ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

KidneyNews

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Many Hemodialysis Patients Have Limited Health Literacy

By Tracy Hampton

Many hemodialysis patients—especially those with lower education levels, African Americans, and veterans—do not understand the health information they need to make appropriate health decisions, according to findings of a recent report in *Clinical Journal of the American Society of Nephrology* (Green J, et al. Prevalence and demographic and clinical associations of health literacy in patients on maintenance hemodialysis).

"Health literacy may be particularly important to the care and outcomes of the more than 350,000 patients in the United States treated with chronic hemodialysis due to the complex nature of end stage renal disease management," said lead author Jamie Green, MD, of the University of Pittsburgh. "Efforts to understand and improve health literacy have the potential to significantly improve the care and outcomes of this high risk population of patients."

Health literacy among hemodialysis patients

Very few studies have examined health literacy—the ability to obtain, process, and understand health information so as to make appropriate health decisions—among hemodialysis patients. To investigate, Green and her colleagues tested 260 patients receiving long-term hemodialysis with a tool—the Rapid Estimate of Adult Literacy in Medicine (REALM)—that assesses one's ability to read common medical words and lay terms for body parts and illnesses. The patients were enrolled in the Symptom Management Involving End-Stage Renal Disease (SMILE) study, a multicenter randomized clinical trial comparing symptom management strategies in patients receiving long-term hemodialysis, and they were determined to have limited health literacy if they had a REALM score of 60 or less. The investigators evaluated the independent associations of demographic and baseline clinical characteristics with limited health literacy.

Green and her team found that 16 percent of the patients receiving dialysis did not understand basic health information. Given this prevalence, the estimated number of patients receiving long-term hemodialysis in the United States affected

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Local Community Program Fights Diabetes Among Latinos and Others in San Diego

By Cathy Yarbrough

In the nation's war against type 2 diabetes (T2D), the search for the "magic bullet" primarily targets drug development. However, one community-based program has been winning the battle—achieving patient outcomes that exceed the National Council for Quality Assurance's benchmarks in T2D care—through a systematic, evidence-based, culturally sensitive approach to patient care that emphasizes self-empowerment.

The 14-year-old program, Project Dulce, has served 18,000 patients at San Diego's community health clinics who are Latinos and members of other ethnic groups that are characterized by low income, inadequate insurance, and disproportionate rates of such T2D complications as kidney disease.

Because its clinical, behavioral, and economic outcomes have been so impressive, Project Dulce has been a model for similar community-based diabetes management programs in the United States. It now is being evaluated in selected T2D patients at Scripps Health, one of the top 10 health systems in the United States, according to Thomson Reuters. The patients in this pilot study have commercial medical insurance coverage but, like the Project

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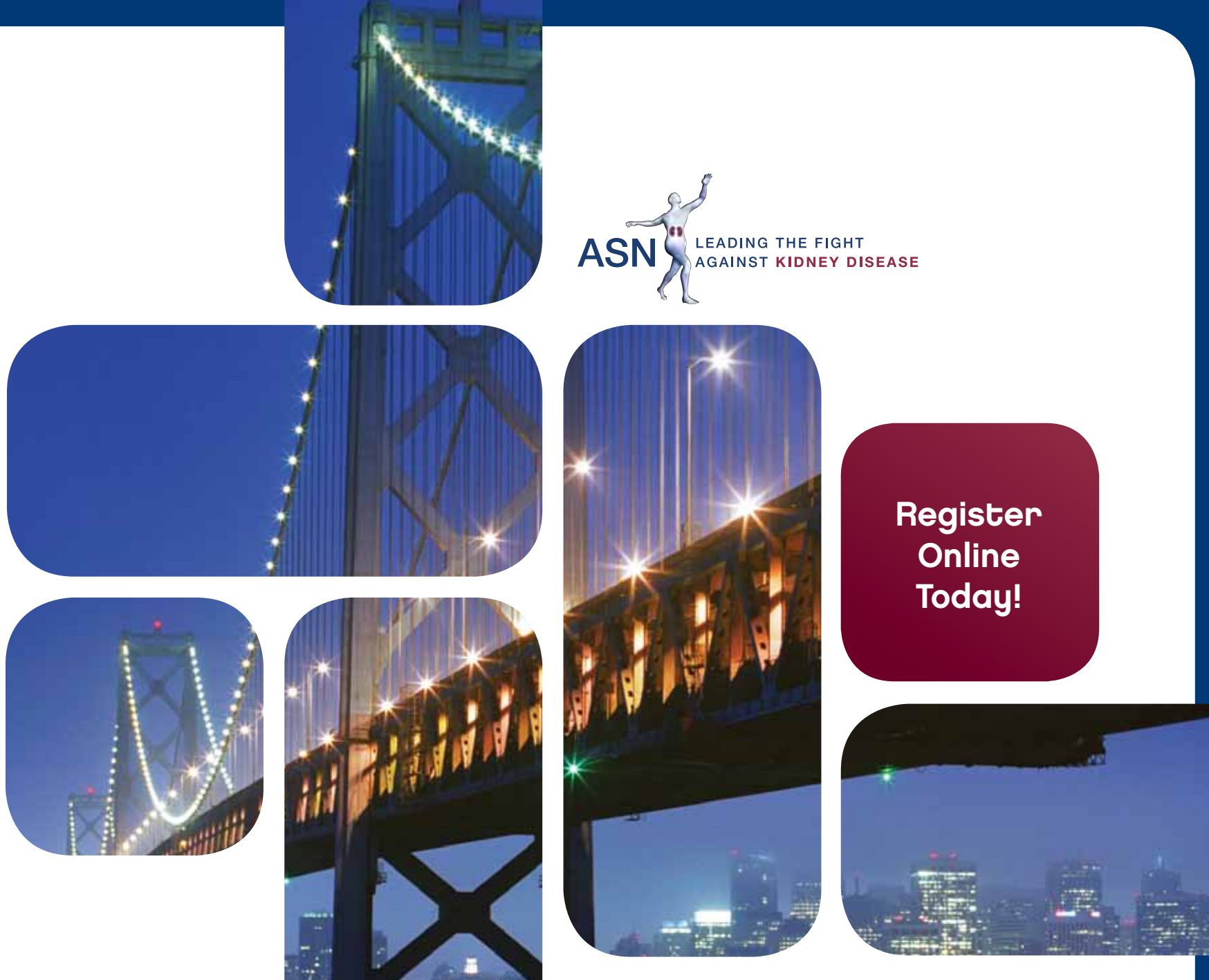

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Limited Health Literacy

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by this problem would be greater than 56,000. Of the 41 patients in this study with limited health literacy, 34 (83 percent) had REALM scores of 45–60 (i.e., seventh- or eighth-grade reading level), six (15 percent) had scores of 19–44 (i.e., fourth- to sixth-grade reading level), and one (2 percent) had a score less than 19 (i.e., less than fourth-grade reading level).

Limited health literacy was present in all subgroups of patients, but those with lower educational levels, African Americans, and veterans were at increased risk. Patients with less than a high school education had an increased risk of more than 12-fold of having limited health literacy, and African Americans and veterans had an increased risk of more than threefold. There were no associations between health literacy and age, gender, or markers of quality of care including hemoglobin level, serum phosphorus and intact parathyroid hormone level, or dialysis adequacy. Quality of life and overall symptom burden were similar in patients with and without limited health literacy.

"What is interesting is how common inadequate health literacy was in a population enrolled in a trial," said Vanessa Grubbs, MD, who was not part of the research effort and is an assistant professor in the division of nephrology of the department of medicine at the University of California, San Francisco. She suggested that perhaps health literacy should be a standard measure in future clinical trials. "On the other hand, I think we have to move beyond documenting that inadequate health literacy is common to demonstrating effective ways to achieve good outcomes in spite of it," she said.

The importance of health literacy

Limited health literacy is estimated to affect more than 90 million Americans and has been associated with adverse health outcomes and higher healthcare costs in patients with a variety of chronic illnesses. In addition, there is evidence that limited health literacy contributes to racial disparities in health outcomes.

Health literacy may be particularly important for patients receiving hemodialysis because they must attend treatment sessions several days a week, follow dietary and fluid restrictions, and adhere to complex medication regimens, all of which require them to understand and act on complicated health-related information. Research has indicated that patients receiving hemodialysis take an average of 19 medications each day, and one-quarter of them take more than 25 medications each day (Chiu YW, et al. Pill burden, adherence, hyperphosphatemia, and quality of life in maintenance dialysis patients. *Clin J Am Soc Nephrol* 2009; 4:1089–1096).

Previous research has shown that limited health literacy is associated with a higher risk of mortality in incident hemodialysis patients (Cavanaugh KL, et al. Low health literacy associates with increased mortality in ESRD (*J Am Soc Nephrol* 2010; 21:1979–1985) and that in patients with chronic kidney disease, limited health literacy is significantly associated with lower knowledge about kidney disease (Wright JA, et al. Development and results of a kidney disease knowledge survey given to patients with CKD. *Am J Kidney Dis* 2011; 57:387–395).

"Despite this growing body of evidence supporting an influential role of limited health literacy in patients with kidney disease, there have not been any studies to evaluate interventions to address health literacy, improve communication and translation of complex information, and determine its impact on clinical outcomes in kidney disease," said Kerri Cavanaugh, MD, who is an assistant professor of medicine in the division of nephrology at Vanderbilt University Medical Center in Nashville, and whose research team uncovered these findings.

Green and her colleagues are currently following up the participants in their study to determine whether limited health literacy affects how patients adhere to dialysis treatment, whether they undergo kidney transplantation, and whether they die prematurely.

"We anticipate our findings will increase awareness of the importance of health literacy in patients with kidney disease, stimulate providers to consider literacy when communicating with patients, and lead to future studies to address limitations in health literacy," she said.

Study coauthors include Maria Mor, PhD, Mary Ann Sevick, Paul Palevsky, MD, Michael Fine, MD, Steven Weisbord, MD (VA Pittsburgh Healthcare System and University of Pittsburgh); Anne Marie Shields (VA Pittsburgh Healthcare System); and Robert Arnold, MD (University of Pittsburgh).

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Program Fights Diabetes

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Dulce patients, are at high risk for the development of disease complications.

"Project Dulce is the model that recent health care reform initiatives have been looking for," said Scripps Health endocrinologist Athena Philis-Tsimikas, MD, whose leadership of Project Dulce was recognized with the Outstanding Service Award for the Promotion of Endocrine Health of an Underserved Population at the annual meeting of the American Association of Clinical Endocrinologists in April 2011.

In addition to improving T2D patients' HbA1c, blood pressure, and lipid parameters, Project Dulce achieves "lower total cost of care due to consistent reduction in hospitalizations," said Philis-Tsimikas, chief medical officer and corporate vice president of the Scripps Whittier Diabetes Institute, one of the largest diabetes education programs accredited by the American Diabetes Association (ADA) in the United States.

The site of the pilot study is the Scripps Health clinic in Rancho Bernardo, a master-planned community in San Diego that is home to residences and regional offices of Sony Electronics and several other corporations.

Like Project Dulce, the pilot study follows the chronic care model, emphasizing productive interactions between patients and their registered nurses and case managers who collaborate with the patients' physicians.

"Because standardized orders are followed, the care process is allowed to move along more efficiently," explained Philis-Tsimikas, who is certified by the American Board of Internal Medicine in the subspecialty of diabetes and endocrinology.

Project Dulce's registered nurses and case managers are certified diabetes educators trained by endocrinologists on the Staged Diabetes Management protocols for stepped-care pharmacologic treatment of glucose and lipid levels and hypertension. Project Dulce's bilingual and bicultural care teams also include medical assistants and registered dieticians.

When Project Dulce began, community health clinic physicians were reluctant to work so collaboratively with the nurses/case managers. However, after two weeks, they were uniformly enthusiastic, Philis-Tsimikas noted. In addition to enhancing the quality of patient care, the nurses/case managers saved physicians time by taking responsibility for the instruction of patients about measuring glucose and achieving target levels by adjusting diet and medication.

In the Project Dulce model, new patients participate in eight weekly two-hour group classes taught by peer educators (promotoras), members of the patients' ethnic group who effectively manage their T2D and have completed three months of training in the ADA-certified curriculum program. In the pilot study, group classes also will be given.

"The promotoras, who are supervised by a health educator, take on the traditional role of the nurse in educating the patient," said Philis-Tsimikas. As trusted sources of information, the promotoras persuade the Project Dulce patients to follow the prescribed medical therapy rather than use home remedies such as eating nopales to cure diabetes.

"In the Hispanic/Latino community, people tend to follow those who relate to them. They think, 'This person is one of my people,'" said Betsy Rodríguez, senior deputy director, National Diabetes Education Program of the U.S. Centers for Disease Control.

Promotoras also can help patients to "unlearn" cultural beliefs—for example, that extreme emotional stress causes diabetes, Rodriguez added.

Or that T2D complications are inevitable. Philis-Tsimikas recalled one patient, José, who came to Project Dulce after experiencing vision loss, coronary artery bypass surgery, and metatarsal amputation.

"His grandmother, mother, and brother all had similar complications. So why shouldn't he? Wasn't that just part of the disease?" said Philis-Tsimikas.

When José enrolled in Project Dulce, his creatinine level was 2.8 mg/dL. Although he learned how to make adjustments in his medications and diet, and achieved normal ranges for blood glucose and low-density lipoprotein, his kidney function continued to worsen, requiring dialysis.

José "exemplifies what is happening to so many people with diabetes in our nation. Opportunities missed! We had opportunities to prevent his heart, vascular, and kidney disease early on," said Philis-Tsimikas.

In 2004, she and her colleagues reported significant improvements in levels of HbA1c and total cholesterol in Project Dulce patients, and that these patients required fewer urgent care visits and hospitalizations than did patients receiving standard care. Project Dulce patients' knowledge about T2D had increased, and their inaccurate cultural beliefs and reliance on cultural-based remedies had decreased. At the 2009 ADA scientific sessions, Philis-Tsimikas and her colleagues reported that in the peer-led educational arm (Project Dulce), glycemic control was significantly improved at the 10-month follow-up: the HbA_{1c} was 9.70 ± 2.00 percent in the standard group versus 8.71 ± 1.98 percent in the peer-led group ($p = 0.15$).

Also at the 2009 ADA meeting, they presented preliminary results in a randomized, controlled, prospective clinical study of over 200 Mexican-American T2D patients who were 21 to 75 years of age and had HbA_{1c} ≥8 percent (9.91 percent in the standard group vs. 10.43 percent in the peer-led group, $p = 0.42$). These patients had been randomly assigned to Project Dulce or to the standard diabetes care of the community health centers.

Philis-Tsimikas and her team will soon publish a paper reporting their findings, which are similar to the results presented at the ADA meeting, she said.

A previous report documented that

Project Dulce is cost effective. In a 2007 *Health Research and Educational Trust* article, University of California San Diego health economist Todd P. Gilmer, PhD, and his colleagues analyzed data on 3893 T2D patients, 61 percent of whom were female and 48 percent of whom were Latino, and used clinical and cost data on Project Dulce as well as on commercially insured patients as inputs into a diabetes simulation model.

The incremental cost ratios per quality-adjusted life expectancy gained were $10,141 for the uninsured, $24,584 for those covered by San Diego County Medical Services, $44,941 for Medi-Cal recipients, and $69,587 for those with commercial insurance.

Scripps Health will soon complete a systemwide electronic diabetes registry, modeled on the Project Dulce registry, that will enable Philis-Tsimikas and her team to measure and monitor clinical outcomes against the ADA guidelines and stratify patients according to their HbA1c, blood pressure, and lipid parameters.

"The registry enables us to be proactive, to quickly identify patients who need extra attention because their outcomes are out of range," said Philis-Tsimikas.

Suggested Reading

Project Dulce: http://www.scripps.org/services/diabetes/project-dulce

Athena Philis-Tsimikas, MD: http://www.scripps.org/physicians/4994-athena-philis-tsimikas

Scripps Health Physician Receives Outstanding Service Award for Diabetes Program: http://media.aace.com/article_display.cfm?article_id=5056

"Scripps Endocrinologist Helps Latinos Better Understand Diabetes": http://www.scripps.org/news_items/3876-scripps-endocrinologist-helps-latinos-better-understand-diabetes

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July Special Feature: Pregnancy and the Kidney

Pregnancy influences kidney function in many ways, and changes in kidney function can seriously impact the outcome of pregnancy. Changes in kidney function can have serious implications in terms of counseling, monitoring, and treating women with kidney issues who wish to become, or succeed in becoming, pregnant.

In the July *Kidney News*, national experts will offer their opinions on several issues regarding pregnancy and the kidney. Articles will discuss normal and abnormal physiologic adaption during pregnancy, how to evaluate acute kidney injury during pregnancy, the role and significance of angiogenic factors in preeclampsia, pregnancy in transplant recipients, and long-term outcomes of women who experience preeclampsia. We hope you find it engaging.

—Richard Lafayette, MD, FACP
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Policy Update

ASN Hill Day 2011

By Daniel Kochis and Rachel Shaffer

Sixteen American Society of Nephrology (ASN) leaders, members of the ASN Council, Public Policy Board, and Board of Advisors, plus seven ASN staff members participated in the first annual ASN Hill Day on May 5, 2011. Through these efforts they helped raise awareness of the growing public health threat of kidney disease and encouraged support among lawmakers for ASN's policy priorities.

In more than 50 meetings with congressional leaders from both parties, ASN raised general awareness of kidney disease, which afflicts one in nine Americans. While kidney disease is a serious public health concern, it is not as well known by policymakers as other chronic diseases such as diabetes and heart disease.

Public Policy Board Chair Thomas Hostetter, MD, found support for ASN's policy priorities on both sides of the aisle.

"Kidney disease is not a partisan issue," echoed ASN President Joseph Bonventre, MD, PhD, FASN. "I met with congressional offices representing both parties and found strong support for the issues we care about across the board, most importantly maintaining funding for medical research. We are very pleased with the conversations we had on Hill Day and look forward to continuing to strengthen our relationships with congressional representatives and their staff members."

ASN members discussed the society's public policy priorities: support for robust, sustained funding for medical research, lifetime immunosuppressive drug coverage for transplant recipients, and access to high-quality care for kidney patients in new care delivery models. ASN members also discussed the top priorities of erasing health disparities in

U.S. Capitol Building.

ASN Board of Advisors members Christine Abrass (left) and Charles Alpers (middle) speak with the office of Sen. Patty Murray (D-WA).

(left to right) Chair of the ASN Public Policy Board, Thomas Hostetter, MD, FASN; Rep. Mike Doyle (D-PA); and ASN Director of Policy and Public Affairs Paul Smedberg.

ASN Councilor Raymond Harris, MD, FASN, and Rep. Marsha Blackburn (R-TN).

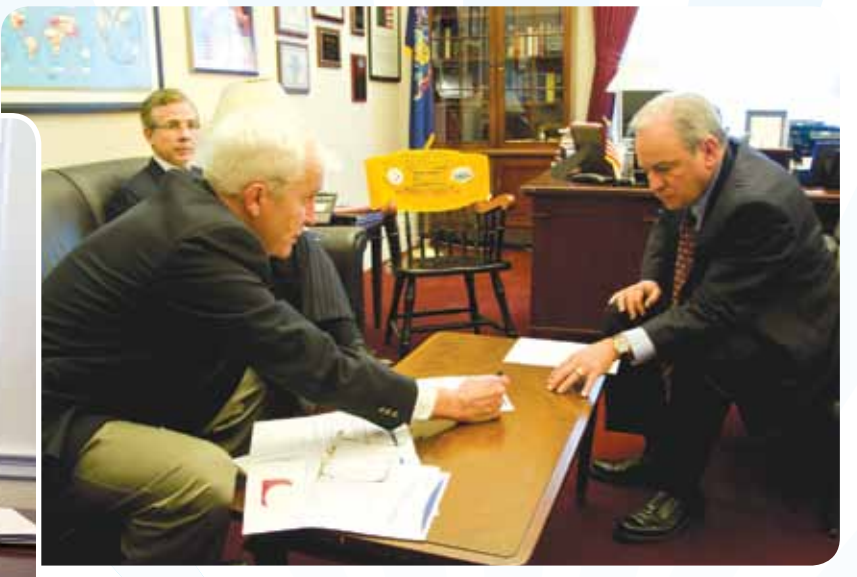
kidney disease care and addressing the nephrology workforce crisis.

According to Public Policy board member William Harmon, MD, "Many people we met with were amazed at how many people in their own states are afflicted with kidney disease. Patients on dialysis represent just the tip of the iceberg, and it's crucial that ASN helps educate congressional representatives and their staff members about the huge number of patients with kidney disease."

Building upon the success of the first ASN Hill Day, the society has scheduled follow-up meetings with several members of Congress and their staff members, including visits to research labs and dialysis facilities. "Witnessing research firsthand in the states they represent is an eye-opening experience for members of Congress, and one that I'm happy to say ASN has helped facilitate," said Councilor Sharon Moe, MD, FASN.

In addition to congressional visits by ASN leadership, ASN members took part in Hill Day 2011 by sending electronic letters to their representatives urging support for ASN's policy priorities. "The support of all ASN members is critical to the success of our advocacy efforts," said Councilor Ronald Falk MD, FASN. "This outreach reaffirms the important messages we brought to Congress on Hill Day 2011 and helps ASN connect with representatives from offices that we were unable to visit on Hill Day.

To learn more about how ASN is leading the fight to bring kidney disease to the forefront of the legislative agenda, about ASN Hill Day 2011, ASN's public policy priorities, or ASN's advocacy efforts in general, please visit the Hill Day 2011 webpage: http://www.asn-online.org/policy_and_public_affairs/hillday2011.aspx.



(left to right) Chair of the ASN Public Policy Board, Thomas Hostetter, MD; ASN Director of Policy and Public Affairs Paul Smedberg; and Rep. Mike Doyle (D-PA).

ASN Councilor Ronald Falk, MD, FASN, speaks with the office of Rep. David Price (D-NC).

(left to right) ASN Policy Analyst Daniel Kochis, Rep. Jim Cooper (D-TN), and ASN Councilor Raymond Harris, MD, FASN.

Some ASN Hill Day participants congregate in front of the U.S. Capitol at midday.

Findings: American Transplant Congress

Proteasome Inhibitor Reverses Major Cause of Graft Loss

By Daniel M. Keller

The proteasome inhibitor bortezomib reverses early and late antibody-mediated rejection (AMR), a major cause of solid organ transplant loss. The drug opens up a new avenue for specifically targeting plasma cells, the cells that produce antibodies.

Speaking at the American Transplant Congress in Philadelphia in May, Steve Woodle, MD, professor and chairman of surgery and chief of the division of transplant surgery at the University of Cincinnati in Ohio, explained that AMR affects all solid organ transplants. "If you look at the reasons why people lose their grafts, there's evidence to suggest that the predominant mechanism is antibody-mediated," he said. "The therapeutic paradigm is to target the plasma cell, and this approach is actually the first plasma cell–targeted therapy that's been used in humans, and so I think that's the significance."

Reporting on 96 episodes of AMR occurring in 81 recipients of kidney transplants, Woodle said that bortezomib effectively reversed AMR and was associated with graft survival and histologic improvement in the majority of patients. In the past decade, AMR has been seen as an important contributor to acute and chronic rejection and graft loss. It typically does not respond to antirejection therapies aimed against T cell–mediated immunity.

In this multicenter study, patients received a single dose of rituximab, an anti–B cell drug, on day 1, followed by four doses of bortezomib on days 1, 4, 7, and 10, preceded each time by plasmapheresis. Further plasmapheresis occurred on days 14, 16, and 18 to remove existing antibodies and allow quantification of antibody production from residual B cell clones. The immunodominant anti-HLA antibodies directed against donor-specific antigens were identified.

"Patient survival has been excellent, to date almost 99 percent," Woodle said. "The time posttransplant to rejection was a median of 11.9 months, a mean of 30 months, with a range from early on to patients 10 years out or more."

About one third of patients experienced early AMR and the rest late AMR, averaging about 5 years after transplant for his institution and 2.5–3 years at the other participating centers. Most of the immunodominant donor-specific antibodies were about equally divided against class I or class II major histocompatibility complex antigens in early rejection. "About 70 percent of those that were biopsied were improved," Woodle said.

During late AMR, antibodies were predominantly directed against class II antigens, especially against DQ specificities. Histologic improvement during late AMR was slightly lower than during early episodes.

Graft survival was about 80–90 percent in early AMR and 67–76 percent in late AMR. Patient survival has been 100 percent for early AMR and about 75 percent for late episodes. Use of the treatment protocol was associated with significant declines in the amount of circulating immunodominant donor-specific antibodies.

Serum creatinine levels improved more after treatment for early AMR than when patients were treated during late AMR episodes. "Late rejection creatinines are higher in general as one might expect, and they don't show improvement to baseline," Woodle said. "They wind up around 2 mg/dL rather than 1.2–1.5 [mg/dL]."

Peripheral neuropathy is probably the most dose-limiting side effect with bortezomib. Woodle said only about 2–3 percent of patients experienced grade 3 neuropathy, meaning that they had painful neuropathy requiring narcotics. This rate is similar to that seen when bortezomib is used in the oncology setting to treat multiple myeloma or relapsed mantle cell lymphoma, the only indications for which it is approved by the U.S. Food and Drug Administration.

Some viral infections occurred in early AMR but responded to antiviral therapy and reduction in immunosuppressive drugs. During late AMR, the rate of opportunistic infections was lower, at about 4 percent. No deaths were related to opportunistic infections, and no malignancies occurred during the study.

"Results with proteasome inhibitor therapy differ between early and late antibody-mediated rejection," Woodle told the audience. "Patient survival has been excellent. Overall graft survival is comparable or higher than reports with other therapies.

"Graft survival is lower with a late AMR. This is typical of what's been reported with IVIG [intravenous immunoglobulin] and other types of therapies," he noted. "The toxicities are acceptable, and the opportunistic infection and malignancy rates are also acceptable." In comparison with the use of bortezomib in the oncology setting to treat multiple myeloma, he said that transplant patients with AMR were exposed to relatively low levels of the drug.

Proteasome inhibitors are "fundamentally different than IVIG, where the primary mechanism of action is not known or is not well sorted out," Woodle told *ASN Kidney News*. He expects to see the development of more drugs and combinations of drugs over the next several years to target the humoral immune response, and he compares today with the era 25 years ago in which T cell–directed therapies came about.

"Early acute rejection is much easier to control and address. Delayed antibody-mediated rejection that is switching into the chronic state is much more difficult to reverse, and the damage is already done and can be somewhat stopped but not reversed," said session moderator Tomasz Kozlowski, MD, assistant professor of surgery at the University of North Carolina at Chapel Hill.

Kozlowski said that he found the protocol used in the study "very exciting," and he expects that future studies will show "which component of this protocol is really contributing to the success and how we actually define the success."

Sexually Transmitted Infection: New Category of High-Risk Organ Donors

By Daniel M. Keller

Sexually transmitted infection (STI) could be considered a high-risk category for HIV transmission through organ donation. But hemophilia should now be dropped as a risk category, given the low incidence of HIV in that population, according to a study presented at the American Transplant Congress in Philadelphia in May.

The U.S. Centers for Disease Control and Prevention (CDC) issued classifications of high-risk organ donors in 1994, but the epidemiology of certain infections has changed since then. Current evidence shows that STI could now be considered a high-risk category, given the high incidence and prevalence of HIV among this population. But given the very low 1 in 100,000 incidence of HIV among people with hemophilia, it should be dropped as a high-risk category, said Lauren Kucirka, ScM, an epidemiologist in the department of surgery at the Johns Hopkins University School of Medicine in Baltimore.

The CDC currently categorizes potential donors as being at high risk on the basis of seven behaviors or circumstances. These individuals include men who have sex with men, injection drug users, people with hemophilia, commercial sex workers, people who have high-risk sex (that is, with people in any of the foregoing groups), people who have been exposed to HIV through blood, and people who are incarcerated.

By these criteria, about 9 percent of donors from whom at least one organ is recovered are classified as being at high risk, and these organs are 26 percent more likely to be discarded than are those from donors not at high risk. Kucirka noted that the CDC guidelines have several limitations: they were designed in 1994, before the advent of highly active antiretroviral therapy; they were aimed in part at HIV but have been extended to hepatitis C virus (HCV) infection; and although they were designed to identify donors at risk of prevalence infection, the real risk from HIV is from incident infection. In the case of hemophilia, for example, the prevalence of HIV is high among people who received transfusions in the 1980s, but because of tests to screen blood the incidence of new infections is low.

To investigate potential new high-risk categories, Kucirka and colleagues performed a systematic review of the literature on the incidence and prevalence of HIV and HCV from 1995 through 2008, as well as a meta-analysis. They identified 272 eligible abstracts for HIV estimates and 218 for HCV estimates.

Window period

A "window period" exists between the time of an infection and when it is detectable by laboratory methods. All donors are screened for infectious diseases, but they will falsely test negative if they are in the window period and may then transmit an infection to one or more recipients. "The window period using nucleic acid testing for diseases like HIV and hepatitis C is about a week," Kucirka said.

From the abstracts, the investigators were able to calculate a "risk of window-period infection" for HIV. For the current CDC categories, "the incidence ranged from two infections per 100 person-years for injection drug users to less than 1 per 10,000 person-years for hemophiliacs," she said.

On the basis of a review of the abstracted data, the authors discerned subgroups of the population with a high incidence of HIV or HCV. Body piercings, tattoos, or intranasal cocaine use did not appear to confer any increased incidence in comparison with control individuals from the same study populations.

"And finally we looked at STI," Kucirka said. "So we found among those who were positive for [any] STI a pooled incidence of 1.7 per 100 person-years, which was similar to the incidence in men who have sex with men and injection drug users and would result in an expected number of 4.2 window-period HIV infections per 10,000 donors." Compared with their peers from the same study population, people with STIs had about twice the prevalence and twice the relative incidence of a window-period HIV infection.

"Addition of new categories should be approached with caution, particularly in light of the high discard rate when a donor is classified as at high risk," Kucirka advised. Nonetheless, STI could be considered a potential high-risk category, given the high incidence and prevalence of HIV infection in this category. But given the very low incidence among people with hemophilia, this category "could potentially be dropped," she said.

The CDC is currently formulating new guidelines and will put them out for comment soon.

"We're operating based on some assumptions that were made in 1994 that were clearly obsolete at this point and inappropriate in some settings and don't reflect either the available testing or the changing demographics of blood-borne pathogens like HIV and hepatitis C and hepatitis B," said Emily Blumberg, MD, professor of medicine and director of transplant infectious diseases at the University of Pennsylvania in Philadelphia and chairperson of the ad hoc disease transmission advisory committee of the Organ Procurement and Transplantation Network.

She emphasized that the field has an excellent track record, citing the transmission of only two HIV infections from deceased donors and one from a living donor since 1987. "We're all trying to figure out how to make all of these things even safer," she said.

Better Management Needed to Lower Cardiovascular Risks After Kidney Transplant

By Daniel M. Keller

Even with protocols in place to improve compliance, many kidney transplant patients did not achieve risk factor targets for cardiovascular disease, a leading cause of graft failure and of death after transplantation, according to study results presented at the American Transplant Congress in Philadelphia in early May. But as time went on after transplantation, the modifiable risk factors of hypertension, hyperlipidemia, and diabetes mellitus could become better controlled, said lead author Rakesh Kumar, MD, of the State University of New York at Buffalo.

Although advances in immunosuppressive therapy can prevent immune-mediated damage to transplanted kidneys and improve short-term allograft survival, the same factors that increase cardiovascular risk—hypertension, dyslipidemia, and diabetes—also affect the function and survival of grafts. Cardiovascular disease in itself accounts for up to 25 percent of patient deaths in the long term.

In this single-center retrospective chart review study performed at the university-affiliated Erie County Medical Center Kidney-Pancreas Transplant Unit, the researchers assessed blood pressure and levels of LDL cholesterol and hemoglobin A1c (HbA1c) annually, starting 1 year after transplant. Data were collected for 1–5 years (2005–2009) depending on the date of the transplant.

Uncontrolled blood pressure was defined as readings above 130/80 mm Hg on three or more occasions over 5 years. The results were compared with the Kidney Disease: Improving Global Outcomes (KDIGO) recommended guidelines of blood pressure no greater than 130/80 mm Hg, LDL cholesterol less than or equal to 100 mg/dL, and HbA1c less than or equal to 7.5 percent. The immunosuppressive regimen was alemtuzumab induction with tacrolimus and mycophenolate maintenance.

The 128 patients (44 women) in the study had a mean age of 51 years; 6 percent were white, 44 percent had a history of diabetes, 83 percent had dyslipidemia at the time of the study, and 96 percent were hypertensive. Thirty-four percent were taking three or more antihypertensive medications.

Results

In general, blood pressure appeared to improve over time. One year after transplantation, 41 percent of patients had controlled hypertension. "After 5 years of transplant, 55 percent of patients had blood pressure less than 130/80," Kumar reported. "There was a greater decline in eGFR [estimated glomerular filtration rate] among patients with uncontrolled hypertension compared with patients with controlled hypertension, although it did not reach a significant level."

At 1 and 5 years, eGFR was 59.2 and 55.1 mL/min, respectively, among patients with controlled hypertension and 52.9 and 45.3 mL/min, respectively, for patients with uncontrolled hypertension. At 1 year, 76 percent of 106 patients had an LDL cholesterol reading at or below 100 mg/dL, and at 5 years, the figure was 91 percent of 12 patients. Seventy percent of 78 patients had HbA1c levels at or below the desired level of 7.5 percent at 1 year, and by 5 years the figure increased to 81 percent of 9 patients for whom there was a reading. Kumar summarized his findings, saying that hypertension was the most prevalent cardiovascular risk factor in this cohort of renal transplant patients and that eGFR declined faster in the presence of uncontrolled blood pressure. Some patients were fairly refractory to the multiple antihypertensive therapies prescribed. "Forty percent of patients with uncontrolled hypertension and 35 percent of patients with controlled hypertension were on three or more antihypertensive medications," Kumar said.

Although compliance with KDIGO guidelines for blood pressure, LDL cholesterol, and HbA1c improved over time, a substantial proportion of transplant recipients missed some of the routine screenings for cardiovascular risk factors, and 30–60 percent of patients failed to reach risk factor goals in the first year after transplant. "Evidence-based guidelines alone were insufficient to uniformly drive ideal care," Kumar concluded, and he said that better strategies are needed to meet treatment objectives.

Session moderator Vinay Nair, DO, a transplant nephrologist at Mt. Sinai Medical School in New York, told *ASN Kidney News* that continued improvement in KDIGO parameters over the years would not be expected. "If anything, when you go further years you'd expect some graft deterioration. It's very common with transplantation," he said. "A lower GFR should mean worse blood pressure control if anything. So it is a little bit surprising" that blood pressure control improved over time but that eGFR was declining.

He agreed that better strategies are needed if outcomes are to improve, but that first it is important to know how well patients do with chronic kidney disease but without transplantation, and how the general population compares. He asked that if patients who have received transplants are doing worse, "are we as transplant nephrologists not doing a good enough job, or it is something with the medications that makes them harder to treat and control?"

Nair also noted Kumar's statement that calcium channel blockers were the majority of first-line antihypertensive medications used for the study patients. However, "JNC 7 [Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 7] suggests that the first medication is a diuretic. We're often, initially at least, reluctant to give diuretics because of rises and falls in creatinine, or ACE [angiotensin converting enzyme] inhibitors," Nair explained. He said that clinicians have historically tended to prescribe calcium channel blockers because some previous data suggested that they may reverse the effects of calcineurin inhibitors on blood pressure, but more recent data have called that idea into question.

Chronic Opioid Use Before Kidney Transplant Shortens Graft Survival

Chronic use of opioids (COU) before kidney transplantation may be associated with an increased risk of early graft loss and higher mortality after transplant, according to a retrospective study from the University of Michigan presented at the American Transplant Congress in Philadelphia in May.

Of the 1064 adult patients who received a kidney graft at the university between 2004 and 2008, 42.5 percent reported that they had chronic pain and 10.2 percent reported that they had used opioids on a chronic basis before their transplants. The patients were followed up until the end of 2010. These figures are in line with published reports showing that 50 percent of patients with ESRD report some degree of chronic pain, and 5–36 percent use opioid analgesics on a chronic basis, said Fidel Barrantes, MD, clinical transplant fellow at the University of Michigan. Barrantes spoke at the session Painful Consequences: Chronic Use of Prescription Opioids Is Associated with Adverse Kidney Transplant Outcomes.

"Four types of opioids were used in more than 90 percent of this population," Barrantes reported. Forty-four percent used hydrocodone, 17 percent propoxyphene, 15 percent oxycodone, and 14 percent tramadol. The most common pain was neuropathic (53 percent of patients), followed by limb pain (39 percent), lower back (16 percent), headache, abdominal, and other pains.

The COU group, comprising 108 patients, had more African Americans than did the non-COU group (25 percent versus 17.5 percent, respectively) and had more comorbidities, double the rate of alcohol abuse (18.5 percent versus 9.9 percent), more illicit drug abuse (20.4 percent versus 11.1 percent), a more positive psychiatric history (51.9 percent versus 27.8 percent), and three times the rate of use of nonopioid analgesics (26.9 percent versus 8.2 percent).

The non-COU group included more employed patients (44.1 percent versus 18.5 percent) and more patients with private insurance (43.8 percent versus 30.6 percent).

The two groups did not differ significantly in terms of age (approximately 50 years), gender (approximately 60 percent male), body mass index (approximately 28.5 kg/m^2), proportion with diabetes, or length of time receiving dialysis.

"Pretransplant chronic opioid use is associated with worse patient survival at 1, 3, and 5 years," Barrantes said, with significant differences in survival between the COU and non-COU groups at 3 and 5 years. The death rates at 3 years were 18 percent for the COU group and 7.5 percent for the non-COU group. At 5 years, death rates were 21 percent versus 12 percent, respectively (p = 0.026).

Reported chronic opioid use before transplant was associated with a 66 percent increased risk of death after transplant, according to a multivariate model. This risk was higher than even for the presence of diabetes before transplant, which conferred a 42 percent increased risk. Receipt of a kidney from a living donor lowered the risk of death after transplant by half.

Graft loss was significantly increased by COU only at the 1-year point in comparison with the non-COU group (5.5 percent versus 1.5 percent, respectively). At 3 years, graft loss was in the range of 4.5–6.5 percent and was around 7–7.5 percent at 5 years. These latter differences were not statistically significant between the COU and non-COU groups.

In the first year after transplant, COU emerged as the major predictor of graft loss. When compared with non-COU, COU conferred almost a threefold increased risk of graft loss (hazard ratio = 2.90). Current smoking was associated with a more than twofold increased risk (hazard ratio = 2.63).

A much smaller study by Walczak and colleagues also presented at the conference again showed that cigarette smoking (n = 9) was associated with a nonsignificant trend toward lower graft survival at 3 and 5 years after transplant, as was alcohol use.

Barrantes noted that his study was retrospective, depended on self-reported use of pain medication, and lacked information on opioid use after transplant—all limitations of the study.

Speaking with *ASN Kidney News*, he said that because the study was retrospective and based on self-reports, it was impossible to discern the reasons for opioid use, leaving open the possibility that patients used the drugs to treat painful conditions, such as diabetes or vascular conditions, that in themselves could affect patient or graft survival.

Barrantes cautioned that the study should not be interpreted to disqualify COU patents from consideration for transplants. However, clinicians should be vigilant to identify such patients and to target them for follow-up by social workers and possibly psychologists, particularly in the first year after transplant.

Findings: American Transplant Congress

Continued from page 9

Communication Gaps Lead to Infections in Organ Recipients

By Daniel M. Keller

Delays and errors in communication from donor organ centers to recipient centers frequently contribute to the transmission of infections. Rachael Miller, MD, presented the results of a study of potential donor-derived infections reported between January 2008 and June 2010 to the Ad Hoc Disease Transmission Advisory Committee (DTAC) of the Organ Procurement and Transplantation Network, administered by the United Network for Organ Sharing (UNOS). Miller is clinical professor in infectious diseases at the University of Iowa Carver College of Medicine in Iowa City.

Communication gaps occur at multiple levels and have been associated with adverse outcomes in organ recipients, but effective communication can minimize or avert the transmission of infections. "If delays and errors in communication occur, they can have a significant impact on recipient morbidity and mortality," Miller said.

Effective detection and management of potential donor-derived infections are made all the more difficult because of the complex and multiple channels of communication, including between donor and recipient transplant centers, diagnostic laboratories, and organ procurement organizations (OPOs) involved. "Clinicians may be unaware as to how to obtain and report relevant donor information," Miller said.

The DTAC classifies donor-derived transmission events as proven, probable, or "intervention without documented transmission," which typically means that an infection was averted through the use of antimicrobial therapy. For the study, a delay in communication was defined as lasting more than 3 days. An adverse event was an unexpected clinical infection, a more severe infection, or death.

The investigators identified 56 infection events involving 169 transplant recipients that met the study criteria for potential communication delays or errors. Thirty-eight events in 120 recipients were ultimately determined not to involve communication problems.

"However, 18 infection events were associated with communication delays or errors among 49 recipients," Miller reported. Eleven of these cases involved bacterial infections, three viral, and four other or parasitic. Of these 18 occurrences, 12 (67 percent) were associated with an adverse event. Of the 20 recipients affected by an infectious adverse event, 6 died.

The researchers pinpointed several gaps involving many of the steps in the communication process. Some cases of communication error involved more than one step. In five instances, the transplant center delayed contacting the OPO to relate a suspected donor-derived infections (range 22–56 days), and in three instances, the OPO delayed contacting the transplant center or the DTAC. There were also four failures of laboratories to relay donor results to the OPO and/or the transplant center, two communications of incomplete test results from the OPO to the transplant centers, and three clerical errors.

"The good news is that if prompt and effective communication was employed it allowed the opportunity for prompt intervention that either minimized or averted recipient infection," Miller said. Of the 38 infection events without communication errors or delays, in 23 cases intervention positively influenced the outcome for 72 recipients. The remaining 15 events affecting 48 recipients required no intervention, or intervention had no effect on the outcome.

Communication can minimize or avert infections in transplant recipients, Miller said. In January the Organ Procurement and Transplantation Network implemented policy changes regarding communication, mainly concentrating on the procedures for OPOs and transplant centers to report and share donor-related information with relevant parties. Also, the involved parties should receive better education to help minimize communication problems and add to the safety of the donation process, Miller said.

Senior author of the study and DTAC chair Emily Blumberg, MD, professor of medicine and director of transplant infectious diseases at the University of Pennsylvania in Philadelphia, told *ASN Kidney News* that clinicians may not be aware that some infections are derived from donors and thus may not report them in a timely manner or at all.

Blumberg said one of her goals is to present her findings at meetings of transplant medical professionals and transplant administrators, and also at UNOS regional meetings, to raise awareness of the problem so people start to ask themselves, "Could this be [a] donor-derived [problem], and before letting this proceed further, can I notify people?" UNOS has implemented a contact process to encourage every transplant program to have a patient safety officer charged with promptly communicating a suspected problem to UNOS and to the OPO so that every center with an organ recipient will be notified.

Session chair David Foley, MD, associate professor of surgery at the University of Wisconsin in Madison, suggested that within each transplant center, "One safeguard measure would be a checklist for the surgeons to maybe potentially follow up with the OPO to make sure that no data have come back that have not been informed to us" concerning a donor.

Shorter Steroid Course Lowers Cardiovascular Risks After Kidney Transplantation

By Daniel M. Keller

Early withdrawal of corticosteroids after kidney transplantation was associated with a lower rate of cardiovascular (CV) events compared with long-term corticosteroid administration, according to a study presented at the American Transplant Congress, held in Philadelphia from April 30 to May 4. Lead author Nicole Schmidt, PharmD, of the University of Cincinnati in Ohio, said that the decrease in CV events became apparent 3–4 years after transplant in the group of patients with early withdrawal, even though these patients had more coronary artery disease before transplant. There were no differences in overall patient survival or in CV-related deaths between the early corticosteroid withdrawal group and the long-term corticosteroid immunosuppression maintenance group, Schmidt said.

In general, CV disease accounts for about 30 percent of deaths among kidney transplant recipients. Schmidt said that clinical trials and a recent meta-analysis showed that corticosteroid avoidance or withdrawal has been associated with a decrease in CV risk factors, including new-onset diabetes, hypertension, hyperlipidemia, and weight gain. But, she said, "We still have limited long-term studies that have actually translated this cardiovascular risk reduction into actual [reduction in] cardiovascular events and ultimately, patient survival."

The investigators therefore evaluated 1004 patients who received renal transplants between 1998 and 2010, 714 of whom underwent early withdrawal and 290 of whom were receiving long-term corticosteroid maintenance. Early withdrawal was defined as steroid withdrawal within 7 days after transplantation. This group tended to be older, had more men, had fewer African Americans, and had more coronary artery disease before transplant.

The early withdrawal group had fewer repeat transplants (9.5 percent) than did the long-term steroid group (14.5 percent), less delayed graft function (7.7 percent versus 15.2 percent, respectively), more HLA mismatches (mean 3.3 versus 2.1), but lower mean class II peak and current cytotoxic panel reactive antibodies.

In terms of immunosuppressive therapy, more of the early withdrawal patients were given tacrolimus (89.9 percent versus 51.7 percent) and sirolimus (22.1 percent versus 0.3 percent) and had less use of cyclosporin (9.1 percent versus 48.3 percent). More than 97 percent of each group was receiving mycophenolate mofetil. The long-term steroid maintenance group received mean steroid doses of 8.6 mg/day at 6 months and was still receiving a mean of 5.3 mg/day at 7 years.

The mean pre- and posttransplant total cholesterol was lower in the early withdrawal group compared with the long-term steroid group (168.6 versus 178.2 mg/dL and 172.9 versus 189.1 mg/dL, respectively. All other pre- and posttransplant cholesterol values, including LDL cholesterol, did not differ significantly between the groups. Other CV risk factors were largely the same except that after transplant, patients in the long-term steroid group had a mean diastolic blood pressure that was 1.9 mm Hg higher, and they were taking more antihypertensive medications. The median follow-up times were 4.2 years for the early withdrawal group and 5.9 years for the patients receiving long-term steroid administration.

"Patients that received chronic steroid regimens experienced definitely more cardiovascular events than those that were withdrawn from steroids within 7 days after transplantation," Schmidt reported. CV events occurred in 14 percent of the early withdrawal group and in 24.5 percent of the long-term steroid administration group. Kaplan-Meier analysis predicted 10-year CV event rates of 24 percent and 35 percent, respectively. The most common CV event experienced in both groups was angina.

The two groups did not show any significant difference in terms of patient survival. "When we looked at just the . . . cardiovascular-related deaths, we found, again, that there was no significant difference between the two groups," Schmidt said.

Session co-chair Ram Peddi, MD, a transplant nephrologist at California Pacific Medical Center in San Francisco, raised the question whether longer follow-up might change the outcomes. Because there were some differences in demographic characteristics between the two groups at baseline, he suggested that a multivariate analysis should be performed to adjust for the differences.

In fact, Schmidt did present such an analysis in a later session during the conference. It showed that early steroid withdrawal was associated with a reduction of 54 percent in the risk of CV events (odds ratio [OR] = 0.459). Risk factors for the development of CV events were pretransplant diabetes mellitus (OR = 2.69) and smoking (OR = 1.88). The investigators concluded that when adjustment was made for multiple risk factors, their 12-year experience provides strong evidence for a protective effect of early corticosteroid withdrawal on CV events.

A third analysis from the same group of investigators showed that at 10 years, patient survival was 76 percent in both groups, and CV-related events accounted for 15 percent of the deaths for both.

Peddi said that it has long been known that patients can benefit in terms of CV disease if corticosteroids are withdrawn early. "I think we all are aware of the cardiovascular risks associated with corticosteroids, but [early withdrawal] is now possible with the newer immunosuppressive drugs that are available because especially the tacrolimus and mycophenolate and also the induction therapy offer better immunosuppression that is enabling us to take the patients off steroids," he said.

Pancreas Transplantation Is Feasible for Older Patients

By Daniel M. Keller

Older patients receiving pancreas transplants have lower rates of acute rejection and total complications than their younger counterparts. With improvements in the management of diabetes, more older patients are presenting for transplantation of pancreases and kidneys. Previous registry data suggested that older patients did not do as well as younger ones, but modern induction and maintenance immunosuppressive therapy has changed the picture for the better for older patients, according to study results presented at the American Transplant Congress in Philadelphia in May.

Through a retrospective chart review of 139 consecutive pancreas transplant patients over a 15-year period at New York–Presbyterian Hospital/Weill Cornell Medical Center in New York City, investigators compared the outcomes in 19 patients 50 years old or older with outcomes in 120 patients younger than 50 years at the time of transplant.

The median age for the older cohort was 53 and for the younger cohort it was 37. Otherwise, the baseline demographic characteristics were not statistically different for the groups. All patients received maintenance triple immunosuppression therapy (calcineurin inhibitor, mycophenolate mofetil, and low-dose steroids). Approximately equivalent proportions of the older and younger groups were receiving hemodialysis preoperatively (74 percent and 83 percent, respectively) and underwent simultaneous pancreas and kidney transplants (58 percent and 67 percent, respectively). The remaining patients received a pancreas after kidney transplant or a pancreas transplant alone (42 percent of the older group and 33 percent of the younger group).

The investigators, led by Cheguevara Afaneh, MD, reported that long-term graft survival was equivalent for the two groups at about 77 percent for the older patients and 50 percent for the younger ones ($p = 0.43$). Patient survival was between 80 and 90 percent for the two groups.

Postoperative complication rates at 30 days were similar (47 percent versus 50 percent, respectively), but the older group experienced fewer major complications (36.4 percent versus 69.7 percent). Similarly, the older patients did better in terms of acute rejection at 1 year (5.3 percent versus 37.5 percent) and of overall acute rejection (10.5 percent versus 53.3 percent). There was no difference between the older and younger groups in the incidence of infections requiring hospitalization, cytomegalovirus infections, or posttransplant lymphoproliferative disorder.

In this study and others, "it does seem like the incidence of acute rejection is lower in older patients, so they require less vigorous induction and maintenance immunosuppression… because their immune systems are not quite as robust," said Kenneth Brayman, MD, PhD, professor of surgery and director of transplantation services and of the kidney and pancreas transplant program at the University of Virginia in Charlottesville.

Older data from the International Pancreas Transplant Registry suggest that pancreas recipients over 45 have problems of poorer graft survival and death, Brayman said. But over the past decade, pancreas transplantation has become more common for older patients. Several centers, including Brayman's, have performed pancreas transplants in patients over 60 with good results.

For the future, Brayman foresees more pancreatic islet transplants. "The results for islet transplantation at 5 years are comparable to the results for a pancreas transplant alone," he said. Currently, Medicare does not pay for islet transplants. He sees that as an impediment to the development of the procedure but said that efforts are under way to change the Medicare reimbursement policy.

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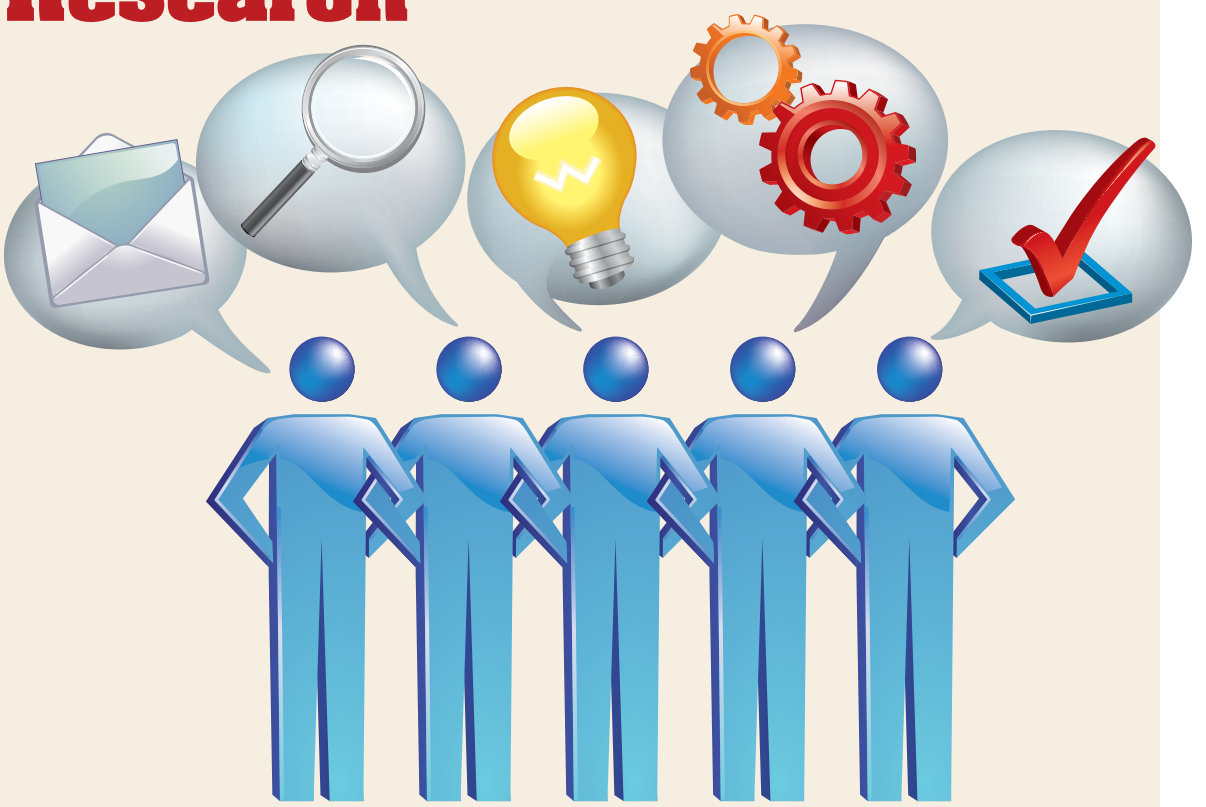
ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

ASN Launches Initiative in Comparative Effectiveness Research



By Wolfgang C. Winkelmayer

The recent introduction of the Centers for Medicare and Medicaid Services (CMS) End-Stage Renal Disease Prospective Payment System and the subsequent discussions about potential quality measures on how to monitor it have once again highlighted a sore point for many in the nephrology community: the evidence supporting most of our practice is weak, to say the least. Large randomized trials that have shaped most of the care in the general population have systematically excluded patients with advanced chronic kidney disease (CKD), including those requiring dialysis. Many of the trials that were specifically conducted in patients with advanced CKD or ESRD were inconclusive, or used surrogate endpoints that were controversial or turned out to be outright invalid. As a result, clinical equipoise exists, which favors the development of predominantly opinion-based guidelines and permits considerable variability in clinical practice. Such variability, however, is usually associated with suboptimal patient outcomes.

There are several definitions of what constitutes comparative effectiveness research (CER). Most would agree that CER seeks to compare competing strategies to detect, treat, or manage a certain condition in a defined set of patients. A typical approach would be to compare two or more types of treatment, such as different drugs, for the same disease. However, a comparison may also be made among medications and procedures (e.g., surgery) for a given condition.

Although purists argue that such comparisons should include only interventions that have previously been proved to be efficacious (superior compared with placebo, or noninferior compared with another treatment that had been superior to placebo), most others would drop that requirement. In its extreme form, the use of a specific treatment could also be compared with its nonuse (e.g., watchful waiting). Implicitly, CER is not just about comparing clinical effectiveness but also has a strong focus on comparative safety among clinical strategies for certain conditions. It is recognized that there is no "one size fits all" approach to medicine. The benefits and risks of certain treatments vary among populations, such as those defined by age, gender, race, or the presence of certain comorbidities. Thus, the key question CER seeks to answer is which treatment works best, for whom, and under what circumstances.

Comparative effectiveness research has gained considerable traction in many medical disciplines, and large resources have been directed toward CER through funds appropriated by the American Recovery and Reinvestment Act of 2009. Unfortunately, most of this research bounty, predominantly managed and allocated by the Agency for Healthcare Research and Quality (AHRQ) through its Effective Health Care program, has bypassed nephrology. Among the 100 initial research priorities for CER compiled by the 2009 Institute of Medicine Report, only one is directly pertinent to our field: the comparative effectiveness of competing dialysis modalities.

Table 1
ASN Comparative Effectiveness Task Force

Wolfgang C. Winkelmayer, MD, ScD (chair) Stanford University School of Medicine	Steven M. Brunelli, MD, MSCE: Brigham and Women's Hospital
Neil R. Powe, MD, MPH, MBA (liaison to the Public Policy Board): University of California San Francisco	Amit X. Garg, MD, PhD: London Health Sciences Centre
Daniel Kochis (staff liaison): American Society of Nephrology	Tamara Isakova, MD: University of Miami Miller School of Medicine
Geoffrey A. Block, MD: Denver Nephrology	Bryan R. Kestenbaum, MD, MS: University of Washington
L. Ebony Boulware, MD, MPH: Johns Hopkins University	Uptal D. Patel, MD: Duke Clinical Research Institute
M. Alan Brookhart, PhD: University of North Carolina	Francesca Tentori, MD: Arbor Research Collaborative for Health

Clearly, there are numerous CER questions to be posed in the context of nephrology, but kidney disease has not been one of the AHRQ Effective Health Care priority conditions in the past. Through its Developing Evidence to Inform Decisions about Effectiveness Network, the AHRQ has awarded two large CER task orders, focusing on studies in the ESRD population of intravenous iron treatment strategies, blood pressure agents, and timing of dialysis initiation.

Recognizing the need to improve the evidence available to guide practice in nephrology, the ASN has launched an initiative focusing on CER. In 2010, a specific Comparative Effectiveness Research Task Force was convened under the auspices of the ASN Public Policy Board (Table 1). The main goals of this task force are to build awareness among the nephrology community about CER, to educate researchers about appropriate designs and analytic techniques, and to lobby key stakeholders, especially funders of CER, about the need for funding support for high-quality CER in nephrology.

Some of the activities have already begun. The ASN offered a well-attended and very successful two-day course on CER at ASN Renal Week 2010 in Denver. In addition, the ASN has also begun to solicit ideas from several of the ASN advisory groups about potential comparative effectiveness topics. We will soon expand our reach to the whole ASN community, and we hope to compile a priority list of CER projects, which will then be presented to key funders of such research in nephrology and other key decision makers and constituents. ASN hopes to accelerate the generation of high-quality evidence so that we can treat our vulnerable patient population using the best strategies possible and thus improve patient outcomes.

Wolfgang C. Winkelmayer, MD, ScD, of Stanford University School of Medicine, is chair of the ASN Comparative Effectiveness Task Force.

Journal View

New Controversy on Salt, Blood Pressure, and Cardiovascular Risk

Lowering salt intake may not reduce population rates of hypertension and cardiovascular disease (CVD) and may even lead to an elevated risk of CVD death, suggests a report in the *Journal of the American Medical Association*.

The researchers analyzed prospective data on 3681 participants in two European population-based studies, all free of CVD at baseline. Data on blood pressure and sodium excretion at baseline and follow-up were available for 1499 participants. The effects of changes in blood pressure and sodium excretion on the incidence of mortality and morbidity were assessed.

At a median follow-up time of 7.9 years, the risk of CVD mortality was highest for participants at the lowest level of 24-hour sodium excretion. Cardiovascular mortality was 4.1 percent in the lowest tertile (mean, 107 mmol) versus 1.9 percent in the middle tertile (mean, 168 mmol) and 0.8 percent in the highest tertile (mean, 260 mmol). On multivariate analysis, the hazard ratio for death in the lowest tertile was 1.56.

In 2096 participants who were followed up for 6.5 years, the risk of hypertension was about the same—between 25.4 percent and 27.0 percent—across tertiles of urinary sodium excretion. Data on 1499 participants who were followed up for 6.1 years showed an increase of 0.37 mm Hg per year in systolic blood pressure. An increase of 100 mmol in sodium excretion was associated with an increase of 1.71 mm Hg in systolic blood pressure but no change in diastolic pressure.

The results pose questions about the recommendation to reduce population salt intake to lower the overall rate of CVD events. Changes in sodium excretion are linked to increased systolic blood pressure but not to increases in diastolic blood pressure or the risk of hypertension. The study also suggests a link between lower sodium excretion and higher CVD mortality in healthy individuals [Stolarz-Skrzypek K, et al. Fatal and nonfatal outcomes, incidence of hypertension, and blood pressure changes in relation to urinary sodium excretion. *JAMA* 2011; 305:1777–1785].

Benefits of Lower Blood Pressure Targets May Depend on Proteinuria

For patients with chronic kidney disease (CKD), there is no firm evidence that a blood pressure target of less than 130/80 mm Hg improves clinical targets, although it may be beneficial for patients with higher proteinuria levels, according to the *Annals of Internal Medicine*.

The investigators searched the literature for trials comparing lower and higher blood pressure targets for patients with CKD. All studies included more than 50 patients per group, had follow-up times of at least 1 year, and assessed outcomes including death, kidney failure, and cardiovascular events. Data analysis considered proteinuria as a possible modifier of the relationship between blood pressure and clinical outcomes.

The review identified three trials comprising 2272 patients. There was little evidence that lower blood pressure targets—less than 125/75 mm Hg to 130/80 mm Hg—had greater benefits than a target of less than 140/90 mm Hg. One study found a reduction of 23 percent in the risk of kidney failure for patients assigned to the lower target.

Some lower-quality evidence suggest that lower blood pressure targets might be beneficial in patient subgroups with proteinuria greater than 300–1000 mg/dL. Of 11 proteinuria subgroup results reported, seven showed benefits for the low blood pressure target. In the trials, patients assigned to low target groups required more antihypertensive medications and had a slightly higher risk of adverse events.

Recent guidelines have suggested that blood pressure targets should be set lower for patients with CKD because of their higher risks of cardiovascular disease and kidney failure. However, on the basis of available data, there is inconclusive evidence that lower blood pressure targets have clinical benefits for patients with CKD. Some evidence suggests that proteinuria is an effect modifier, with lower blood pressure targets improving outcomes in patients with proteinuria greater than 300–1000 mg/dL [Upadhyay A, et al. Systematic review: blood pressure target in chronic kidney disease and proteinuria as an effect modifier. *Ann Intern Med* 2011; 154:541–548].

Early Dialysis Isn't Cost-Effective, Either

An economic analysis of patients from the Initiation of Dialysis Early or Late (IDEAL) trial finds that the higher costs of planned early dialysis don't produce significant improvements in quality of life, reports the *American Journal of Kidney Diseases*.

The economic study included 642 of the original 828 patients enrolled in IDEAL. Previous reports from IDEAL found no significant effect on all-cause mortality, cardiovascular events, infection, or dialysis complications for patients with stage 5 chronic kidney disease assigned to an early or late start of hemodialysis: estimated GFR 10–14 mL/min/1/73 m^2 versus 5–7 mL/min/1.73 m^2, respectively. The total costs and quality of life outcomes were compared from a societal perspective for the early- and late-start groups.

The median follow-up time was 4.15 years, with a 6-month difference in duration of dialysis. Early initiation of dialysis was associated with an increase of approximately $11,000 in direct dialysis costs. The early dialysis group also had an increase of nearly $19,000 in total costs, including the costs of managing adverse events, although this difference was not significant. With adjustment for baseline values, there was no difference in quality-adjusted survival between the early and late dialysis groups.

There is a trend toward earlier initiation of dialysis based on estimated kidney function, in the hope of improving survival and quality of life while reducing long-term costs. Adding to previous IDEAL reports that planned early dialysis doesn't reduce mortality and other major adverse events, this economic evaluation finds that early dialysis increases costs without improving quality of life. The authors conclude that dialysis can be "delayed safely" until a GFR of less than 7 mL/min/1.73 m^2 or another traditional clinical indicator is reached [Harris A, et al. Cost-effectiveness of initiating dialysis early: a randomized controlled trial. *Am J Kidney Dis* 2011; 57:707–715].

Meta-Analysis "Refutes" Increased Myocardial Infarction Risk with ARBs

Treatment with angiotensin-receptor blockers (ARBs) doesn't produce an absolute increase of as much as 0.3 percent in the risk of myocardial infarction, reports the *British Medical Journal*.

In a systematic review of the literature, the researchers identified 37 randomized trials comparing ARBs with other treatments or placebo. The studies—which included 147,020 participants with a total follow-up time of 485,166 patient-years—provided outcome data on myocardial infarction, death, cardiovascular death, angina pectoris, stroke, heart failure, and new-onset diabetes mellitus.

Meta-analysis showed no increase in the risk of myocardial infarction associated with ARBs. There was also no increase in the risk of angina pectoris or death, overall or from cardiovascular causes. Treatment with ARBs was associated with modest reductions in the relative risk of stroke (0.90), heart failure (0.87), and new-onset diabetes (0.85).

A trial sequential analysis ruled out an increase of as little as 5.0 percent to 7.5 percent in the relative risk of myocardial infarction, corresponding to an absolute increase of 0.3 percent. There was no evidence of an increased risk of death or cardiovascular death with ARB treatment, but there was strong evidence for reductions in stroke, heart failure, and new-onset diabetes. For the latter outcomes, the average relative risk reduction was 10 percent. The reduction in risk of stroke was significant in comparison with placebo only.

The 2004 Valsartan Antihypertensive Long-term Use Evaluation trial raised concern about a possible increase in the risk of myocardial infarction with ARB treatment. The new meta-analysis, which included nearly 150,000 patients, seems to rule out even a small increase in risk of myocardial infarction in patients taking ARBs. At the same time, it shows small reductions in stroke, heart failure, and diabetes risk [Bangalore S, et al. Angiotensin receptor blockers and risk of myocardial infarction: meta-analyses and trial sequential analyses of 147,020 patients from randomised trials. *BMJ* 2011; 342:d2234].

Who's Taking Combined ACE Inhibitor/ARB Therapy?

Older adults receiving combination therapy with an angiotensin-converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB) usually don't have established indications for such therapy and show an increased rate of adverse renal outcomes, according to a study in *CMAJ: Canadian Association Medical Journal*.

Administrative data were used to identify older adults in Alberta who started treatment with an ACE inhibitor, an ARB, or both between 2002 and 2006. The characteristics and outcomes in patients receiving combination therapy versus monotherapy were assessed.

The study identified 32,312 new users of either type of medication. Their mean age was 76.1 years, and their median creatinine level was 92 µmol/L. The rate of combination therapy with an ACE inhibitor and an ARB was 5.4 percent. However, 86.4 percent of these patients had no established indication for combination therapy, such as heart failure or proteinuria.

Renal disease events were more frequent in patients receiving combination therapy: mean 5.2 versus 2.4 events per 1000 patients per month, adjusted hazard ratio 2.36. The rates of hyperkalemia were 2.5 versus 0.9 events per 1000 patients per month, hazard ratio 2.42. Most patients soon stopped taking combination therapy; the median time to stopping one or both drugs was 3 months.

The combination of an ACE inhibitor and an ARB has benefits for certain groups of patients but has been linked to an increased risk of renal dysfunction. This study finds that 5 percent of older adults starting treatment with either drug are receiving the combination of both drugs. Most don't have indications for combination therapy, which is associated with a higher rate of adverse renal events. Combination therapy is often stopped within a few months, even in the absence of adverse events [McAlister FA, et al. The safety of combining angiotensin-converting-enzyme inhibitors with angiotensin-receptor blockers in elderly patients: a population-based longitudinal analysis. *CMAJ* 2011; 183:655–662].

Everolimus Improves Renal Transplant Function

A strategy using everolimus for early elimination of calcineurin inhibitor leads to improved renal function after kidney transplantation, with good maintenance of efficacy and safety, reports a trial in *The Lancet*.

The multicenter ZEUS trial included 503 patients undergoing de novo kidney transplantation. All received initial treatment with cyclosporine, mycophenolate sodium, corticosteroids, and basiliximab. At 4.5 months, 300 patients were randomly assigned to calcineurin inhibitor elimination, with a regimen of everolimus plus mycophenolate sodium and corticosteroids, or to continued cyclosporine-based immunosuppression. The main outcome of interest was the GFR 12 months after transplantation.

About 80 percent of both groups completed treatment with study medications for as long as 12 months. The mean GFR was 71.8 mL/min/1.73 m^2 with everolimus versus 61.9 mL/min/1.73 m^2 with cyclosporine. After randomization, everolimus was associated with a higher rate of biopsy-proven acute rejection: 10 percent versus 5 percent. However, for the full 12-month period, acute rejection rates were 15 percent in both groups. Everolimus-treated patients had higher lipid levels, a slight increase in urinary protein excretion, and lower hemoglobin levels. Thrombocytopenia, aphthous stomatitis, and diarrhea were more common with everolimus, and hyperuricemia was more frequent with cyclosporine.

Some non-nephrotoxic approach to immunosuppression is needed that will reduce exposure to calcineurin inhibitors in kidney transplant recipients. The ZEUS study suggests that immunosuppression using the mammalian target of rapamycin inhibitor everolimus is a promising approach to early elimination of calcineurin inhibitor use. By improving renal function while maintaining efficacy and safety, this strategy may improve the long-term outcomes in selected groups of kidney recipients [Budde K, et al. Everolimus-based, calcineurin-inhibitor-free regimen in recipients of de-novo kidney transplants: an open-label, randomised, controlled trial. *Lancet* 2011; 377: 837–847].

Detective Nephron

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

Nephron (relaxed) What do we have today, my dear apprentice?

Henle (worried) A 70-year-old woman with hematuria and an acute rise in creatinine.

Nephron I see that you have taken a break from electrolyte disorders and moved to the glomerular disease world. This is why nephrology is so much fun—it has so much variety to offer to us diagnosticians.

Henle Hmmm… getting back to the case, she was in her usual state of health until a few weeks ago, when she started noticing unexplained joint pains and weight loss and a feeling of uneasiness. She also felt feverish.

Nephron What is her creatinine level now?

Henle It was 0.7 mg/dL four months ago and 1.2 mg/dL two months ago. Now it is 3 mg/dL. A subacute rise, I would say.

Nephron OK; did you look at her urine?

Henle Yes, of course I did. There are many red blood cells and a few white blood cells. The red cells are dysmorphic, but there are no red cell casts that I could notice, and no signs of any granular casts.

Nephron Is there any proteinuria?

Henle Yes, there is: 4 g via a 24-hour urine collection.

Nephron I am sure they did serologic studies before they called you.

A knock on the door is heard.

Nephron Come on in, Dr. Podocyte. You are just in the nick of time.

Henle looks at Dr. Nephron as Dr. Podocyte enters the room.

Nephron Meet Dr. Podocyte, the world's expert on glomerular disease. Perhaps this case might be better solved by two of us together. What say you, Slit?

Podocyte Good morning, Henle. I am Dr. Slit Podocyte. Nice to meet you.

Nephron Henle has a case here of an elderly lady with hematuria, a subacute decline in renal function, and a nonspecific review of systems with findings of weight loss and fever.

Henle (anxiously) Her antinuclear antibodies result is positive; her anti–double-stranded DNA result is positive, with 1:160 titer; and her anti–myeloperoxidase antibody (MPO) is positive at 1:360. Her complement levels are normal.

Nephron Stop right there. So you are telling me you already have a diagnosis? Why are we presenting this case, then?

Podocyte Sounds like you have a vasculitic disease process.

Henle It appears that this was a rapidly progressive glomerulonephritis (RPGN). Her lupus serology results are positive, but her anti-MPO test result is also positive. That is confusing, and it bothers me.

Podocyte As you said, this is an RPGN. There are five known presentations of RPGN. The first type is anti—glomerular basement membrane. The second is immune complex–mediated. The third is pauci-immune, positive for antineutrophil cytoplasmic antibodies (ANCA). The fourth is pauci-immune, negative for ANCA. Last is a combination of anti-GBM and pauci-immune ANCA vasculitis. Clearly, a sixth possibility can occur with a combination of immune complex and ANCA vasculitis (in this case a combination of anti–double-stranded DNA and ANCA).

Henle Yes, and that is bothering me. Do we see lupus nephritis together with ANCA vasculitis?

Nephron My dear apprentice, you still have a lot to learn. First and foremost, can you give me this individual's medication list from five months ago?

Henle Five months ago? I can try.

Nephron Please go get that while I drink my coffee.

While L.O. Henle leaves to get the information, Podocyte and Nephron have some warm coffee. Henle returns after a few hours.

Nephron Read off all the medications to me.

Henle She was taking labetalol 400 mg twice a day, aspirin 81 mg once a day, and hydralazine 25 mg three times a day.

Podocyte Let me guess—the hydralazine was new in her regimen.

Henle No, not really. She had been taking it for many years. Four months earlier, she did see her gastroenterologist because she has a known history of ulcerative colitis. She was given a trial regimen of infliximab. She received 5 mg/kg at the first visit and then two weeks and six weeks later. The plan was to continue the same dosage every eight weeks after that. The last dose was given six weeks ago.

Nephron Interesting!

Podocyte What's so interesting? Just because it's not an electrolyte case. This is actually fascinating!

Henle (with awe) Is there a connection between this and the presentation?

Podocyte (with confidence) Was a kidney biopsy done?

Henle Yes, and the biopsy confirmed necrotizing glomerulonephritis with crescents, pauci-immune by immunofluorescence. Electron microscopy showed the presence of necrotic leukocytes within the intracapillary space.

Podocyte (confidently) So she has a pauci-immune RPGN likely associated with her anti-MPO. And you are thinking that this might be related to her anti–TNF-α agent or the hydralazine?

Henle (confused) Hmm… so is that the connection?

Nephron I am assuming she was given treatment with cyclophosphamide and steroids for this disease that was identified from the kidney biopsy.

Henle Yes… but now you are telling me that this is secondary vasculitis from the drugs?

Podocyte (with ease) Let's discuss this in more detail. Drug-induced lupus and vasculitis can occur. Drugs can interact with lupus in two ways. Either they make it worse, or they induce lupus in a predisposed patient. This patient is interesting, given that you mentioned two medications in her case that have been associated with drug-induced disease. Did this patient have antihistone antibodies?

Henle No.

Nephron Antihistone antibodies can be present with lupus induced by hydralazine, but usually (not always) they are absent in lupus induced by anti–TNF-α agents like infliximab.

Henle (with a confused look) Where does ANCA fall in this spectrum?

Podocyte Good question. These same drug-induced lupus syndromes are sometimes associated with an ANCA-associated necrotizing vasculitis. Usually these are anti-MPO or atypical ANCA positive (lactoferrin or elastase). In the kidney, biopsy specimens from such patients have usually shown a vasculitis component with necrotizing glomerular disease, which is most of the time pauci-immune in nature. This combination is most commonly seen with hydralazine-induced vasculitis-like syndrome, but we cannot rule out lupus induced by anti–TNF-α in this case, either. Now, could this be idiopathic lupus with ANCA vasculitis?

Henle I suppose; why not?

Nephron That is in the differential diagnosis, but the two possible drug-induced medications and the timing make the anti–TNF-α agent a more likely culprit. The normal complement levels and pure pauci-immune (predominant vasculitic) nature make drugs a more likely cause than primary systemic lupus or primary small vessel vasculitis. I suggest that you continue treatment with cytotoxic agents and stop the offending drugs. In vasculitis induced by an anti–TNF-α agent, steroids and cessation of that agent might be enough, but in hydralazine-induced cases, cytotoxic agents might be needed. I don't think maintenance therapy will be needed in this case.

Podocyte Good work, Dr. Nephron. You have done well!

Henle (shocked) This is very revealing.

Henle exits.

Nephron Fine work, Detective.

Podocyte Always nice to drop in and discuss a good case of glomerular disease. Until next time, professor!

A few months later

Henle The patient is doing well. We discontinued both the hydralazine and the anti–TNF-α, and her renal function normalized, her joint pains are gone, and she has no more proteinuria. She will complete her six months of treatment and stop after that. She was told not to take those medications in the future.

Nephron This tells us a very important point in medicine. We prescribe medications all the time, and we have to be careful regarding the potential drastic effects they can have on the body. My dear apprentice, again from a single entity of ANCA vasculitis, you diagnosed a life-threatening disease caused by a medication in this case.

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

Industry Spotlight

Biomarker Test Gives Early Warning of Acute Kidney Injury

A retrospective study shows that a new biomarker-based diagnostic test is more effective than the current standard for early detection of adverse outcomes after acute kidney injury (AKI), which can be fatal for an estimated half of the critically ill patients with that condition.

The April 26 issue of the *Journal of the American College of Cardiology* reported that a kidney injury biomarker called neutrophil gelatinase–associated lipocalin (NGAL), detected in urine or blood specimens, can uncover early AKI in critically ill patients.

Notably, these same patients did not have diagnostic increases in serum creatinine, which is considered the standard for detecting AKI. The authors concluded that early NGAL testing may allow earlier conventional medical interventions or novel treatments that could improve the prognosis of AKI.

"This study describes a new biomarker (NGAL) that completely outperforms the current serum creatinine–based criteria for the early detection of AKI," said the study's first author, Prasad Devarajan, MD, director of Nephrology and Hypertension at Cincinnati Children's Hospital Medical Center. "This has enormous implications because AKI affects about 30 percent of all critically ill patients, in whom current therapeutic options are limited and unacceptably delayed. We concluded that these substantial numbers of patients might reasonably be classified as having subclinical AKI, even though they do not fulfill current creatinine-based criteria for AKI."

The retrospective study pooled data from 2322 critically ill adult and pediatric patients, who mainly had type 1 cardiorenal syndrome, in which heart problems injure the kidneys. The researchers found that 40 percent of the patients showed unexpected early increases in urine or blood NGAL levels, but no increases in serum creatinine.

The study showed that elevated NGAL levels, in the absence of elevated serum creatinine, were associated with increased rates of hospital mortality, a higher number of intensive care and in-hospital days, and a greater likelihood that patients might require dialysis.

Genetic Engineering News reported that the researchers "suggest NGAL-positive, but serum creatinine–negative, patients could be reclassified as having subclinical AKI, and are pushing for more research to determine whether the more timely initiation of treatment for AKI in these patients could help improve outcomes."

The Street, a financial news services company, has the full news release: http://www.thestreet.com/print/story/11086097.html, which includes reported potential conflicts of interest.

Statin Drugs Improve Postsurgical Kidney Health

For older patients, statins before surgery day may keep kidney problems at bay. Researchers at the University of Western Ontario in London, Ontario, have found that patients over age 65 who were receiving statins before surgery had better kidney outcomes and lower mortality rates than did those who were not taking statin drugs, according to a study published in mid-April in the *Journal of the American Society of Nephrology (JASN)*.

Statins are strong cholesterol-lowering drugs, and they make up one of the "most important sectors of the pharmaceutical industry, with total revenues exceeding $25 billion in 2009," according to a report referenced at pharmaceutical-market-research.com.

A *HealthDay* article about the study said that author Amit Garg and coauthors noted in their study, "If the evidence base of statin benefit for perioperative nonrenal complications and mortality continues to grow, withholding statins before surgery may become unethical."

The research team designed the retrospective study, published in the *JASN*, because animal studies had shown that statins help protect against renal injuries.

The researchers looked at a large group of 213,347 men and women who underwent elective surgery in Ontario, Canada, between 1995 and 2008. Heart operations, lung operations, vascular surgery, abdominal surgery, and procedures involving the bladder, ureter, and kidneys were assessed, but transplants and kidney removals were excluded from the study data.

During the first 14 days after surgery, 1.9 percent (4020 patients) experienced acute kidney injury, and 0.5 percent (1173 patients) required short-term dialysis. The 30-day mortality rate was 2.8 percent (5974 patients).

Before surgery, 32 percent of patients were taking a statin. After adjustment for patient and surgical characteristics, statin use was related to 16 percent lower odds of acute kidney injury, 17 percent lower odds of acute dialysis, and 21 percent lower odds of mortality, the study showed.

Statin users had an additional 16 percent reduction in the incidence of renal injury, a 17 percent reduction in the risk of dialysis, and a 21 percent lower mortality rate per 30 days.

The findings bear out the hypothesis derived from animal models that statins could hold benefits for patients undergoing surgery, Canadian investigators reported in *JASN*.

Statins do have side effects, however. These drugs can cause an increase in liver enzymes, which can be cleared by discontinuing the drug for a while. Statins also can cause muscle problems, known as statin myopathy, in some people. In severe cases, according to the National Heart, Lung and Blood Institute, muscle cells can break down and release myoglobin into the bloodstream, which can damage the kidneys.

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