in his or her area of expertise. This latter activity includes choosing the abstract reviewers and working with the chairs of the abstract review sessions to develop oral and poster sessions.

How is the ASN Program Committee different from the ASN Postgraduate Education Committee in terms of responsibilities and objectives?

In general, it is the goal of the Program Committee to develop symposia and invite speakers to highlight the latest advances in all areas of nephrology. The symposia developed by the Postgraduate Education Committee are designed to be educational and to update attendees on generally accepted state-of-the-art practices for subject areas.

What were the main highlights from this year's ASN annual meeting?

This year's program covered major areas in basic, translational, and clinical sciences. The four featured topics were: Epithelial Transport and Cell Biology, Renal Immunology and Transplantation, New Insights into Glomerular Structure and Function, and Kidney Development and Stem Cells.

Each topic was the focus of a Meeting-Within-a-Meeting (MWM) consisting of clinical and basic science symposia as well as free communication sessions. To encourage scientific interchange and to make the annual meeting more user-friendly, each MWM was held in the same area throughout the week. ASN encourages abstract submissions that present new research findings in areas covered by the featured topics.

What was new at this year's meeting?

We were extremely pleased to present a Steven C. Hebert Memorial Symposium in honor of the late Dr. Hebert's many scientific achievements.

In addition, a session on late-breaking clinical trials featured the results of a number of large trials, including the FAVORIT trial, the TREAT trial, and the ROADMAP trial.

How do you decide which programs go into Renal WeekEnds?

These decisions are made by the chair for Renal WeekEnds, in association with the ASN Education Committee.

What are the typical challenges you and the committee members encountered in planning for Renal Week? Do you think one year of preparation allows enough time to get all you want into the program?

The biggest challenge of the program committee is obtaining commitments from speakers to participate. Luckily, this year's program committee consisted of individuals who were very organized, diligent, and persistent, so we were able to attract a stellar group of speakers.

What is your advice to your successor and to next year's committee members?

David Ellison will be the chair of next year's Program Committee, and I know that he has already chosen another outstanding group of committee members. Just as I did, David served as a committee member for two years prior to becoming chair, so he is well versed in the operations of the committee, and I am absolutely certain that the 2010 ASN meeting will be wonderful.

I would like to be a member of the ASN Program Committee and be involved in preparation for Renal Week. What would you advise me to do?

The program committee is chosen to represent the diversity of the research and clinical activities of ASN members. Therefore, a committee member should have an area of expertise in order to effectively develop symposia and oversee the abstracts.

The committee members are usually chosen three to six months before the next year's ASN annual meeting. Although no guarantee of success, an individual may contact the program chair for upcoming meetings to volunteer as a potential committee member.

Industry Spotlight

Amgen Lawsuit Alleges Kickback Scheme to Spur Sales of Aranesp

The same day that a major national lawsuit was announced against it, Amgen released the published results from TREAT (the Trial to Reduce Cardiovascular Events with Aranesp Therapy), a large, randomized, double-blind, placebo-controlled, Phase III study of patients with chronic kidney disease. Published in the *New England Journal of Medicine* and presented at the ASN annual meeting, the study showed the anemia drug Aranesp failed to meet its primary objectives of a reduction in all-cause mortality and found a higher risk of stroke for patients on Aranesp compared with those taking a placebo.

The lawsuit was not about the performance of the anemia drug, however, but about the performance of the drug company representatives, who allegedly encouraged medical providers to bill insurers for samples of Aranesp that were supposed to be free to patients.

The suit alleges a subtle process through which Amgen, based in Thousand Oaks, Calif., provided beyond the usual amount of overfill in Aranesp samples while using less overfill in Procrit samples. Procrit is also manufactured by Amgen, but it is sold by Amgen's competitor, Johnson & Johnson.

The suit says that Amgen told medical practices that they would make more money if they used Aranesp, because they could bill insurers for that extra amount—whether they gave it all to a single patient or saved the extra portions to give to other patients, according to a report in *The New York Times*. The lawsuit also alleges that Amgen invited doctors on retreats and paid them for food and lodging, as well as for payment as advisers.

David Polk, a spokesperson for Amgen, said that the company could not comment on the lawsuit, but that Amgen has a solid compliance program and a code of conduct that employees are encouraged to follow.

The suit, filed in federal court in Massachusetts, includes plaintiffs in New York, California, Delaware, the District of Columbia, Florida, Hawaii, Illinois, Indiana, Louisiana, Massachusetts, Michigan, Nevada, New Hampshire, Tennessee, and Virginia.

NxStage Announces FREEDOM Study Interim Results

NxStage Medical accounced results from its FREEDOM (Following Rehabilitation, Economics and Everyday-Dialysis Outcome Measurements) trial during Renal Week 2009.

The FREEDOM study is a multicenter prospective cohort study designed to measure the clinical and economic benefits of daily home hemodialysis compared with conventional, thrice-weekly, in-center hemodialysis. Key interim findings included:

- a nearly 50 percent reduction in the average number of prescribed antihypertensive medications over 12 months;
- discontinuation of antihypertensive medications by 33 percent of patients; and
- a 50 percent or greater decrease in use of antihypertensive medications among 56 percent of patients.

Additional FREEDOM data demonstrated a 40 percent reduction in expected mortality of patients using daily home hemodialysis therapy with the NxStage System One compared with patients from the United States Renal Data System.

Toward a Wearable Kidney

AWAK Technologies, Inc., of Singapore, unveiled its peritoneal dialysis-based wearable artificial kidney at Renal Week 2009 in San Diego.

The idea that a two-pound, comfortable AWAK (Automated Wearable Artificial Kidney) could be coming is heartening news for patients, and the company spoke of two pounds as a goal. Right now, the AWAK is a six-pound battery-operated prototype. The kidney would provide continuous dialysis through a peritoneal dialysis platform.

AWAK Technologies hopes to begin clinical trials soon, perhaps in early 2010, in Singapore and Los Angeles. The AWAK Technologies website notes that the company hopes the product will be commercially licensed by 2011.

The device works by infusing dialysate into the peritoneal cavity so dialysis can occur. "What differentiates AWAK from either existing peritoneal dialysis or hemodialysis technology is that it is both wearable and self-contained," the company states. "Patients are able to live their lives with unrestricted mobility. More importantly, they do not have to regularly replace the dialysate as the AWAK continually regenerates the used dialysate through a sorbent cartridge."

The technology is based on original joint research done at the University of California, Los Angeles, and the U.S. Department of Veterans Affairs.

In 2007, Xcorporeal of Los Angeles completed a study of its artificial kidney prototype and demonstrated feasibility. However, Xcorporeal was delisted from the NYSE AMEX exchange in August 2009 because the company had large financial losses.

Alexion's Soliris Approved for Orphan Drug Status

Two international bodies approved the drug Soliris (eculizumab) for orphan drug status, giving manufacturer Alexion Pharmaceuticals, Inc., of Cheshire, Conn., special consideration on its way through the drug approval process. Orphan drugs are those that most likely wouldn't be developed because of the rarity of the disease they treat, in this case atypical hemolytic uremic syndrome (aHUS).

The prognosis for aHUS patients is grim. About 70 percent of patients with the most common mutation for aHUS experience chronic renal insufficiency, chronic dialysis, or death within one year of the first clinical episode.

Both the U.S. Food and Drug Administration and the European Commission have approved the orphan status. The intervention by government on behalf of orphan drug development can take a variety of forms, including tax incentives, better patent protection, and financially subsidized clinical research.

Alexion is currently enrolling patients in four clinical studies of Soliris as an investigational treatment for adolescent and adult patients with aHUS. Clinical studies are also currently being planned on the use of Soliris as a treatment for children with aHUS.

If the drug is approved for treatment, the drug's orphan status would let Alexion market Soliris for 10 years exclusively in Europe and for seven years exclusively in the United States.

Letters

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

inverness medical

The body talks. We translate.

Triage® NGAL Test

For Fast Quantitative Determination of NGAL*

in about 15 minutes
in EDTA whole blood or plasma

Triage® NGAL

Neutrophil Gelatinase-Associated Lipocalin

Biosite

For further information contact:
info.cardiology@invmed.com

* Not Available for Sale in the United States