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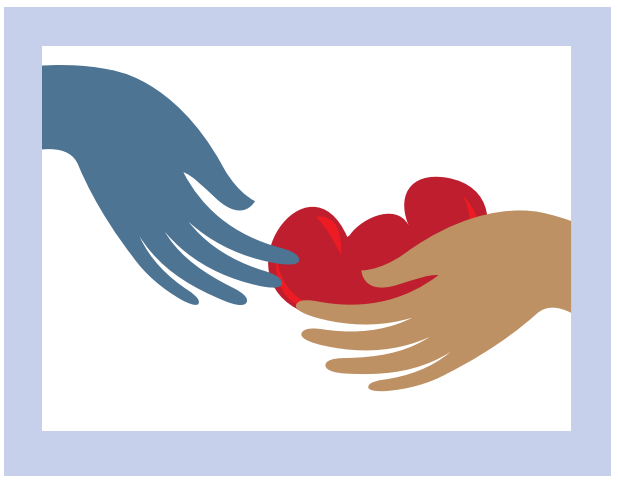
New Donor Chains Could Change Approach to Paired Donation

By Eric Seaborg

A new approach aimed at turning one altruistic kidney donation into a never-ending chain could be the next step in increasing the number of transplanted kidneys, a recent report in the *New England Journal of Medicine* proposes. The new system is called a nonsimultaneous, extended, altruistic donor (NEAD) chain.



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"Before this article, everybody in the field of kidney transplantation thought that we had to do everything simultaneously," said lead author Michael Rees, MD, PhD, professor of urology at the University of Toledo and medical director of the Alliance for Paired Donation (APD). "All kidney paired donation transplants had to happen simultaneously because of that great harm that would happen if somebody cheated and somebody was permanently harmed by the loss of their donor."

The insight behind the innovation is that starting a chain with an altruistic donor—someone who volunteers a kidney with no strings attached—fundamentally changes the ethical consequences of a potential donor reneging down the line. Critics, however, contend that the paper downplays these consequences and that the approach widens the gap between patients with incompatible donors and those without.

Paired donation to domino chains

Paired donation began as a way to address the problem that many patients with end stage renal disease have a friend or loved one willing to give them a kidney, but incompatibilities in blood type or human leukocyte antigen (HLA) crossmatching prevent a transplant. Simple swaps between recipient-donor pairs with complementary compatibilities provided a first step in addressing this issue, but the matches were limited in number.

Computer matching programs enabled more complicated swapping

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Pre-Dialysis Care Varies by Patient, Center, and Region

Links to First-Year Mortality Warrant Quality Improvement Initiatives

By Timothy O'Brien

For patients with advanced chronic kidney disease (CKD), how much does getting recommended pre-dialysis care affect outcomes? Quite a bit—not only for the individual patient, but also at the level of the dialysis center, according to a study in the May *Journal of the American Society of Nephrology*.

Based on analysis of U.S. ESRD Network data, the study identified geographic "clusters" where patients are particularly unlikely to receive recommended pre-dialysis care. "Our observations suggest that pre-ESRD care may not vary randomly across communities and that less than optimal care aggregates within some treatment centers, and these centers tend to aggregate geographically," said lead author William McClellan, MD, of Emory University School of Medicine in Atlanta. "This suggests that assistance to improve pre-ESRD care might be profitably targeted to these treatment centers and the health systems they serve."

Better pre-dialysis care, better one-year survival

McClellan and his colleagues analyzed data on more than 30,000 patients starting he-

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References: 1. Renvela [package insert]. Cambridge, MA: Genzyme Corp; 2007. **2.** Delmez J, Block G, Robertson J, et al. A randomized, double-blind, crossover design study of sevelamer hydrochloride and sevelamer carbonate in patients on hemodialysis. *Clin Nephrol*. 2007; 68:386-391.

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New Donor Chains

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schemes involving more patients, and altruistic donors enabled "domino" chains in which an altruistic donor might give to recipient A, whose incompatible donor would donate to recipient B, whose incompatible donor would give to recipient C, with the chain ending with a donation to a patient on the United Network for Organ Sharing or similar waiting list who did not have an incompatible donor.

Before the advent of paired donation, an altruistic donor's kidney would go to the top match on the waiting list, resulting in a single transplant. A domino chain leverages that single donation into several transplant opportunities. So far, the longest domino chain was a six-way swap involving 12 individuals at Johns Hopkins University in April, done in six operating rooms with nine surgical teams over 10 hours.

Paired donations have always been done simultaneously to prevent the possibility of anyone reneging on a commitment to donate, which could result not only in a would-be recipient missing out on getting an expected kidney, but also losing the "bargaining chip" if her incompatible donor gave a kidney away, removing any chance for a paired donation in the future.

The paper posits that a NEAD chain can change this approach: "When an altruistic donation initiates a chain of transplantation, each subsequent donor makes the donation only after the co-registered recipient in his or her pair has already received a transplant. Thus, although reneging in the middle of a chain would still be problematic, it would not irreparably harm the remaining parts of the chain." Instead of being required to donate immediately, a "bridge donor" can be asked to wait while a solid match is found.

How NEAD works

The chain reported in the *NEJM* paper was initiated by the APD, a coalition of 70 transplantation programs that pool patients in a single registry.

A 28-year-old altruistic donor from Michigan started the chain by traveling to Phoenix to donate to Recipient 1. Eight days later, the husband of Recipient 1 (Donor 2) traveled to Toledo to donate to Recipient 2. Two months later, the mother of Recipient 2 (Donor 3) traveled to Columbus, Ohio, where simultaneous transplants extended the chain to Recipient 3 and Recipient 4.

After finding no matches for Donor 5 for three months, the APD contacted the Incompatible Kidney Transplantation Program at Johns Hopkins University to find Recipient 5. The next three donations were then performed simultaneously, with donations 6 and 7 performed at Johns Hopkins, while the kidney from Donor 8 was shipped by commercial airline to Wake Forest University and transplanted into Recipient 8.

About two weeks later, Donor 9's kidney was removed at Wake Forest and shipped on a charter flight to Johns Hopkins. On the same day that Recipient 9 received this organ, the kidney of his brother (Donor 10) was flown by commercial airline to Toledo and transplanted into Recipient 10. The chain is still open, pending the identification of the next recipient.

Theoretically, the NEAD chain could go on indefinitely, in contrast to domino chains, which always end with a recipient on the waiting list who does not have an incompatible donor.

Rees said that his group currently has six ongoing NEAD chains, with 13 bridge donors to date, and no one has cheated. The second chain has run to five transplants. "We are so confident that people are not going to cheat that we have let the next four NEAD chains start with only one transplant," he said.

However, one of the paper's coauthors, Dorry L. Segev, MD, associate professor of surgery at Johns Hopkins University, is less sanguine: "The NEAD has certain risks associated with it. The first is that the donor who is asked to wait around will renege." A Johns Hopkins chain was broken by the first bridge donor.

Although the paper downplays the importance of losing this kidney to others who would have been in the chain, the loss is still "devastating" because it denies a potential recipient this valuable resource, said Ron Shapiro, MD, professor of surgery at the University of Pittsburgh and president of the Paired Donation Network, a consortium of 80 kidney transplant

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Editorial Staff
Editor-in-Chief: Pascale H. Lane, MD, FASN
Managing Editor: Dawn McCoy
Design: Lisa Cain

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New Donor Chains

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programs. The person who loses out can be considered to be a patient on the deceased donor waiting list who might have been a beneficiary at the end of a domino chain.

"The second limitation of NEADs is that we are furthering the disparity between people who have live donors available to them and people who do not and are stuck on the waiting list," said Segev.

"There are many good things about the chain, but if the chain doesn't end with a kidney going to somebody on the deceased donor waiting list, then the patients who are waiting for a kidney transplant who don't have a donor are permanently cheated," said Shapiro.

Rees counters that if a NEAD works as the first one did, taking 10 people off the waiting list—four more than the longest domino chain has—almost everyone on the waiting list benefits by moving closer to the top.

As the demand for kidneys continues to outpace the supply, creativity is needed to find the best use of a limited resource, and the appeal of leveraging a donation into a long chain could bring out more altruistic donors. The publicity that the paper has generated—ABC, NBC, CBS, and CNN all covered it—could also make a difference. Following the publicity, more than 500 people have registered at the APD website to donate a kidney.

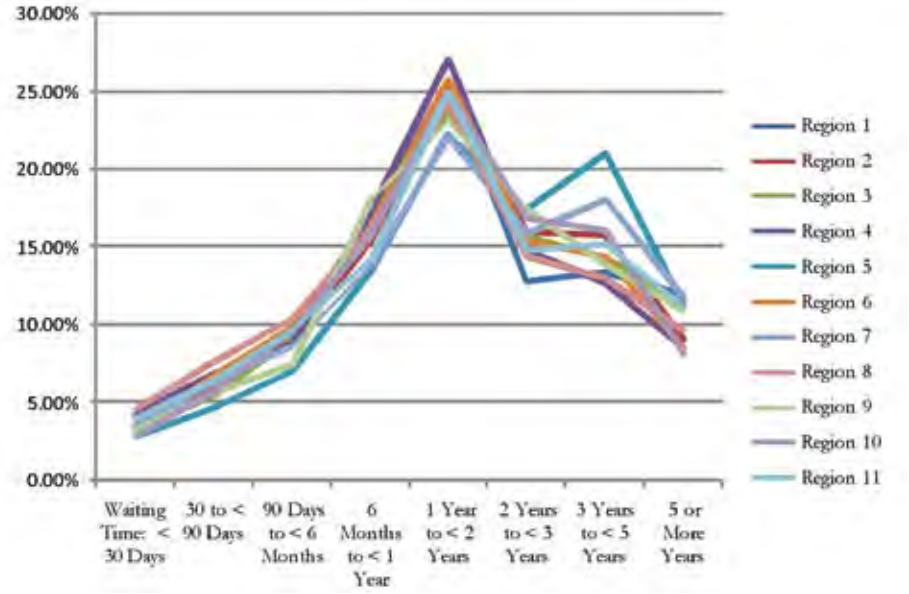
The paper noted that NEAD chains also increase the universe of possible matches, and thus can improve their quality and provide donors for hard-to-match recipients.

The concept certainly bears watching. Despite his reservations, Shapiro called the paper "a huge contribution" and said that his own transplant institution is negotiating to begin a similar program, although with adaptations to address his concerns.

Rees MA, Kopke JE, Pelletier RP, et al. A nonsimultaneous, extended, altruistic-donor chain. N Engl J Med *2009; 360:1096–101.*

Data Snapshot

Wait times for kidney transplant



Region Name		Current Waiting List Candidates	Wait Time Index*	Wait Time > 1 Year (%)
All Regions		78,957		
Region 1	Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Eastern Vermont	2,851	2.53	63.65
Region 2	Delaware, District of Columbia, Maryland, New Jersey, Pennsylvania, West Virginia, Northern Virginia	10,714	2.54	65.75
Region 3	Alabama, Arkansas, Florida, Georgia, Louisiana, Mississippi, Puerto Rico	10,479	2.56	64.88
Region 4	Oklahoma, Texas	7,142	2.47	62.98
Region 5	Arizona, California, Nevada, New Mexico, Utah	18,065	2.70	71.95
Region 6	Alaska, Hawaii, Idaho, Montana, Oregon, Washington	2,009	2.50	63.95
Region 7	Illinois, Minnesota, North Dakota, South Dakota, Wisconsin	6,489	2.6	67.67
Region 8	Colorado, Iowa, Kansas, Missouri, Nebraska, Wyoming	3,513	2.46	61.26
Region 9	New York, Western Vermont	6,913	2.57	65.45
Region 10	Indiana, Michigan, Ohio	5,613	2.55	66.05
Region 11	Kentucky, North Carolina, South Carolina, Tennessee, Virginia	6,921	2.55	65.98

* The Wait Time Index measures average wait time on a scale in which 0.5 = <30 days, 1= 30–90 days, 1.5 = 90 days to 6 months, 2 = 6 months to 1 year, 2.5 = 1-2 years, 3 = 2–3 years, 3.5 = 3–5 years, and 4 = 5 or more years.

Pre-Dialysis Care

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modialysis in five of the 18 U.S. ESRD Network regions in 2005–06. Physician responses to a standard Medicare form were used to determine whether each patient had received at least six months of care from a nephrologist before starting ESRD therapy.

Early referral to a nephrologist—including creation of an arteriovenous fistula (AVF) six months before the expected start of hemodialysis—is an important part of current recommendations for the care of patients with CKD. The final analysis included 28,135 patients, mean age 62.8 years. Fifty-four percent were male and 56 percent white; 44 percent had diabetes.

Just over half of the patients—51.3 percent—received at least six months of pre-dialysis care from a nephrologist. Older patients, women, patients with diabetes as their primary cause of ESRD, and those with comorbid coronary atherosclerosis were more likely to receive recommended care. Factors associated with reduced rates of recommended care included heart failure, unemployment, being unable to walk, need for help with daily activities, and nursing home residence.

By several measures, patients receiving recommended care were in better shape for starting dialysis—including the presence of an AVF in 84.5 percent of patients. Patients receiving at least six months of nephrologist care were fitted with an AVF at four times the rate of those not receiving such care. They were also more likely to have been treated with an erythropoiesis-stimulating agent (ESA), to have received dietary counseling, and to have hemoglobin and albumin levels within the recommended range, compared with those who did not receive such care.

All of these advantages translated into a reduced risk of death during the first year on dialysis. One-year survival was 85.5 percent for patients receiving recommended pre-dialysis care, compared to 79.3 percent for those who did not receive recommended care. On adjusted analysis, the odds of survival were 50 percent higher for patients receiving recommended care.

Once other factors—including AVF, hemoglobin and albumin levels, ESA use, body mass index, and dietary counseling—were taken into account, the effect weakened. However, the odds of survival were still 31 percent higher for patients receiving six months of nephrologist care.

"Ours is one of the larger studies to show an association between pre-dialysis care and outcomes," McClellan said. "It has the additional advantage of being population-based, including all hemodialysis patients in the population at risk.

The findings echo reports on the Canadian experience with advanced CKD, according to Jerry Yee, MD, head of the division of nephrology and hypertension at Henry Ford Hospital in Detroit. "If clinical practice guidelines and recommendations are attained before the advent of dialytic care, the improvement conferred by earlier care is borne out," said Yee. "Patients whose health is relatively better, do better."

Variations by center, with clusters of low-quality care

The data came from 1641 dialysis centers, which showed "substantial variation" in the percentage of patients receiving recommended pre-dialysis care. On average, just under half of patients starting care at a particular center had received recommended care, with a 25th to 75th percentile range of 33 to 64 percent.

Centers at the lower end of the range had fewer patients meeting recommendations for laboratory levels, AVF, and other factors. They also had the highest one-year mortality rate: 19.6 percent, compared to 16.1 percent at centers with high rates of recommended pre-ESRD care. The centers with high levels of pre-dialysis care had a 15 percent relative reduction in mortality.

When center-level data from four southern and southeastern ESRD Network regions were plotted on a map, a surprising picture emerged: a "significant circular cluster" of low pre-dialysis care centers in Alabama and Mississippi. One edge of the circle "appear[ed] to line up with the Mississippi River corridor from New Orleans up to Memphis, the other edge comprising most of the state of Alabama," according to the study report. In the center of the circle was a conspicuous "hole," in which there were no centers with high rates of pre-dialysis care.

Many potential contributors to center and regional variations

So what to make of this cluster of low-quality pre-ESRD care? "For as yet undetermined reasons, some geographic areas and their medical communities manage stage 4 CKD less successfully than others," said McClellan. "It is possible that factors not directly related to the medical communities per se may contribute to this variation. In looking at potential risk factors for these outcomes, we are interested in socioeconomic factors, population density (rural/urban), access to medical care and similar factors."

"This very interesting paper shows the prevalence of health-care disparities in pre-ESRD care," said Cleveland Clinic nephrologist Sankar Navaneethan, MD. Navaneethan was lead author of a recent review on factors associated with late referral in CKD (*BMC Nephrology* 2008; 9:3). The results showed that lack of communication between primary care physicians and nephrologists was a significant contributor to late referral, along with older age, minority status, lower education, and multiple comorbidities.

"The treatment center variation might be attributable to several causes. Insurance or socioeconomic status, availability of nephrologists in the vicinity, and the CKD knowledge of referring physicians could all play a significant role," Navaneethan said. "It would be useful to see if eGFR reporting in these areas might have contributed to the better pre-ESRD care in some but not in others. This would help to clarify if the lack of knowledge of referring physicians contributed to this variation."

While morbidity and mortality are obviously crucial, the center-level differences could affect other outcomes as well, according to Nancy Kutner, PhD, director of the rehabilitation/quality of life special studies center of the U.S. Renal Data System (USRDS) and Emory University in Atlanta.

"Treatment center differences in patterns of care have been shown to be associated with differences in dialysis patient-rated health status and employment levels," Kutner said. "Identifying clinic and/or regional differences in patterns of patient activity levels and nutritional status—as assessed for example in the USRDS's recent Comprehensive Dialysis Study—would also be informative. Of course, many patient-level variables that cannot be controlled in these observational studies are likely to influence patient outcomes."

"This is an extremely important study that identifies significant variation in pre-ESRD care from community to community," said Neil Powe, MD, James F. Fries Professor of Medicine and University Distinguished Service Professor of Medicine, Epidemiology and Health Policy and Management at the Johns Hopkins Medical Institutions. "It suggests that where a person with chronic kidney disease lives and receives care can have a profound effect on their health outcome. We need to better understand why these variations occur in order to improve care."

Maps may help target areas for quality improvement

Would maps of pre-dialysis care in other U.S. ESRD Network regions show similar clusters? "In the absence of data, that's a tough question," said McClellan. "The southeastern United States is characterized by a unique, intense clustering of poverty—the clustering may be a characteristic of the region." He pointed to a recent study applying spatial analytic techniques to the Community Health Status Indicators database, which showed a striking "continental poverty divide" between the northern and southern United States. (See http://www.cdc.gov/pcd/issues/2007/oct/07_0091.htm.)

"Mapping of geographic variations in patient characteristics and outcomes may point to locations where racial and/or ethnic disparities are elevated," Kutner said. "And, as a recent *NEJM* editorial suggests, identification and analysis of regional variations and associated outcomes might provide some lessons about ways to slow the growth of health-care costs." (*N Engl J Med* 2009; 360:849–852.)

Meanwhile, the results identify specific regions that might benefit from focused efforts to improve care for advanced CKD. "Our primary observations are the non-random distribution of the less-than-recommended pre-ESRD care among treatment centers and geographic regions," according to McClellan. "This may identify opportunities to target quality improvement interventions to improve stage 4 CKD care. "

Some projects targeting regional variations in CKD care are already underway. "Information on center-to-center variations and geographic clustering were applied to identify medical communities for a population-based CKD quality improvement pilot project being conducted by CMS in one of the Network states," said McClellan. "In addition, the CMS is piloting an intervention to improve CKD care among type 2 diabetes in 10 states. If successful, this pilot could serve as the basis for targeted interventions during future Medicare QIO and ESRD Network scopes of work."

Meanwhile, nephrologists and other professionals must work to realize the benefits of recommended pre-ESRD care. "Earlier chronic kidney disease care must occur, in order to achieve the outcomes associated with reduction in mortality," Yee said. "The time threshold for this to occur is at least six months before the initiation of renal replacement therapy. All of us must do better."

Disclosure: McClellan is a clinical consultant for the Georgia Medical Care Foundation, a Medicare quality improvement organization, which is participating in the Centers for Medicare & Medicaid Services pilot.

New Online: Discuss and Debate Hot Topics in Nephrology

The American Society of Nephrology is pleased to introduce the *ASN Kidney News* Discuss and Debate readers' forum, a moderated web page that will link to articles of interest. This month's forum will be on the articles:

"New Kidney Allocation Policy: God Squad Resurrection. . ."

". . . Or Allocating a Scarce Medical Resource?"

The articles appear on pages 14–15 in our special section, "Transplantation: Issues and Controversies." The forum will be open for comment from May 18 to June 3. We welcome and invite your comment on this important topic.

This is a moderated forum. All comments submitted must be reviewed and approved before appearing. Please review carefully the Guidelines for Posting. By commenting, you agree that you have read and will abide by these guidelines!

We look forward to receiving feedback on these articles.

Policy Update

State Initiatives Aim to Protect Transplant Recipients and Increase Organ Donation

By Caroline Jennette and Scott Sanoff

The National Kidney Foundation's "End the Wait" campaign, launched earlier this year, is an ambitious agenda aimed at improving access to kidney transplants. The campaign reflects an increasing recognition nationally that kidney transplantation is the treatment of choice for most individuals with end stage renal disease (ESRD) and a growing awareness of the imbalance between available organs and the number of patients on the waiting list.

The campaign has four overarching goals: 1) improve the outcomes of first transplants, reducing the need for re-transplantation; 2) increase deceased organ donation; 3) increase the number of living donors; and 4) improve the system of transplantation and donation throughout the United States by eliminating regional variations and racial disparities.

In the past decade, many states have begun to address goals similar to those of the "End the Wait" campaign, sometimes with the help of federal legislation. These efforts offer a potential model for those interested in promoting organ donation and transplantation. Table 1 is a state-by-state listing of policy initiatives that seek to increase organ donation and improve outcomes for transplant recipients.

Incentivizing living donation: The Federal Organ Donation & Recovery Improvement Act

In 2004, Congress amended the Public Health Service Act (Public Law 108-216) to increase public awareness of organ donation. The amendment aims to educate the public about the process for living organ donation, to appropriate funding for states to reimburse living donors for expenses related to donation, and to fund research investigating best practices promoting organ donor awareness and education.

Although a grant program for reimbursing living donors has not yet been funded, 16 states have enacted legislation to help reimburse living donors for travel, lodging, and/or missed wages as a result of organ donation (Table 1). Most states do this in the form of a tax credit or tax deduction of up to $10,000. Twenty-seven states provide a leave of absence (paid or unpaid, depending on the state), usually up to 30 days, for state employees who wish to be organ donors. Two states offer tax credits to employers if they provide a leave of absence for their employees to be an organ donor.

These tax credits and leave of absence provisions are not seen as violating the National Organ Transplant Act, which bars the donation of an organ for "valuable consideration," because they do not provide a direct case benefit. However, they are still seen as controversial by groups who view any compensation for organ donation as a slippery slope to paying donors outright for their organs. A national tax credit bill (Living Organ Donor Tax Credit Act of 2007) was introduced in Congress but was never passed.

As of mid-March 2009, six states had introduced bills offering a tax credit (one state offering both a tax credit and a paid leave of absence), and one state had introduced a bill granting a leave of absence for organ donors.

Reframing organ donation: the Uniform Anatomical Gift Act

The Uniform Anatomical Gift Act (UAGA) was first created in 1986 by the State Conference of Legislatures as a means to create uniform policy governing organ donation and the process by which a person may gift their body to medical science. States could voluntarily adopt the policy. In 2006, new provisions were added, including one designating organ donor status on drivers' licenses as legal consent for organ donation. Before this provision, a driver's license designation did not pass for legal consent and familial consent had to be obtained. Thirty-two states have enacted the revised UAGA and it is currently in session in eight states.

Protecting transplanted kidneys: transplant immunosuppressive drug coverage

The journey to full coverage of immunosuppressive drugs for kidney recipients continues, punctuated with small victories. In 1993, Medicare coverage for immunosuppressive medication was extended from 12 to 36 months for Medicare-covered ESRD patients. In 2001, coverage was extended for the life of the transplant for patients otherwise eligible for Medicare (those 65 or older, or disabled by Medicare standards for reasons other than ESRD).

However, significant gaps in coverage remain. According to the U.S. Renal Data System (USRDS), approximately 80 percent of kidney transplant recipients are currently under the age of 65, leaving them at risk of losing all or part of their immunosuppressive drug coverage if their 36-month limit is up this year, unless they are otherwise eligible for Medicare. Legislation has been introduced to extend immunosuppressive coverage for the life of the transplant to this population of younger, non-disabled transplant recipients at every congressional session since 2001 but has yet to pass.

While the battle for lifelong transplant medication coverage continues at the national level, many states are trying to protect patients from medication cost-saving measures. Some states are trying to bar non-physicians from switching brands or changing dosages without signed prior authorization from the physician and/or the patient. Two states have passed this legislation, and six states have introduced it for the 2009–2010 legislative session.

Washington state has introduced a bill that bars insurance plans from creating a separate lifetime limit on coverage for transplant recipients, and Illinois is working on similar insurance protections. Oregon has a bill in session that would require its state department of human services to pay for brand name rather than generic immunosuppressive drugs prescribed in connection with organ transplants. Lawmakers in California are working on extending state Medicaid coverage for anti-rejection medications for up to three years posttransplant unless recipients become eligible for other insurance.

Organ donation on the public radar: statewide initiatives to educate and raise awareness

National awareness campaigns have helped raise awareness about the need for organ donation, and as a result, many states have funded public outreach initiatives, although none have focused specifically on kidney

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Table 1

Transplant and organ donation policy initiatives by state, 2002–2009

	Tax credit/ deduction for living donors	Leave of absence for living donors	Revised UAGA	Immuno-suppressive drug protections	$ for organ donation education/ awareness
Alabama			●		
Alaska			●		
Arizona		●	●		
Arkansas	●	●	●		●
California		●	●	○	○
Colorado			●		●
Connecticut	●	●	○		
Delaware		●			
District of Columbia		●	●		
Florida			○		●
Georgia	●	●	●	○	
Hawaii	○	●			○
Idaho	●	●	●		
Illinois		●	●	○	●
Indiana		●	●		
Iowa	●	●	●		
Kansas			●		
Kentucky	○	○	○		
Louisiana	●				●
Maine		●	●		
Massachusetts	●	●		○	
Michigan			●	○	○
Minnesota	●	●	●		
Mississippi		●	●		
Missouri		●	●		●
Montana			●		
Nevada			●		
New Jersey	○		●	○	○
New Mexico	●	●	●		
New York	●	●		●	●
North Carolina			●		○
North Dakota	●		●		
Ohio	●	●	●		
Oklahoma	●	●			
Oregon	○		●	○	○
Pennsylvania	●	●			●
Rhode Island			●		○
South Carolina		●	○		
South Dakota			●		
Tennessee			●	○	
Texas		●	○		●
Utah	●	●	●	●	
Vermont			○		
Virginia	●		●		○
Washington			●	○	○
West Virginia	○	●	●	○	
Wisconsin	●	●			
Wyoming			○		
TOTAL	**22**	**28**	**40**	**12**	**18**

● = Policy enacted

○ = Policy currently in session as of 3/20/2009

UAGA = Uniform Anatomical Gift Act

Industry Spotlight

Vascular Access Coding Stays Same

The Centers for Medicare and Medicaid Services decided against coding edits that would have changed the way vascular access procedures are billed.

Coding guardians at the American Society of Diagnostic and Interventional Nephrology (ASDIN) and other industry groups formed a coalition that succeeded in keeping certain codes and definitions unchanged.

A Medicare coding program, the National Correct Coding Initiative, proposed changes that would have bundled the HCPCS codes G0392 and G0393. (During a percutaneous transluminal balloon angioplasty at a hemodialysis access site, if access to the "vessel" for the procedure is through an artery, code G0392 should be reported, and if access is through a vein, code G0393 should be reported.) The industry coalition argued that the codes should remain separate. As separate codes, they can still be billed together for the procedure in certain circumstances.

The coalition also successfully fought against creating a new definition of an arterial versus venous angioplasty, and against ending the use of code 35476 for draining a forearm fistula. Code 35476 generally is for a separate procedure outside of the fistula or graft location. Angioplasty may be coded a second time, with clear documentation, when a separate procedure is needed at a different site.

Policy Update

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donation. Nine states have passed legislation in the past seven years to fund organ donation education and public awareness programs. Nine other states have proposals pending in the 2009–2010 session.

New Jersey is working on legislation that would mandate education in public high schools and colleges to dispel myths about being an organ donor and the donation process. New Jersey is also working on legislation to create an education program for state contractors and their employers. New York and North Carolina hope to pass legislation similar to that of Florida and Louisiana, to create "Donate Life" license plates, with the funds generated going to organ donation awareness education. Colorado passed legislation to add a check-off box on state tax forms so taxpayers could contribute funds to the state's Organ and Tissue Donation Awareness Fund. On a national level, the Department of Heath and Human Services offers grants to states to implement educational campaigns.

Examining federal and state legislative activities, it is clear that transplantation and organ donation are on the radar. During these hard economic times, it is hoped that state-based efforts, supplemented and enhanced by campaigns such as NKF's "End the Wait," and by members of the organ donation and nephrology communities, can expand access to kidney transplantation and promote a new level of awareness about the importance of organ donation.

For more information on these and other kidney-related state policy initiatives currently in session, please visit http://www.unckidneycenter.org/healthpolicy/kidneypolicystate.html.

ASN Kidney News *editorial board member Caroline Jennette, MSW, is legislative liaison and Scott Sanoff, MD, is a renal transplant fellow at the University of North Carolina Kidney Center.*

Letters

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

Identifying optimal predictive markers

Better predictors of long-term outcomes are needed in renal transplantation

Treatment advances have resulted in improved short-term posttransplant outcomes.[1] Clinical endpoints have evolved along with these improvements.[1] For years, acute rejection was the standard endpoint used in clinical trials to evaluate immunosuppressants and assess posttransplant outcomes.[1] Data suggest that decreasing acute rejection rates, however, have not led to an increase in long-term graft survival.[2] Therefore, acute rejection may not be considered a reliable predictor of long-term outcomes.[1]

Alternative short-term surrogate markers, such as renal function, histologic findings, and immunologic markers, have been assessed.[1] Markers that reliably predict long-term graft and patient survival in renal transplantation are needed to better assess therapeutic success.[1,3]

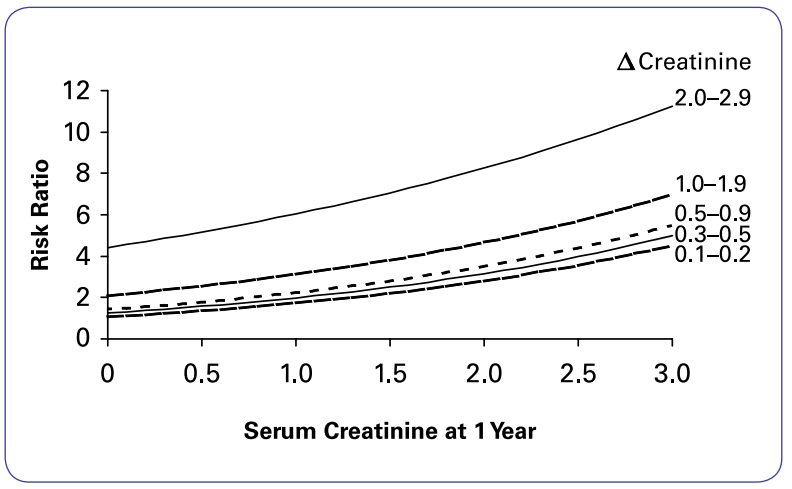
Is renal function a better predictor of long-term outcomes?

Renal function has emerged as a better marker than acute rejection in predicting long-term patient and graft survival.[4-6] Studies demonstrate that preservation of renal function is critical for long-term graft survival.[2,4]

Hariharan et al conducted a retrospective study in 105,742 adult renal transplants performed between 1988 and 1998, examining renal function 1 year posttransplant to determine long-term renal graft survival.[4] Results demonstrated a statistically significant link between renal function and long-term 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).[4]

When assessing the impact of posttransplant variables on long-term outcomes, 1-year serum creatinine and change in serum creatinine from 6 to 12 months had a significant effect ($P<.0001$) on graft failure.[4] Acute rejection within 1 year, however, did not reach significance ($P=.8853$).[4]

Figure 1. Relative hazard for graft failure according to 1-year creatinine and Δ creatinine values.[4]



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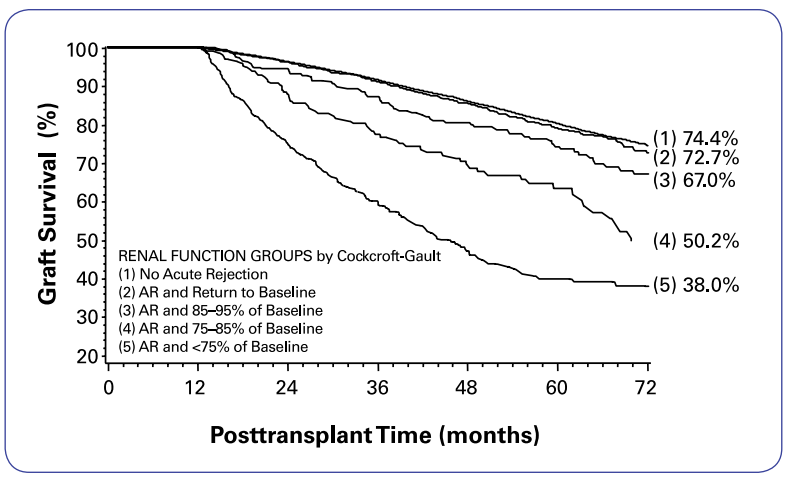
To evaluate the impact of renal function on long-term graft survival in the absence or presence of acute rejection, Meier-Kriesche et al retrospectively studied 38,426 adult renal transplants performed between 1995 and 2001.[2] This study reported that only those acute rejection episodes that impair renal function negatively affect long-term graft survival.[2] 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).[2] The data showed that in the presence of acute rejection episodes, renal function is the better predictor of long-term outcomes.[2]

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



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in solid organ transplantation

GFR: An important marker of renal function

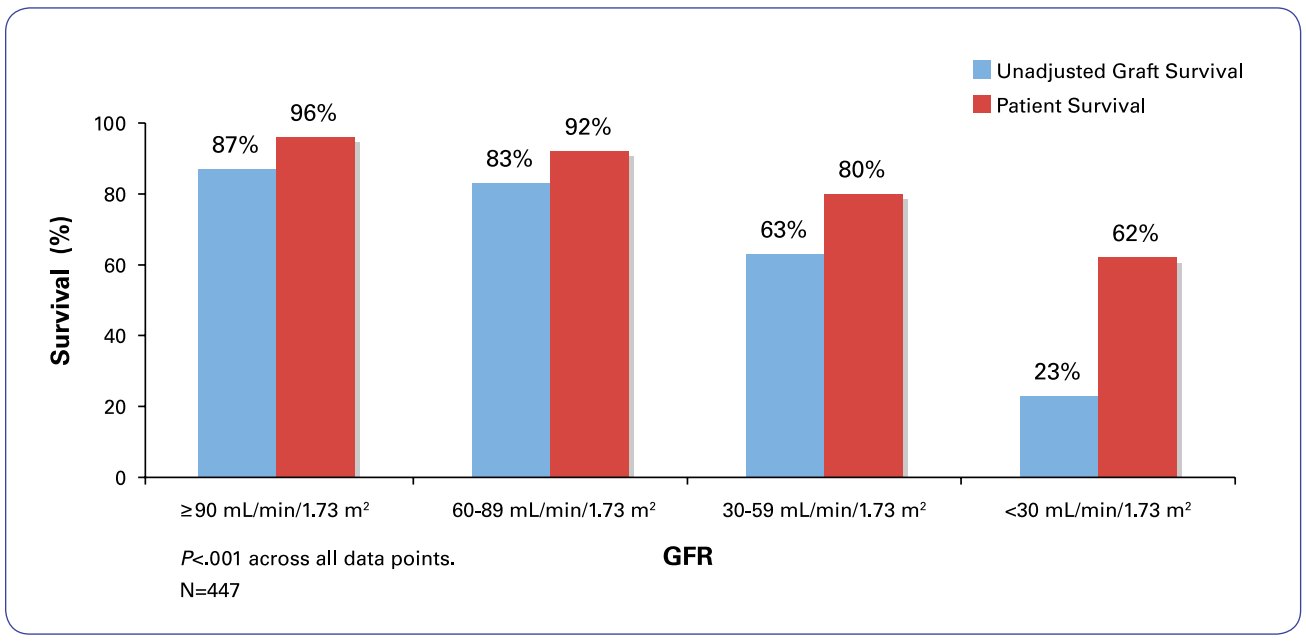
Glomerular filtration rate (GFR), measured through clearance assays, may be a more accurate method of estimating renal function versus serum creatinine, by avoiding the dependence on age, gender, race, and body weight.[3]

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 at 12 months posttransplant was predictive of 10-year, long-term graft and patient survival (Figure 3).[7] Results from this study are consistent with the findings from Hariharan et al, demonstrating renal function, as measured by GFR, to be an important marker of long-term graft survival.[7] In addition, this research shows GFR at 12 months also correlates to long-term patient survival.[7]

Signaling the future: Using renal function to predict long-term outcomes

Short-term, surrogate endpoints that predict long-term renal transplant survival are needed to better evaluate success in renal transplantation.[1,3] Research findings demonstrate renal function may be the best predictor of long-term outcomes.[6,7] Renal function should therefore be incorporated into clinical studies as a clinical endpoint to assess posttransplant success.[1]

Figure 3. 10-year graft and patient survival by GFR levels at 12 months posttransplant.[7]



References:
1. Hariharan S, McBride MA, Cohen EP. Evolution of endpoints for renal transplant outcome. *Am J Transplant.* 2003;3(8):933-941. **2.** 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. **3.** 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. **4.** 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. **5.** 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. **6.** 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. **7.** Marcén R, Pascual J, Tenorio M, et al. Chronic kidney disease in renal transplant recipients. *Transplant Proc.* 2005;37(9):3718-3720.

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Journal View

Patient Dialysis Knowledge Linked to Arteriovenous Access

Patients with lower levels of knowledge about chronic hemodialysis are less likely to have arteriovenous access for dialysis, according to a study in the *Clinical Journal of the American Society of Nephrology*.

The prospective cohort study included 490 adult patients starting chronic hemodialysis and followed up for six months. The Chronic Hemodialysis Knowledge Survey (CHeKS) was used to assess dialysis knowledge; the median score was 65 percent out of 100 percent. Older, nonwhite, and less educated patients had lower scores.

Dialysis knowledge was significantly related to dialysis access type. On adjusted analysis, the likelihood of having arteriovenous fistula or graft access at the start of dialysis increased by about one-third per 20 percent increase in CHeKS score. A similar association was noted for access at six months. The CHeKS score was not significantly related to most laboratory measures, except for a modest association with serum albumin.

Low dialysis knowledge appears to be a risk factor for not having arteriovenous access at the start of dialysis and at follow-up. Evaluation of patient knowledge may provide a quick tool for identifying at-risk patients who could benefit from targeted educational interventions, the authors believe [Cavanaugh KL, Wingard RL, Hakim RM, Elasy TA, Ikizler A: Patient dialysis knowledge is associated with permanent arteriovenous access use in chronic hemodialysis. *Clin J Am Soc Nephrol* 2009; 4:950–956].

Gum Disease Linked to Reduced Survival in ESRD

Dialysis patients with periodontal disease are at higher risk of death from cardiovascular causes, suggests a study in *Kidney International*.

The retrospective analysis included 168 patients at dialysis centers in New York City and North Carolina. Dental examination revealed moderate to severe periodontal disease—defined as 2 or more teeth with at least 6 mm of interproximal attachment loss—in 68 patients. The remaining 100 patients had mild or no periodontal disease. Dialysis registry data were used to compare rates of death from cardiovascular disease and from all causes.

There were more women in the periodontal disease group. Of 22 deaths during an 18-month follow-up period, 14 were from cardiovascular causes. Patients in the periodontal disease group were at significantly higher risk of cardiovascular death, with a hazard ratio of 5.0. The association was not weakened by adjustment for other factors, including dialysis center, smoking, diabetes, and hypertension. All-cause mortality was similar between groups.

If confirmed, the results suggest that periodontal disease is a strong risk factor for death from cardiovascular disease in ESRD patients receiving dialysis. More study is needed to determine whether periodontal treatment can reduce cardiovascular mortality [Kshirsagar AV, Craig RG, Moss KL, Beck JD, Offenbacher S, Kotanko P, Klemmer PJ, Yoshino M, Levin NW, Yip JK, Almas K, Lupovici EM, Usvyat LA, Falk RJ: Periodontal disease adversely affects the survival of patients with end stage renal disease. *Kidney Int* 2009; 75:746–751.

Better Survival in African Americans with Non-Dialysis-Dependent CKD

As in dialysis patients, African Americans with advanced non-dialysis-dependent CKD (NDD-CKD) have higher survival than white patients, reports a study in the *Clinical Journal of the American Society of Nephrology*.

The study included two groups of men with moderate or advanced NDD-CKD: 298 African Americans and 945 white patients seen at one Veterans Affairs center. The outcomes of mortality and ESRD were compared at a median follow-up of 2.8 years.

African Americans with NDD-CKD had significantly lower crude mortality, unadjusted hazard ratio 0.75. However, the difference became nonsignificant on sequential adjustment for differences in baseline variables—particularly case-mix characteristics. African Americans with cardiovascular disease had the highest mortality.

African Americans also had a higher crude incidence of ESRD, unadjusted hazard ratio 1.64. Again, the difference became nonsignificant on adjusted analysis. Mixed effects models showed no significant racial difference in the slope of the estimated glomerular filtration rate.

Thus differences in clinical characteristics appear to account for the lower mortality in African American men with NDD-CKD, compared to white men. The fact that African Americans are more likely to die in the earlier stages of CKD may lead to selection of a group with less comorbidity and better survival later in the disease process. The apparent increase in ESRD risk may reflect the reduction in late-stage CKD mortality, rather than faster CKD progression [Kovesdy CP, Anderson JE, Derose SF, Kalantar-Zadeh K: Outcomes associated with race in males with non-dialysis dependent CKD. *Clin J Am Soc Nephrol* 2009; 4:973–978].

Lowering Blood Pressure Reduces Cardiovascular Risk in Dialysis Patients

In patients receiving dialysis, treatment to lower blood pressure reduces cardiovascular morbidity and mortality by about 30 percent, reports a systematic review and meta-analysis in *The Lancet*.

A comprehensive literature search was performed to identify randomized controlled trials of blood pressure–lowering therapy for patients on dialysis that included data on cardiovascular outcomes. Meta-analysis was performed using pooled data on 1679 patients from eight trials, including 495 cardiovascular events.

Patients receiving blood pressure lowering–therapy had a 4.5/2.3 mm Hg reduction in weighted mean blood pressure. Rates of cardiovascular events and cardiovascular death were significantly lower for treated patients: relative risk 0.71 for both outcomes. The protective effects of blood pressure lowering were similar for patients with and without hypertension and other comorbid conditions, and across different antihypertensive drug classes.

Patients on dialysis usually have high blood pressure, but the cardiovascular benefits of blood pressure reduction have been unclear. The new meta-analysis concludes that blood pressure lowering reduces the very high rates of cardiovascular events and cardiovascular death in this group of patients. Routinely considering treatment to reduce blood pressure might prevent a substantial number of deaths among patients undergoing dialysis, the authors suggest [Heerspink HJL, Ninomiya T, Zoungas S, de Zeeuw D, Grobbee DE, Jardine MJ, Gallagher M, Roberts MA, Cass A, Neal B, Perkovic V: Effect of lowering blood pressure on cardiovascular events and mortality in patients on dialysis: a systematic review and meta-analysis of randomised controlled trials. *Lancet* 2009; 373:1009–1015].

New Classification System Would Improve Prediction of ESRD

Adding information on urinary albumin to estimated glomerular filtration rate (eGFR) would be more accurate in identifying patients at risk of progression to ESRD, suggests a study in the *Journal of the American Society of Nephrology*.

Analysis of nearly 66,000 participants from a Norwegian population-based health study identified 124 subjects who progressed to ESRD over 10.5 years' follow-up. Multivariate analyses were performed to determine how well the combination of baseline eGFR and urine albumin predicted progression to ESRD. Other potential renal risk factors were also evaluated for their independent predictive value.

Both eGFR and urine albumin were strong independent predictors of progression to ESRD. Hazard ratios associated with eGFR increased from 6.7 at 45–59 mL/min/1.73 m^2, to 18.8 at 30 to 44 mL/min/1.73 m^2, to 65.7 at 15–29 mL/min/1.73 m^2. Hazard ratios for microalbuminuria and macroalbuminuria were 13.0 and 47.2, respectively. Information on hypertension, diabetes, smoking, obesity, and a range of other factors offered no additional predictive value.

At the current eGFR threshold (15 to 59 mL/min/1.73 m^2), 4.7 percent of the study population would have been referred, resulting in identification of 69.4 percent of participants expected to progress to ESRD. With addition of information on urinary albumin, only 1.4 percent of the population would be referred, while still detecting 65.6 percent of those expected to progress to ESRD.

Adding urinary albumin to eGFR would improve the ability to identify patients likely to progress to ESRD. Classification systems combining these two variables will provide a "simple and powerful tool" for risk assessment in CKD, the researchers believe [Hallan SI, Ritz E, Lydersen S, Romundstad S, Kvenild K, Orth SR: Combining GFR and albuminuria to classify CKD improves prediction of ESRD. *J Am Soc Nephrol* 2009; 1069–1077].

Transplantation: Issues and Controversies

By Titte Srinivas and Jesse Schold

Titte Srinivas

Jesse Schold

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We are delighted to introduce a series of articles that address select areas of controversy in kidney transplantation in this issue of *ASN Kidney News*. These articles, which provide provocative views on contentious topics, are authored by some of the leading thinkers in the field. One of the key driving forces behind this special edition on transplantation was to elicit thoughtful yet uninhibited information and commentary beyond what is already available at scientific meetings or in peer-reviewed journals. These articles tap into the core of some of the intellectual discourse among many academicians, industry leaders, and policymakers in the field of kidney transplantation.

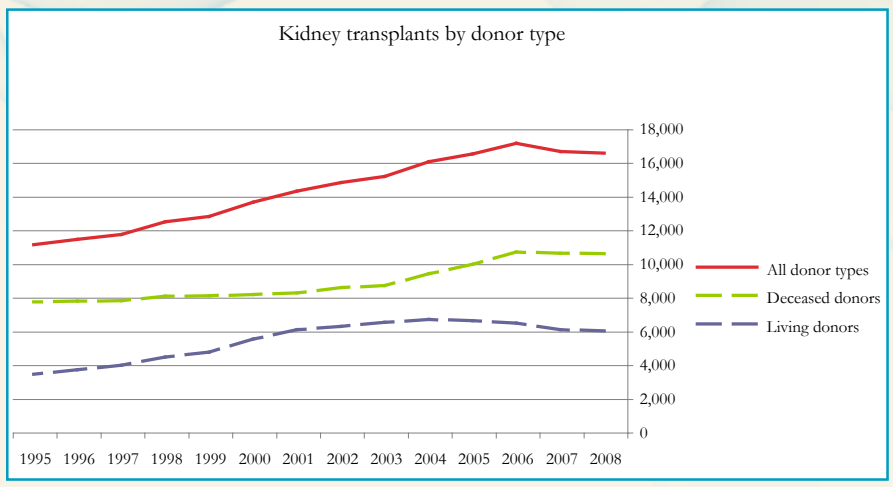
Dr. Richard Howard provides an insightful overview of increased regulatory oversight, a contentious issue facing kidney transplant centers. He points out how the increased regulatory oversight of kidney transplant performance has led many centers to question the utility of these evaluations. Dr. Howard then discusses some of the unintended consequences that may result from this oversight, in particular, the potential impact on many patients who may be deemed "too risky" to transplant.

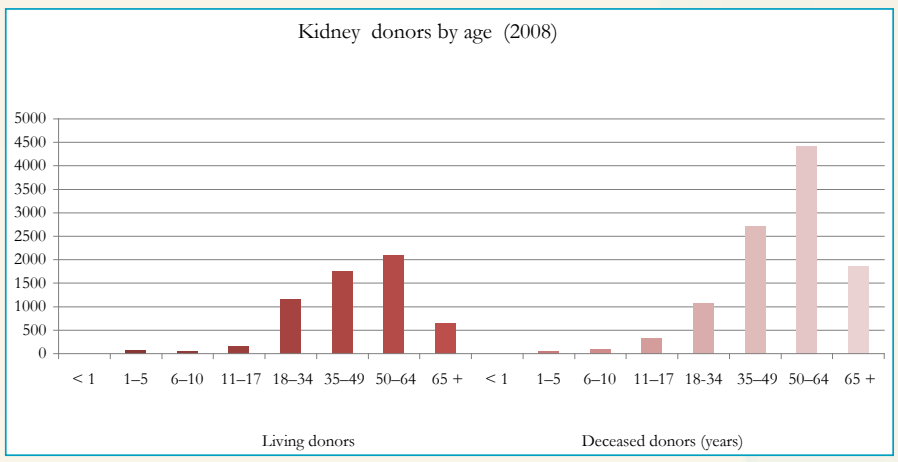
Dr. Curtis provides a highly provocative and sobering perspective on efforts to implement a new kidney allocation system for deceased donor organs, while Dr. Stegall discusses the merits that may be associated with changes to current policies of organ allocation. Dr. Ojo shares his experienced perspectives on changes and failures in efforts to ameliorate well-known disparities in care for renal disease patients with a focus on racial issues.

Drs. Page and Woodward present important research regarding the impact of availability of long-term financial coverage of immunosuppression medications for renal transplant recipients, an issue especially relevant in today's economic climate. Drs. Augustine and Dharnidharka provide two perspectives on the increasing prevalence of immunosuppressive regimens without maintenance steroids in kidney transplantation. Finally, Dr. Foley discusses the important issue of potential risks to living donors and the evidence that exists concerning higher risk living donors.

And, to kick off our coverage, take a look at the data snapshots here. These visual displays address important metrics such as yearly trends in numbers of living versus deceased donors and donor type by age. This synopsis will help put many of these important issues into perspective.

Please join us online at www.asn-online.org in discussing these important issues. From May 18 to June 3, ASN will host an online forum, "Discuss and Debate" on the articles "New Kidney Allocation Policy: God Squad Resurrection. . . Or Allocating a Scarce Medical Resource?" We look forward to your comments.





Source: Based on OPTN data as of March 20, 2009. The United Network for Organ Sharing (UNOS) administers the OPTN under contract with the U.S. Department of Health and Human Services. (www.optn.org).

Titte Srinivas, MD, is staff physician in the department of nephrology and hypertension at the Glickman Urological and Kidney Institute at the Cleveland Clinic, and Jesse Schold, PhD, is assistant professor of medicine at the University of Florida in Gainesville.

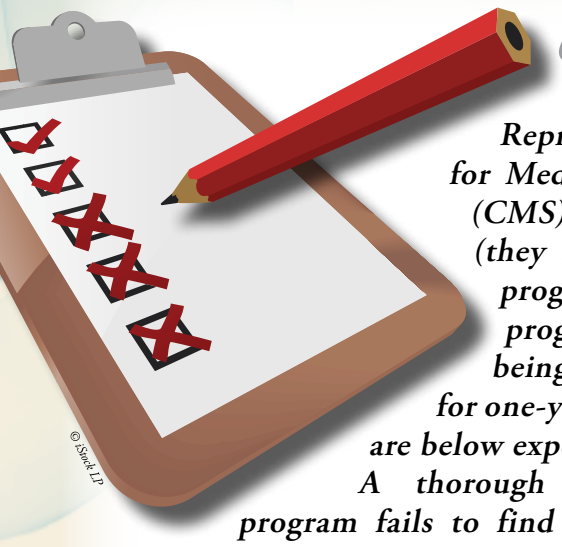
Oversight of Transplant Center Performance Can Impact Patients and Care Providers

By Richard Howard

The United States has the highest per capita cost of medical care in the world—medical care consumes 17 percent of the gross domestic product. Yet the United States ranks far from the top in most measures of health.

In recent years, government, insurance companies, business groups, and others have placed great emphasis on improving the quality of medical care because of the perception that physicians, hospitals, and others have done an insufficient job of improving outcomes and reducing costs. These groups want to control the ever-increasing costs and improve the quality of medical care.

Imagine...



You're the director of a kidney transplant program. Representatives from the Centers for Medicare and Medicaid Services (CMS) recently conducted a site visit (they are visiting every transplant program in the country). Your program might be in danger of being closed because the outcomes for one-year grafts and patient survival are below expectations.

A thorough self-examination of your program fails to find any systematic deficiencies. You have good personnel, the hospital supports the program adequately, the follow-up care is good, and your program uses commonly accepted immunosuppression and the latest protocols for evaluating and following your patients. You are even recognized as an innovative center with experimental protocols that bring the advantages of kidney transplantation to patients who have been turned down by other transplant centers.

As if the visit by CMS were not enough, your transplant administrator received a letter from an insurance company that refers many transplant candidates to your center. It does not want to renew its contract with your center because of the below expected results.

Why are your results below expectations? Does your program transplant riskier patients than other programs? The Scientific Registry of Transplant Recipients (SRTR) calculates risk-adjusted outcomes that are used by CMS and insurance companies, so even though you think your patients might be high-risk, that has presumably been taken into account by the risk-adjustment model.

Many initiatives have been instituted to improve the quality of care. Some are joint efforts by several groups. Among these initiatives are the National Quality Forum, the National Healthcare Quality Report (Agency for Health Research and Quality), National Quality Measures Clearinghouse, National Surgical Quality Initiative Program, and the Surgical Care Improvement Project. Other groups concerned with quality are the Leapfrog Group, the Integrated Healthcare Association, Hospital Quality Initiative (CMS), Hospital Quality Alliance, American Medical Association-Physician Consortium for Performance Improvement, Ambulatory Care Quality Alliance, Institute for Healthcare Improvement, and the Surgical Quality Alliance (American College of Surgeons).

The Organ Procurement and Transplant Network (OPTN), using SRTR data, and CMS oversee quality in transplantation. These initiatives may establish performance measures or "report cards" for physicians and hospitals.

Performance measures can have profound effects on medical care and providers. The goal, of course, is to improve the quality of care and to reduce costs—to achieve better value. Physicians and hospitals that do not meet certain performance measures can be denied insurance contracts, can have their poor performance made available to the public, and can even be closed. Certainly, no one can deny that we should all have a goal of improving patient outcomes, the quality of medical care, and reducing costs.

Risks to risk adjustment

In order to account for differing patient characteristics, models that measure performance adjust for risk. Risk adjustment is a statistical technique using patient variables to make comparisons valid. It is supposed to level the playing field. But there are risks to risk adjustment. Models may omit important variables, data collection may be incomplete, or data collection forms may not be filled out correctly. Even the models used for risk adjustment can vary, so that a provider may meet performance measures calculated with one model but not with another (1).

Every transplant center in the United States must report the results of every transplant to the SRTR. This reporting includes many patient and donor characteristics. Using a Cox regression model,

the SRTR calculates the graft and patient survival for each organ for each transplant center. The SRTR also calculates the expected outcomes using national donor and patient characteristics.

The SRTR uses a two-sided t-test to compare the transplant center's observed outcomes with the expected outcomes. CMS, on the other hand, uses a one-sided t-test for comparison. A transplant center's outcome is more likely to fall below the expected outcome using a one-sided t-test and is thus more likely to be flagged as a poor performer. Because of the way in which outcomes are calculated, there will always be some transplant centers that have graft or patient survivals below expected results. Therefore, it is possible that CMS could close some transplant centers each time it has a round of transplant center evaluations.

The SRTR risk stratification model

Even though the SRTR employs excellent statisticians and uses numerous donor and patient variables that are submitted by the transplant centers themselves, its determination of poor center performance has been criticized. Despite the approximately 55 variables the SRTR model uses, the model does not include some important determinants of patient outcome, such as the degree of cardiac or coronary disease and social class, although it would be difficult to get such data for all patients.

Other important patient characteristics may also be missed in the SRTR model, including presence of other disease states, genetics, patient support networks, and subjective characteristics of patients that experienced caregivers may recognize to be important for patient compliance and overall prognosis. If the OPTN required that transplant centers collect and provide this information, the SRTR would be able to place cardiac and social class variables into its model.

The potential impact of factors not known is reflected in the relatively low predictive values of models in kidney transplantation. The c-statistic, a measure of model discrimination, is significantly lower in transplantation than for other disease outcomes. The c-statistic varies from 0.5, which is no predictive ability, to 1.0 for a model that is 100 percent predictive. For kidney transplant survival statistics, the c-statistic is 0.67 for graft survival and 0.72 for patient survival, generally regarded as quite low. This number compares to 0.86 for deaths after myocardial infarction, 0.83 for coronary artery bypass grafting, 0.85 for pneumonia, and 0.87 for stroke (1).

This low number for the predictive ability of the model for transplant outcomes strongly suggests there is a lot that we do not understand about determinants of transplant outcomes. In fact, transplantation models fail to account for the reasons the majority of grafts fail or patients die (2). Thus transplant outcomes and performance evaluations are related in a significant way to factors that may not reflect quality of care. Furthermore, government regulators, insurance companies, patients, and even transplant professionals may assume that these assessments are completely reliable and interpret them accordingly (2).

It is difficult to argue with the concept of evaluating transplant center performance, but the evaluation tool should be accurate and reliable. The complex nature of transplantation renders quality assessments problematic. We must work to ensure that the goal of high quality for all patients is not compromised by the assessment tools used to evaluate quality (2).

What transplant centers can do

Given that measures of poor performance—whether valid or not—may lead to severe outcomes for the transplant program, either elimination of insurance contracts or even closure of the program, what can transplant programs do to protect themselves?

First, transplant centers should ensure that there are no problematic systems issues. Do they have the right personnel who can select appropriate candidates, perform the surgery, and manage the patients after transplantation with sufficient skill? Are the protocols for immunosuppression and other medications, candidate evaluation, and posttransplant follow-up appropriate? Does the hospital provide sufficient support for the transplant program with staff, facilities, and laboratory and radiological availability?

If the transplant center is convinced there are no systems issues, one of the few remaining choices is to try to select transplant patients who are more likely to have successful outcomes. Despite the SRTR's risk adjustments, many transplant surgeons believe that the model nevertheless does not control for important variables. For example, one of the risk-adjustment parameters is age. However, the model includes all patients who are 65 years old and older in one group. Most transplant surgeons probably believe that patients in the 70-year-old age group are at higher risk of dying than patients between 65 and 69 years old and may choose to not transplant patients in this age group. In fact, this is already happening. Some transplant centers have decreased the age of acceptable transplant candidates.

Cardiac disease is generally regarded as one of the most important risk factors for patients undergoing kidney transplantation. Certainly, the risk of a 60-year-old man with no history of heart problems, a normal cardiac stress test, and no coronary artery disease is much less than that of a 60-year-old man who has had two myocardial infarctions and four-vessel coronary artery bypass grafting. Yet the SRTR model does not include cardiac disease in its risk adjustment model.

Social class (generally measured by education level and income) is an important determinant of outcome (3). The SRTR does not include measures of social class—other than whether or not the patient has private insurance—in its risk adjustment model. This is not to be critical of the SRTR. After all, it can only include the data it has in its model.

Many transplant centers are undertaking innovative procedures and techniques to transplant certain patients who might not otherwise have an opportunity for transplantation. Other centers may have experimental protocols testing new drug regimens or other treatment protocols that may pose higher risk for their patients. But because of possible CMS sanctions, some transplant centers may be forced to restrict the introduction of new and innovative treatment regimens—regimens that could ultimately improve the outcomes of transplantation.

If transplant centers restrict the kidneys they are willing to transplant to only those they believe to be the best quality, the unintended outcome may be that fewer transplants will be performed.

Ethical issues a concern

Transplant centers that might receive poor performance scorecards and possibly have insurance contracts withheld or be threatened with closure by CMS will likely try to reduce these possibilities by transplanting only patients they perceive as having a lower risk of graft loss or death. This is already happening at many transplant centers.

Personnel at these centers are not convinced that the SRTR risk adjustment model adequately adjusts for risk and believe that their patients are different from centers that have better outcomes. We have shown that transplant centers with the highest candidate mortality rates have lower kidney transplant graft and patient survival after transplantation, even after risk adjustment (4).

Ethical issues are raised by the possible refusal of transplant centers to transplant certain patients who would do better with a transplant than without one, but who might have comparatively poor outcomes and thus threaten the transplant center with losing insurance contracts or even with closure.

The culture of medicine dictates that the physician put the interests of the patient before other interests. The transplant candidate comes to the transplant center with the understanding that the best clinical decision will be made for her. Transplantation increases the longevity of patients with renal failure compared to dialysis, and the quality of life is also greater with a transplant. Yet transplant centers may refuse to list and transplant some patients perceived to be at high risk in order to preserve their very existence.

Another strategy transplant centers could use to improve their results is to avoid using kidneys that are thought to be associated with lower graft survivals. Although the SRTR risk-adjustment model incorporates many donor characteristics, some, such as biopsy findings, are not accounted for. Transplant centers may also feel other important donor variables are not included in the risk-adjustment model. This refusal to use some kidneys might result in fewer patients being transplanted.

Almost certainly no program wants to be closed or rendered nonviable because of a loss of insured patients. Furthermore, if the program is closed, it may be that other potential transplant recipients will either have to travel great distances to receive transplants or not receive access to transplantation at all. This outcome particularly threatens the poor, who may find the additional costs of travel beyond their means.

Strategies for preserving the transplant center, then, will have the effect of limiting access to care for some patients. And that may not necessarily be entirely bad. Such strategies may result in kidneys being transplanted into individuals who may live longer. Thus life-years after transplantation may be increased. In fact, the United Network for Organ Sharing is currently considering instituting a new allocation system that does just that by favoring younger recipients in the allocation of kidneys.

But if transplant centers also restrict the kidneys they are willing to transplant to only those they believe to be the best quality, the unintended outcome may be that fewer transplants will be performed.

This trend may already be happening. In 2007, for the first time ever, the number of deceased organ transplants decreased in the United States by 1 percent, even though the number of deceased donors increased by 0.8 percent. It appears that the trend for a reduced number of deceased donor transplants will hold for 2008 as well.

Richard Howard, MD, PhD, is the Robert H. and Kathleen M. Axline Professor of Surgery at the Shands Transplant Center and the department of surgery at the University of Florida.

References

1. Iezzoni LI: The risks of risk adjustment. *J Am Med Assoc* 1997; 278:1600–1607.
2. Schold JD, Howard RJ: Prediction models assessing transplant center performance: can a little knowledge be a dangerous thing? *Am J Transpl* 2006; 6:245–246.
3. Howard RJ: The challenging triangle: Balancing outcomes, transplant numbers, and costs. *Am J Transpl* 2007; 7:2443–2445.
4. Schold JD, Srinivas TR, Howard RJ, Jamieson IR, Meier-Kriesche HU: The association of candidate mortality rates with kidney transplant outcomes and center performance evaluations. *Transpl* 2008; 85:1–3.

New Kidney Allocation Policy

God Squad Resurrection...

By John Curtis

In 1962, Life *Magazine coined the term "God Squad" to refer to medical center committees that had been set up to determine which patients would receive life-saving therapy for end stage renal disease (ESRD) and which ones wouldn't (1). Thought, discussion, and criticism of these "God Squads" of the '60s often pointed out that the doctors on the committees granted treatment to individuals who had lifestyles like the committee members themselves. Is it possible that the committee creating the new Kidney Allocation System (KAS) might also favor individuals who are like the middle-aged, productive, male surgeons and statisticians who developed the policy?*

In the 1980s, medical ethicist Arthur Caplan, PhD, referred to "dirty little secrets" of the kidney waiting list and said "…physicians feel that people who are richer, have jobs, and are more assertive will do better as transplant recipients than people who are poor, unemployed, and passive"(2). I believe the proposed KAS is not better than the current system, and, despite the early well-meant attempts of the committee, allocation is in danger of being made both less just and less effective. I was asked to write this article in a fashion that would provoke thought and discussion of the issues concerning allocation of deceased donor kidneys as proposed by KAS.

Imagine...

You're 62 years old and have retired after having had 6.2 percent and 1.45 percent of your paychecks withheld for Social Security and Medicare, respectively. Having worked since you were 18, that's 44 years of withholding, quite a sum of money, you think. Your precocious, 5-year-old granddaughter keeps telling you that 62 really is the new 52. Despite these reassuring thoughts, you're feeling more tired than you should at age 62 (or even 52).

According to your doctor, you have something called end stage renal disease (ESRD). The good news is that Medicare covers ESRD treatment (thanks to Social Security) despite your age. The bad news is that the best ESRD treatment, deceased donor kidney transplantation—which, on average, would double your life expectancy and improve the quality of your life—is not really available to you. It's not because of Medicare rules. It's because of your age—and a committee called KAS. You sure wish you could double your time with that granddaughter. Seems like your 62 may be the new 92.

You're 33 years old, you find out that you have kidney failure, and your doctor does not know why. Your kidneys are very small, and it could be hypertension or diabetes or maybe some pain medicines you took in the past. You don't think you have diabetes, although another doctor once reported that your fasting blood sugar was 110 mg/dL—slightly above what he thought it should be—and he claimed you had diabetes. Although you never took insulin or pills, the diabetic label stuck in your medical records.

Now you need a deceased donor kidney transplant, which could double your life expectancy, even if you actually have diabetes. The doctor says it is much less likely you'll get a transplant than other "nondiabetic" patients your age, thanks to a committee called KAS that you've never heard of before, a committee that your own doctor does not sit on. This committee developed a formula that decides who might have their life expectancy doubled and who should not have that priceless, twofold increase in their years on earth.

Organ transplantation in the United States involves a whole new alphabet of acronyms. The National Organ Transplant Act (NOTA) was enacted in 1984 to codify organ allocation (3). The United Network for Organ Sharing (UNOS), a private organization, applied for and won the government contract for these services; it was the sole applicant. UNOS has held the contract for the U.S. Organ Procurement and Transplantation Network (OPTN) since 1986 and is considered by many to be a quasi-government organization. UNOS had its roots in the Southeastern Organ Procurement Foundation and initially was a completely voluntary not-for-profit organization set up by transplant centers.

UNOS has evolved in association with the Health Resources and Services Administration (HRSA). Now, if transplant centers don't belong to or abide by the rules of UNOS/OPTN, their entire institution, not just the transplant unit, will be ineligible to be a Medicare provider. Thus, it no longer is considered a voluntary organization. Over the years, like many quasi-governmental organizations with little or no competition, UNOS/OPTN has grown in authority and scope. Recently, for example, it has expanded its concerns about sharing deceased donor organs to work with living donor transplantation. Originally, the directors of UNOS were almost exclusively kidney transplant surgeons, but in more recent years, the network has included nephrologists and nonphysicians (donors and recipients) among its committees and board of directors. Voluntary sharing of donor organs was the original idea behind UNOS—the United Network of Organ Sharing. No one could have guessed at its founding that this sharing organization would develop into a regulatory body that, for example, now prescribes how many liver surgeons a center must have and how many procedures these surgeons must perform before their center is recognized as a liver transplant center. Obtaining the contract from HRSA is seen, even today, as a mixed blessing.

UNOS/OPTN, despite changing from a voluntary to a nonvoluntary organization, despite having no competition for its HRSA grant in the last 20-plus years, despite being dominated by transplant surgeons, and despite expanding

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...Or Allocating a Scarce Medical Resource?

By Mark Stegall

An unfortunate fact of organ transplantation is that there are not enough deceased donor kidneys for everyone who might benefit. How to best allocate such a scarce medical resource remains unclear. In 2004, the Board of the United Network for Organ Sharing/Organ Procurement and Transplant Network (UNOS/OPTN) charged its Kidney Transplantation Committee with conducting a comprehensive review of kidney transplantation in the United States in order to consider possible changes in the allocation of deceased donor kidneys. Since that time, through a series of public hearings, open forums, regional meetings, and a recent Request for Information (RFI) that included a draft allocation proposal, the OPTN and the transplant community have become engaged in an active debate about how deceased donor kidneys should be allocated.

Organ allocation principles: justice versus utility

While never explicitly stated in any policy document, kidney allocation in the United States historically has attempted to strike a balance between two sometimes conflicting ethical viewpoints best termed justice and utility.

The justice viewpoint emphasizes that all candidates for a kidney transplant be given an equal chance to receive a transplant even if the outcome of the transplant (patient or graft survival) is very different among candidates. The current allocation system allocates deceased donor kidneys using a point system in which most of the points are accrued via wait time (defined as time since listing). This use of wait time is perceived by many to be a dominant justice factor in organ allocation.

In contrast, the utilitarian viewpoint supports allocation systems designed to maximize the overall benefit achievable from the few organs that are available. Proponents of this view would rank candidates expected to have better graft or posttransplant patient survival higher than those with lower expected survival.

The OPTN Final Rule

The OPTN Final Rule, issued in 1999, was intended to provide guidelines for development of organ allocation policy. The recommendations of the Final Rule appear sufficiently broad to leave room for a wide range of allocation policies with language that appears to support both a justice approach ("the equitable allocation of organs") and a utilitarian approach (organ allocation policy should make "best use of donated organs" and "avoid wastage").

However, while the Final Rule is quite general in some areas, it is surprisingly specific in others. For example, the Final Rule requires that organ allograft candidates be "ranked using objective medical criteria" and that "the use of waiting time in allocation should be de-emphasized." The current kidney allocation system's emphasis on wait time and its lack of ranking using objective medical criteria make it poorly compliant with the Final Rule.

Areas of general agreement

Through my participation in numerous discussions, including the February 2009 OPTN Public Forum, I believe there is general agreement in the transplantation community on several issues regarding a new kidney allocation system including:

- any new system should strive to balance justice and utility;
- one of the most important problems in the current system that negatively affects utility is the allocation of kidneys with long projected posttransplant survival to candidates with very short projected survival;
- every candidate should have a reasonable chance at receiving a kidney transplant regardless of their health status and age;
- any new allocation system should be as simple as possible;
- any new allocation system should be as predictable as possible, especially for candidates who are high risk, in order to aid in wait-list management.

Possible new kidney allocation systems

The draft proposal included in the RFI issued in the fall of 2008 described a possible allocation system with three major novel components: 1) ranking donor kidneys using a donor profile index (DPI) that provides a more granular grading system compared with the current grading system; 2) ranking candidates using Kidney Allocation Scores (KAS) in which points are awarded for wait time (defined as time on dialysis), sensitization, and Life Years from Transplant (LYFT, defined as the predicted median patient survival with transplant minus the predicted median patient survival with transplant); and 3) a novel combination of donor and recipient scores in which the KAS for kidneys with good DPI scores is primarily based on the LYFT score and the KAS for kidneys with poor DPI scores is primarily based on wait time (1).

Simulations demonstrated that using this approach would likely fix the problem of allocating kidneys with long life expectancies to candidates with short life expectancies and increase the overall utility achievable from donated kidneys. The draft proposal in the RFI and the response from the American Society of Transplant Surgeons are available online (2).

The RFI accomplished one of its major goals in that it generated spirited discussions in the transplant community. One of the major criticisms was that older candidates have a much decreased chance of receiving a kidney transplant compared with the current system. For example, candidates over 65 currently receive 12 percent of deceased donor kidneys and would only receive 7 percent under the draft proposal.

In rebuttal, I contend that the draft proposal is very flexible, and minor modifications can achieve major differences in the types of patients transplanted. For example, Figure 1 shows that applying LYFT only to candidates with the highest LYFT scores and allocating a larger percentage of kidneys (in this case, approximately 50 percent) by wait time alone might accomplish two important goals: 1) allocating kidneys with long life expectancies to candidates with long life expectancies and 2) providing the opportunity for transplant to a large number of candidates regardless of age or health status.

Another criticism is that the methodology of LYFT is not adequately predictive of overall transplant outcome. While the current model poorly predicts the actual LYFT for the entire wait list population, it very accurately predicts differences in survival when comparing candidates with the longest survival to those with the shortest survival. Thus, it appears that even our current model would be useful if we were to apply it to candidates with the highest LYFT scores. This modest introduction of LYFT would provide incentive for the improvement of the LYFT using new factors.

Yet another criticism is that the system outlined is just too complex. Yet LYFT could be simplified to include only the three or four major factors (age, diabetes, time on dialysis, prior kidney transplant) and thus would be similar to the current liver allocation system (MELD). The general concepts of this system are actually quite simple, and I believe that they would make sense to candidates.

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Modifying the draft proposal to address concerns

In the draft proposal, kidneys are ranked using a donor profile index (DPI). A Kidney Allocation Score (KAS) is computed differently for different donor kidneys depending on their DPI (Figure 1a). Thus, kidneys with the poorest DPI scores are allocated by wait time (WT) alone, similar to the current system for expanded criteria donors. The KAS for the best DPI kidneys is computed as 80% of the LYFT score + 20% WT.

Because earlier discussions raised concerns that transplanting patients with good LYFT scores immediately after they were listed would decrease the number of living donors, the draft proposal capped LYFT at 80% for the best DPI kidneys. This was intended to ensure that all candidates would be forced to wait at least a year or two before receiving a transplant. In the draft proposal, the weight given to DPI decreased linearly with worsening DPI score.

In the modified proposal (Figure 1b), the impact of LYFT is limited to a smaller percentage of kidneys (those with best DPI scores into those candidates with the best and most predictable LYFT score). In addition, a larger percentage of kidneys (50% in this case) are allocated by WT alone. This accomplishes two of the major goals that have emerged from the policy discussions: 1) allocating kidneys with long expected posttransplant survival to candidates with long expected posttransplant survival and 2) ensuring a reasonable chance of receiving a kidney transplant to all candidates.

Figure 1a

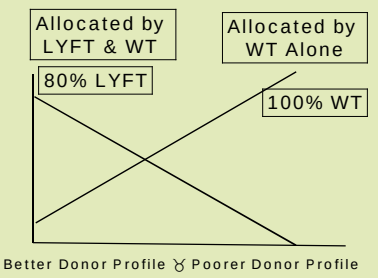
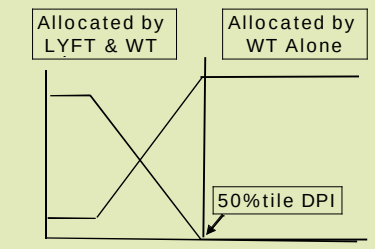


Figure 1b



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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.

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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

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AMAG PHARMACEUTICALS

God Squad…

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its rules and regulations at a speed like a HRSA bureaucrat on methamphetamine, has, I think, done an excellent job. Even the Kidney Committee drafted the KAS proposal only after considerable difficult and altruistic work by its members.

But, in my view, the task of providing a fair allocation system for kidney transplantation is not one that any insider committee can accomplish. This discussion needs to be moved from UNOS and OPTN to a wider arena. The American Association for the Advancement of Retired Persons (AARP), representing individuals over 50, and the American Diabetes Association (ADA), for example, might find the two anecdotal cases above of interest.

The UNOS/OPTN webpage includes a number of documents and a PowerPoint slide show arguing the affirmative case for KAS. The KAS proposal remains controversial and currently has strong advocates and opponents.

With the KAS proposal enacted, UNOS could be seen by some as a kind of national "God Squad" of this decade. With limited deceased donor organs and a burgeoning number of patients on the wait list, deceased donor kidney allocation is a zero sum game. The KAS proposal attempted to adjust this zero sum game with a concept called "net benefit." It was a purely utilitarian proposal in which the major losers were groups that do not, historically, do as well with allograft survival, on average, as other groups. African Americans (4), older recipients (5), people with diabetes (6), and possibly women (7,8) fall into the groups that might not fare well in a "net benefit" unmitigated utilitarian system.

Pure utilitarian philosophy—"the greatest good for the greatest number"—is seductive. This philosophical position dates to the early Hedonism philosophy of Epicurus ("greatest pleasure for the greatest number," 200 BCE). It peaked as a school of thought in 18th-century England. Outcome is the most important aspect of this philosophy that also tends to hold that "the end justifies the means."

The usual and unavoidable clash of utilitarianism systems is with the concept of justice. Concepts of "net benefit" led to conflict, and those who were (at first) attracted to the "greatest good" idea began to reconsider their position. They not only changed the name to life years from transplant (LYFT), but they also added some new provisions to the calculation in an effort to be both utilitarian and just (an impossible task).

Utilitarianism is an all-or-none proposition. Once one compromises pure utility to try to make things just, the outcome becomes more political than utilitarian. This is what has happened to the KAS proposal over the last four or five years, and the losing groups appear to be older patients—ageism is the subtlest of the isms (9)—and patients with diabetes. Neither the AARP nor the ADA were represented at the meetings discussing KAS.

Currently, allocation criteria are straightforward. Those under the age of 18 and those waiting the longest on the kidney wait list get priority. These rules are easily understood by patients. The formulas currently put forward by KAS are complex and not likely to be understood by the people most affected. The unintended consequences of the complex proposal, the ability to "game the system" by physicians for their patients, and the overall effects on the transplantation of solid organs in the United States have neither been tested prospectively, nor are they likely known. Those who will be hurt by the new system have not been clearly identified or notified. As of this writing, the KAS proposal is out for public comment before being put into effect.

Those who advocate the KAS proposal and were instrumental in writing it often come from the arena of statistical database analysis. They work with computer models and large group averages rather than dealing with actual individual patients. Under criticism, their usual response is threefold:

1) The government made us do it. This reminds me of "the devil made me do it" excuse. UNOS/OPTN and HRSA have become so tied that sometimes it is impossible to tell who is the cart and who is the horse. It seems unlikely that these government agencies that ultimately answer to the public would punish older individuals (voters).
2) Don't criticize because the proposal isn't even finished yet. Waiting for so-called "final rules" and completed regulation before offering criticism can result in a lot of damage before problems can be corrected.
3) Sure, there are problems, but KAS is better than the current system. If you don't like KAS, come up with a better system. Well I, for one, doubt that the proposal is better than the current system and may be—probably is—much worse. Unlike the current system, KAS has not been tested. I must admit that coming up with any system, even a "better system," is difficult. As long as there are far more patients on the wait list for kidney transplants than there are deceased donor kidneys available, all systems of allocation will appear imperfect at least, or even greatly flawed.

Allocation policy should be transparent, currently a popular concept in Washington, DC. If the policy denies deceased donor kidneys to anyone older than 55 years, they should clearly state it. If the policy gives special advantages to certain minority groups or women or people with diabetes, then say so. Don't use some adjustment factor like "dialysis time" (DT in the current formula) that is a nontransparent parameter with implications unclear to the general public. Indeed, the complexity of the current formula takes us away from the original infatuation with utility toward the animosity of political policy. Matas even suggested that we stop using the term "allocation" and replace it with the more correct and less misleading term "rationing" (10).

I was asked to write this article in a fashion that would provoke thought and discussion of the issues concerning allocation of deceased donor kidneys as proposed by KAS. I hope I have succeeded, and I hope readers of *ASN Kidney News* will continue the discussion online.

John Curtis, MD, is with the department of internal medicine–nephrology at the University of Alabama in Birmingham.

References

1. The God Squad. *Life Magazine*. November 9, 1962.
2. Blakeskee S: Studies and unequal access to kidney transplants. *New York Times*. January 24, 1989.
3. Schaeffer MJ, Alexander DC: U.S. system for organ procurement and transplantation. *Am J Hosp Pharm* 1992; 49(7):1733–40.
4. Eckhoff DE, Young CJ, Gasgon RS, Fineman SW, Deierhoi MH, Foushee MT, et al.: Racial disparities in renal allograft survival: a public health issue? J *Am Coll Surg* 2007; 204 (3): 894–902.
5. Kasiske BL, Snyder J. Matching older kidneys with older patients does not improve allograft survival. *J Am Soc Nephrol* 2002; 13(4): 1067–72.
6. Cosio FG, Hickson LJ, Griffin MD, Stegall MD, Kudva Y: Patient survival and cardiovascular risk after kidney transplantation: the challenge of diabetes. *Am J Transpl* 2008; 8(3): 593–9.
7. Moosa MR: Impact of age, gender, and race on patient and graft survival following renal transplantation—developing country experience. *S Afr Med J* 2003; 93(9): 689–95.
8. Segev DL, Kucirka LM, Oberai PC, Parekh RS, Boulware LE, Powe NR, et al.: Age and comorbidities are effect modifiers of gender disparities in renal transplantation. *J Am Soc Nephrol* Jan 7 2009.
9. Palmore EB: Ageism in Canada and the United States. *J Cross Cult Gerontol* 2004; 19: 41–46.
10. Matas AJ: Allocation or rationing—word choice is crucial. *Am J Transpl* 2009; 9(1): 9–10.

…Or Allocating a Scarce Medical Resource?

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The Kidney Transplantation Committee at times used the phrase, "the right kidney for the right recipient." I would tell candidates that they would be offered a kidney that matches their projected life expectancy. In addition, a projected time to offer for a kidney with a specific DPI score could be generated, giving a patient a better idea about their projected wait time and making the entire concept of the wait list more transparent.

One of the important positive aspects of LYFT is that it incorporates several important outcomes into one metric that actually compares the benefit of receiving a transplant versus the alternative therapy, dialysis. Giving the patient information about their relative survival with transplantation will enable them to make a more informed decision about the appropriateness of transplantation in general. This data is not available to patients today.

The path forward

While there are many different views, I believe that the current discussions will lead to the development of a kidney allocation system that appropriately balances justice and utility and is compliant with the Final Rule. As demonstrated here, the components of the draft proposal are flexible and can be altered to achieve a wide range of outcomes. Open discussion with a focus on common goals is the best path forward to a better kidney allocation system.

Mark Stegall, MD, is chair of the division of transplantation surgery at the Mayo Clinic, Rochester, Minn., and former chair of the OPTN/UNOS Kidney Transplantation Committee.

References

1. Kidney Allocation Concepts: Request for Information. United Network for Organ Sharing (UNOS). Circulated for consideration September 24, 2008, through December 18, 2008. http://unos.org/SharedContentDocuments/KidneyAllocationSystem—RequestForInformation.pdf. Accessed 31 March 2009.
2. Response from OPTN/UNOS Kidney Transplantation Committee to American Society of Transplant Surgeons regarding possible revisions to kidney allocation system. 20 August 2008. www.asts.org/Tools/Download.aspx?fid=809. Accessed 31 March 2009.

Transplant Disparities

By Akinlolu Ojo

The development of large databases for end stage renal disease (ESRD) and organ transplantation in the late 1970s and 1980s revealed a number of disturbing trends: 1) blacks in the United States (African Americans) had a disproportionately higher rate of end stage renal disease; 2) access to the kidney transplant wait list and the waiting times for deceased donor kidney transplantation were worse for African Americans; 3) the rates of both living and deceased kidney donation for African Americans were much lower than those for whites; and 4) the results of kidney transplantation (short- and long-term allograft survival and acute rejection rates) were significantly inferior in African Americans compared with non-Hispanic white recipients (1–5).

The limited access to an optimal therapy and poorer clinical outcomes seen in kidney transplantation were not different from the observations of racial disparities in other areas of medical care in the United States, including coronary artery disease, prostate cancer, lung cancer, orthopedic surgery, hypertension, diabetes mellitus, and preventive gynecological health (6). This pattern warranted attention because the Medicare End Stage Renal Disease program was not only pivotal to kidney transplantation but also represented a celebrated policy enshrining the democratic principles and egalitarian ideals embodied in the constitutional fabric of the United States. That a flagship Medicare program flunked the fundamental premise of equal access for all without regard to socioeconomic status, age, race, or sex has always turned heads and remains newsworthy.

The seminal publication by Held et al. (7) and the subsequent Institute of Medicine report (8, 9) galvanized the transplant community to address racial disparities in kidney transplantation. To date, much has been accomplished to redress the inequities. HLA-A and HLA-B matching has been eliminated from the point system for allocating deceased donor kidneys. Time since the onset of ESRD has been added to the waiting time. Concerted effort has led to significant increases in deceased donation by African Americans. Pioneering empirical research at a few centers has led to tailored immunosuppressive regimens with better clinical outcomes in African American kidney transplant recipients (10).

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Notwithstanding these important achievements, and after more than three decades of half-hearted measures, grandstanding, and hand-wringing, there remain unsettling racial disparities in ESRD therapy. Suboptimal results of kidney transplantation in African American recipients endure in as much magnitude as decades ago. To be sure, suboptimal access and inferior outcomes also exist for Hispanic kidney transplant candidates and recipients, respectively. Unlike other racial issues in the United States, racial disparities in kidney transplantation defy simplification to a "white versus nonwhite" inequity issue—the best allograft survival results and the most optimal access to kidney transplantation are obtained in individuals of Asian extraction.

It is instructive to briefly review where we stand today and what has been done to date. Today, African Americans have a 50 percent lower probability of getting on the kidney transplant wait list compared with whites. This probability has changed very little over time. However, the rate of kidney transplantation once on the wait list has improved because of the changes to the allocation system described above. Even with this improvement, the median wait time remains twice as long in African Americans compared with non-Hispanic whites.

The largest disparity is now evident in kidney transplantation from living donors, in which the rate is two to three times higher in African Americans. The rate of deceased donation in African Americans has improved significantly from 7–8 percent to 13 percent of all deceased donors. The improvement in deceased kidney donation is largely a result of the innovative and tireless efforts of agencies such as the regional organ procurement organizations in Pennsylvania, Texas, Florida, Alabama, and South Carolina, the Association of Organ Procurement Organizations (AOPO), and the Minority Organ Tissue Transplant Education Program (MOTTEP).

Acute rejection rates in the first year after transplant—which used to be 40 to 50 percent in blacks compared with 20 to 30 percent in whites—have been reduced to a much lower rate of 8 to 15 percent in both African Americans and whites. The one-year graft survival rate is now similar in both African Americans and whites at 85 to 90 percent for deceased donor transplants and 95 to 97 percent for living donor kidney transplants, respectively. This is a marked and much welcome contrast to the 1980s and 1990s when the rate of graft loss in the first year was 1.5 to two times as high in African Americans compared to whites.

These improvements in short-term graft survival are largely driven by increased intensity of immunosuppression and posttransplant surveillance. Patient survival has remained comparable between the racial groups over time. Long-term graft survival (five to 10 years) has improved by approximately 10 percent in whites, but African Americans continue to have a long-term graft survival rate that is relatively inferior by 15 to 20 percentage points.

Race-tailored treatments and practices

The kidney transplant literature is inundated with hundreds of articles on racial disparities in kidney transplantation, but progress has been slow and much remains to be done. "Racial" titles on manuscripts are eye-catching, and journal editors may pay homage to race issues by readily accepting manuscripts with such titles whether or not the content is germane or informative on the subject.

Likewise, high-intensity immunosuppressive strategies have been widely adopted in African Americans on the basis of limited empirical and most often weak experimental evidence. Yet there has been an aversion to studying new immunosuppressive drugs in African American recipients so that "high risk" recipients would not dilute the putative findings of registration trials. Transplant professional thought leaders and funding agencies that set research agendas have shown a lack of commitment to study and address racial disparity issues.

Little of what is offered as explanation or basis of action to improve outcomes of kidney transplantation is based on rigorous evidence because seeking such evidence and finding answers takes finances and time—two scarce resources that no one is yet willing to spend. After all, there has not been a single large national scientific gathering with a comprehensive agenda that has been devoted to this problem.

A larger pool of African American transplant professionals is a desirable social objective, but it would not necessarily lead to improved living kidney donation or better care for African American recipients. We remain mired in the prevailing notion that lack of organ donation, noncompliance with immunosuppressive regimens, and physiologic differences in the mean serum concentrations of the 100th cytokine largely account for the problems

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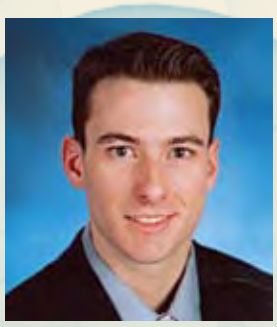
Medicare Coverage of Immunosuppression Medications: FOR LIFE FOR ALL?

By Timothy Page and Robert Woodward



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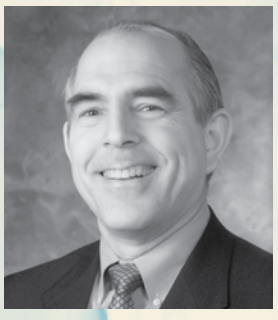


Robert Woodward

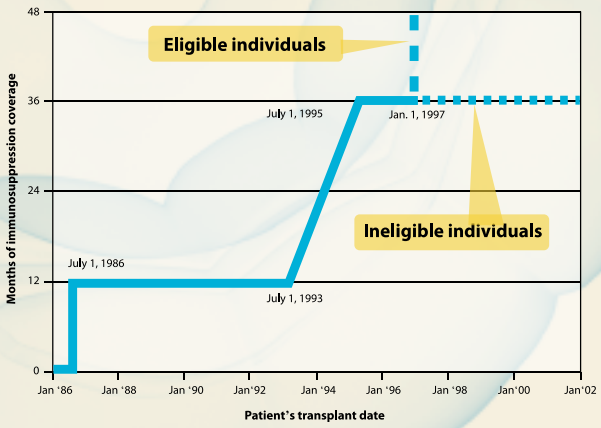
Medicare has provided at least some insurance coverage for individuals with end stage renal disease (ESRD) since 1972. In that year, Medicare implemented coverage of dialysis treatment following a 90-day waiting period. Coverage of posttransplant maintenance immunosuppression (IS) medications began in 1986 when Medicare added IS medication coverage to Part B for one posttransplant year.

Between 1993 and 1995, Medicare gradually increased the duration of IS medication coverage from one year to three years. In 2000, Medicare extended its IS medication coverage from three years to lifetime, but only for transplant recipients who were over 65 and disabled (Figure 1). This article summarizes the impacts of the changes in Medicare's coverage of ESRD, including who has demonstrably benefited from the changes, what lifetime coverage for every transplant recipient might have cost Medicare, and how shifting the coverage from Medicare Part B to Part D will affect out-of-pocket costs.

Medicare's extension of IS medication coverage from one year to three years posttransplant was a natural experiment that enabled a statistical estimate of the importance of the IS coverage on income-related disparities in graft survival (1). Before the extension of IS medication coverage, income-related disparities in graft survival were not apparent for the one posttransplant year when coverage existed but were apparent after the coverage ended. Specifically, income-related disparities in graft survival for the bottom three income quartiles were 3.9 percentage points below graft survival rates in the highest income quartile (Figure 2). But after Medicare extended its coverage of IS medication to three years, there were no significant income-related disparities (Figure 3).

Figure 1

History of Medicare's coverage of immunosuppression medications



Medicare's extension in 2000 of IS medication coverage from three years to lifetime for the approximately 50 percent of transplants eligible provided a second opportunity to estimate statistically the importance of IS coverage (2). But because this extension only benefited transplant recipients who were over 65 and who were disabled, a more complicated two-dimensional analysis was required. One dimension compared results before the 2000 IS extension with results after the extension. The second compared those who were eligible with those not eligible for lifetime coverage.

These 2008 findings supported the conclusions of the 2001 publication (1). Significant income-related differences in graft survival were found after the expiration of Medicare's IS medication coverage in all three groups not eligible for lifetime coverage. For example, five-year graft survival among patients in the lowest income quartile was 5.4 percentage points lower than graft survival among patients in the highest income quartile in the eligible cohort before the extension. The only cohort with no significant differences in graft survival at five years posttransplant was the cohort with patients transplanted late enough to be eligible for the coverage and who were eligible because of age or disability (Figures 4 and 5).

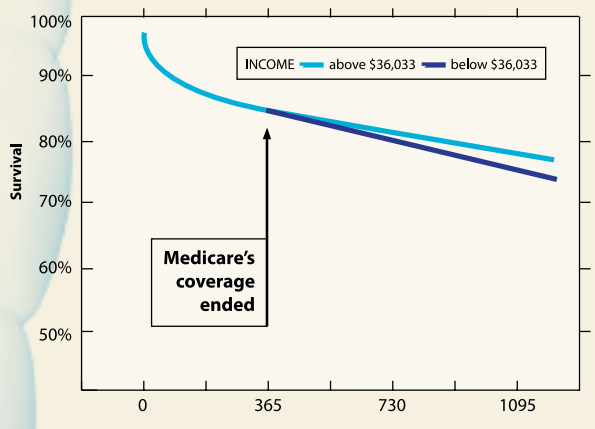
These two retrospective studies of income-related graft survival have several weaknesses. First, because the transplant recipient's income was not collected, the studies used the median family income of the transplant recipient's zip code as a proxy. Although this was a second-best alternative, the error it introduced should have reduced the significance of the income variable, not biased the result. Second, the studies did not address causality. Although their results were consistent with the hypothesis that patients with low incomes have a harder time paying for expensive IS medications, no information on compliance was available.

We then considered whether Medicare could have actually reduced its expenditures over time if it had extended lifetime IS medication coverage to all transplant recipients (3). Although extending coverage from three years to lifetime for those currently ineligible would have increased Medicare's cash outflows, a cost savings was possible if enough patients avoided graft failure (and therefore the expense of returning to dialysis) as a result of not having their medication coverage canceled.

We failed to demonstrate that Medicare would have saved money if the year 2000 extension had been applied to all transplant recipients. We did find evidence that a cost savings would have occurred had the benefit only been extended to the lowest income patients, i.e., those who experienced the largest decline in graft survival rates following the cancellation of IS coverage. This result should not be taken

Figure 2

Three-year graft survival among 1992–1993 transplants

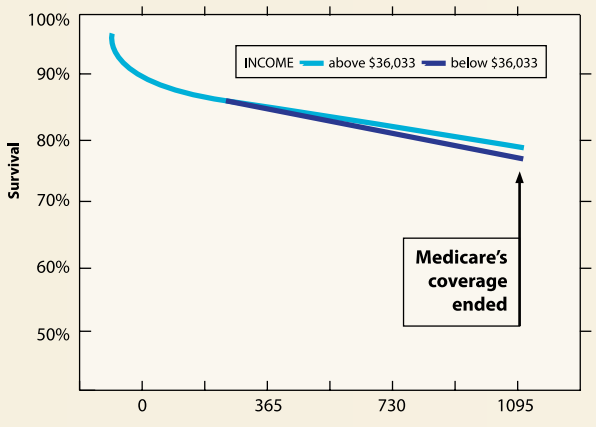


Numbers of uncensored patients	At transplant	At 1 year posttransplant	At 2 years posttransplant	At 3 years posttransplant
Income above $36,033	2787	2264	2097	1950
Income below $36,033	8049	6588	6001	5469

Source: Woodward et al.: Effect of extended coverage of immunosuppression medication by Medicare on the survival of cadaveric renal transplants. (Wiley-Blackwell). *Am J Transpl* 2001; 1:69–73

Figure 3

Three-year graft survival among 1995–1997 transplants



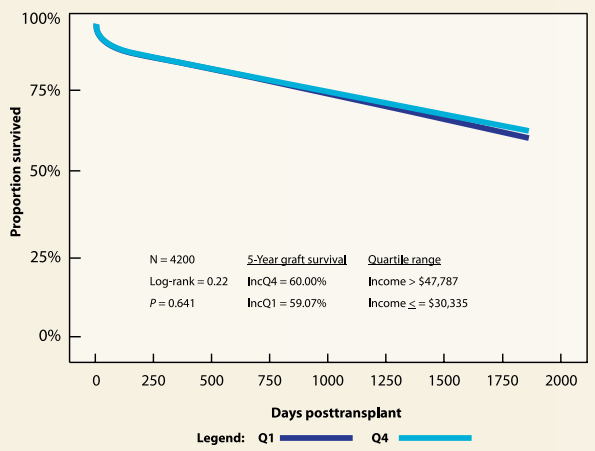
Numbers of uncensored patients	At transplant	At 1 year posttransplant	At 2 years posttransplant	At 3 years posttransplant
Income above $36,033	4128	3260	2025	815
Income below $36,033	12,603	9956	5978	2302

Source: Woodward et al.: Effect of extended coverage of immunosuppression medication by Medicare on the survival of cadaveric renal transplants. (Wiley-Blackwell). *Am J Transpl* 2001; 1:69–73

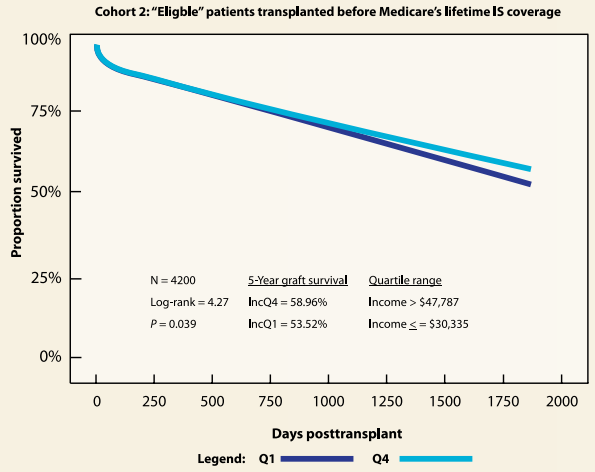
Figure 4

Five-year graft survival among those eligible for lifetime coverage

Cohort 1: Patients who actually received lifetime immunosuppression coverage



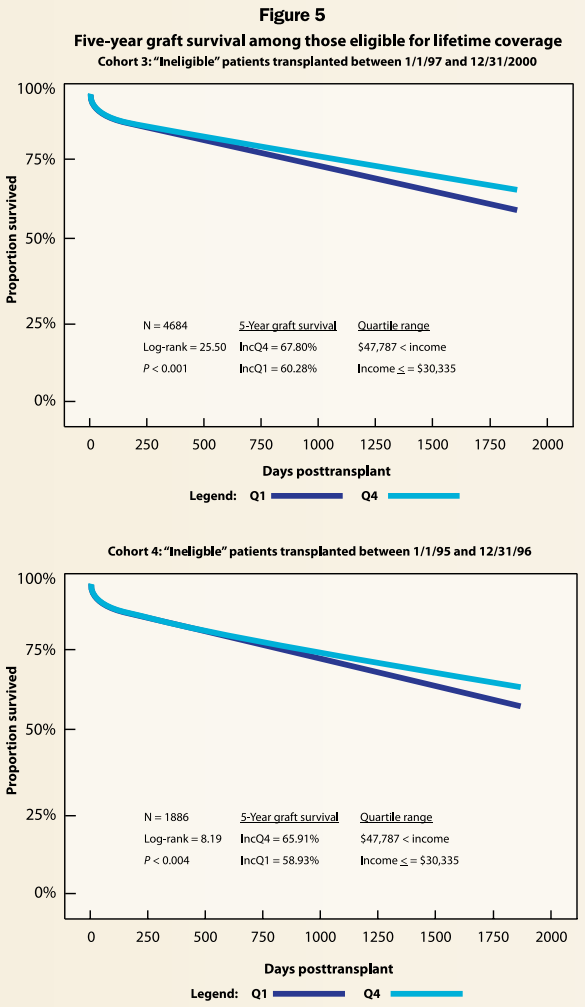
Cohort 2: "Eligible" patients transplanted before Medicare's lifetime IS coverage



Source: Woodward et al.: Income-related disparities in kidney transplant graft failures are eliminated by Medicare's immunosuppression coverage. (Wiley-Blackwell). *Am J Transpl* 2008; 8:(12):2636–46.

Figure 5

Five-year graft survival among those eligible for lifetime coverage



Source: Woodward et al.: Income-related disparities in kidney transplant graft failures are eliminated by Medicare's immunosuppression coverage. (Wiley-Blackwell). *Am J Transpl* 2008; 8:(12):2636–46.

as an argument against providing lifetime coverage to all recipients. Further work is needed to determine whether lifetime coverage can be justified on the basis of the cost-effectiveness of improvements to quality of life for patients who avoid graft failure as a result of having lifetime drug coverage.

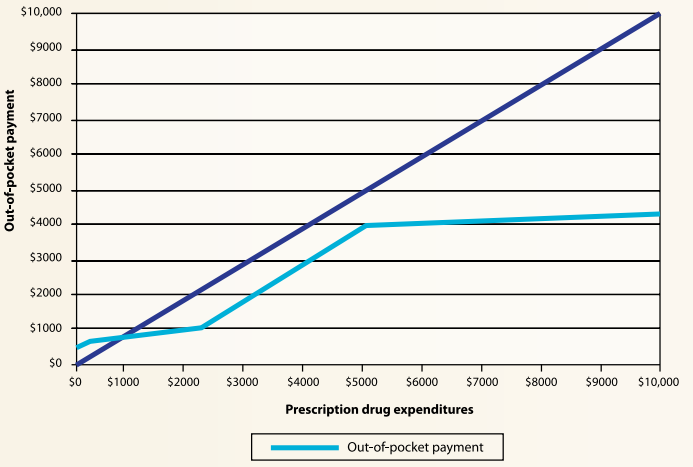
Although these previous coverage extensions provided encouraging evidence that lifetime drug coverage could eliminate long-term disparities in graft survival related to income, we have been unable to demonstrate that the coverage extensions similarly reduced racial disparities in transplant outcomes. Many have documented the disparities in long-term outcomes associated with race (4, 5). We found that Medicare's earlier extension of IS medication coverage had no significant effect on race-related differences in graft survival at three years (6).

In unpublished work, we applied a similar methodology to the year 2000 coverage extension, in which we compared the ethnic disparity in transplant outcomes before and after the coverage implementation among those eligible for the lifetime benefit. In models controlling for other significant recipient, donor, and transplant characteristics, lifetime coverage eliminated the income-related disparity in five-year kidney graft survival rates within the African American population (P = 0.05 for those whose graft survived for at least one year and P = 0.06 for those whose graft survived for at least two years). However, the ethnic disparity in long-term outcomes persisted even in the presence of lifetime medication coverage.

Researchers are now speculating on the effects that Medicare Part D coverage may have on long-term outcomes. IS medications are sufficiently expensive to put most recipients through the "doughnut hole" portion of Medicare Part D, defined in 2006 as the patient's responsibility to pay 100 percent of drug costs between $2250 and $5100 (Figure 6).

Figure 6

Prescription drug expenditures vs. out-of-pocket payments under Medicare part D (2006)



Source: Authors' tabulations based on Medicare Part D (2006) rate structure.

Transplant recipients with IS medications costing $10,000, for example, would have an out-of-pocket responsibility for $4265, more than double the $2000 that constituted the 20 percent responsibility of Part B. Given our findings that graft survival improvements following previous coverage extensions occurred primarily among low income patients, the substantial out-of-pocket payments that would be required if lifetime coverage were included in Medicare Part D could dampen any potential improvements in long-term outcomes among low income patients.

We have previously shown that coverage extensions from one year to three years and then from three years to lifetime had a beneficial impact on the long-term graft survival of low income patients. Although a coverage extension would be unlikely to pay for itself through a reduction in the number of patients who return to dialysis, we have not yet determined whether lifetime coverage would be considered cost effective based on the quality of life improvements among those who would avoid graft failure. Other considerations include the lack of evidence that previous coverage extensions had any effect on racial disparities in long-term outcomes and the potentially large out-of-pocket payments that would be required from patients if lifetime coverage were administered under Medicare Part D.

Timothy Page, PhD, is assistant professor in the department of health policy and management at Florida International University in Miami, and Robert Woodward, PhD, is McKerley Professor of Health Economics in the department of health policy and management and the department of economics at the University of New Hampshire.

Colloquium Addresses Contentious Issues in Transplantation

"Contentious Issues in Transplantation—A Colloquium" will be held October 7–9, 2009, at the Cleveland Clinic in Cleveland, Ohio. This novel forum will offer healthy and nonpartisan debate on contentious issues impacting transplantation and exposure to important and provocative topics affecting the field that otherwise are not offered in training.

The three-day conference is designed to juxtapose representatives from the academic, clinical, political, regulatory, industry, patient advocacy, and research communities. A key theme will be the education and mentoring of young and minority investigators. These individuals will interact with some of the top investigators and thinkers in the field, with an eye toward enriching transplant outcomes research in the future.

Participants will have the opportunity to author publications reflecting the proceedings of the conference. The proceedings will address key issues pertaining to organ allocation, access to transplantation, center-specific reports, pay for performance, and prescription drug coverage.

For more information, see www.clevelandclinic.org/transplantsummit2009.

Avoiding Steroids can be Successful Strategy After Kidney Transplantation…

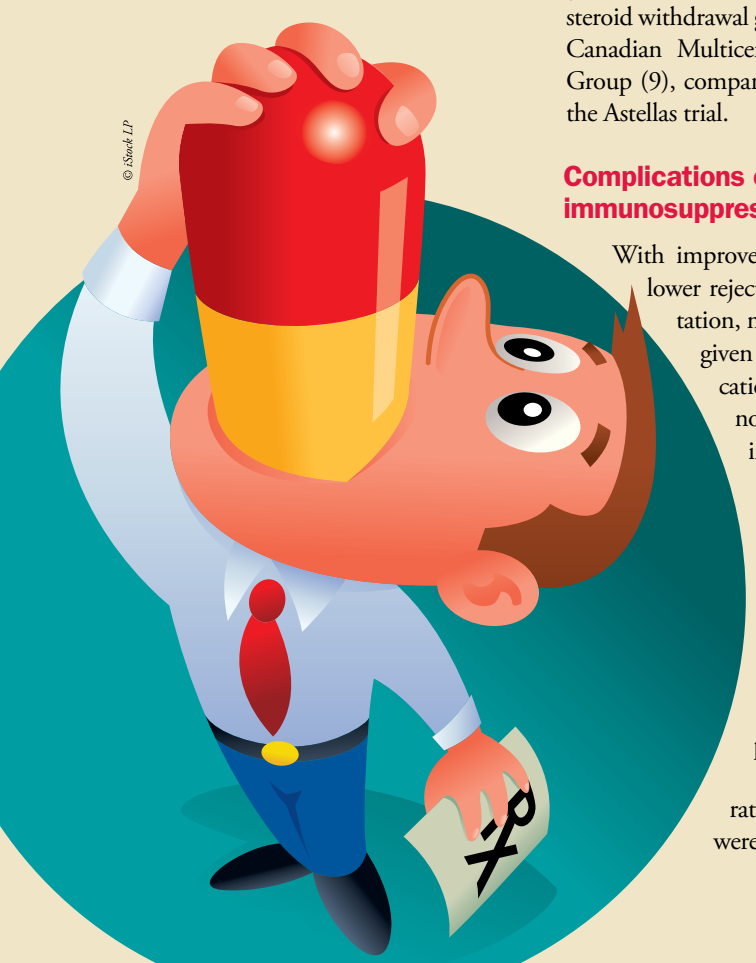
By Joshua Augustine

Acceptance of steroid avoidance in kidney transplantation has grown appropriately in recent years as a result of a lower rate of acute rejection and increased potency of immunosuppressive therapy. Until recently, steroid withdrawal was associated with a greater negative impact on allograft function and survival. Data on steroid avoidance from uncontrolled single center studies (1–4), nonrandomized multicenter trials (5), and registry analyses (6) have suggested excellent outcomes with relatively low rates of acute rejection, stable renal function over long periods of time, and patient and graft survival rates comparable to those of nonrandomized control groups. More recent data from randomized trials have shed further light on the benefits and risks of steroid withdrawal.

The Astellas Steroid Withdrawal Study was a randomized, double-blind, placebo-controlled study in which patients treated with induction antibody therapy (either antithymocyte globulin or an anti-IL-2 receptor antibody), tacrolimus (TAC) and mycophenolate mofetil (MMF) were randomized to either early withdrawal of steroids (day 7) or to maintenance prednisone therapy (7). Of the 386 patients enrolled, 43 percent were deceased donor recipients, and 20 percent were African Americans. TAC target trough levels were 10–20 ng/mL in the first 90 days posttransplant, and MMF dosage was initially 2 g/day. Importantly, patients randomized to maintenance steroid therapy were receiving only 5 mg of prednisone daily by six months posttransplant.

After five years of follow-up, the cumulative incidence of biopsy-proven acute rejection was 17.8 percent in patients in the steroid withdrawal group versus 10.8 percent in the group maintained on steroids (P = 0.04, by Kaplan Meier analysis) (7). However, the composite primary end point of death, graft loss, or moderate to severe acute rejection (defined as Banff stage 2A or higher or requiring treatment with an antibody) was similar between groups, occurring in 15.7 percent of patients withdrawn from steroids versus 14.4 percent of patients maintained on steroids (P = ns). This trial demonstrated that steroids could be withdrawn safely in the majority of patients with acceptable acute rejection rates using induction therapy and TAC/MMF maintenance immunosuppression.

Compared with previous transplant eras, the rates of rejection have dropped dramatically in steroid withdrawal patients. A meta analysis of seven clinical trials from the 1980s and early 1990s reported rejection rates of 48 percent in steroid withdrawal patients (8). Death censored graft loss was 19 percent at five years in the steroid withdrawal group from the original Canadian Multicentre Transplant Study Group (9), compared with 6.3 percent in the Astellas trial.



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Complications of immunosuppressive therapy

With improved early outcomes and lower rejection rates in transplantation, more attention has been given to long-term complications related to immunosuppressive therapy, including infection, malignancy, cardiovascular disease, and metabolic complications. Infection remains a prominent cause of morbidity and the second highest cause of mortality in transplant patients (10).

In the Astellas trial, rates of specific infections were not significantly different between groups, but the overall adverse event rate for infection reported in the trial was 16.4 percent for the steroid maintenance group versus 9.4 percent for the steroid withdrawal group (P = 0.04). A recent meta analysis of 30 randomized controlled trials in kidney transplantation also found a lower rate of infection in steroid withdrawal patients (11).

Metabolic benefits related to the severity of diabetes after transplantation have been demonstrated in recent clinical trials. In the Astellas trial, the number of patients requiring treatment with insulin was lower in the steroid withdrawal group than in the steroid-maintained group (3.7 percent versus 11.6 percent, P = 0.05) (7). These data were consistent with the CARMEN study, which examined outcomes in 260 European kidney recipients randomized to daclizumab, TAC, and MMF with one-day steroid exposure and compared to a group of 278 patients treated with TAC/MMF and maintenance steroids (12).

The CARMEN study found that rates of insulin usage were 0.4 percent in the steroid avoidance group and 5.4 percent in the steroid maintenance group (P = 0.001). In the Astellas trial, hemoglobin A1c was significantly lower at two years in steroid withdrawal patients with newly onset diabetes after transplantation. In both of these trials, it may be safe to conclude that quality of life was superior in patients who were able to avoid insulin therapy after steroid withdrawal.

Bone complications, including avascular necrosis and pathologic fractures, can be devastating late complications in patients with long-term transplant survival. Avascular necrosis is a painful condition resulting from ischemic injury to bone. Most commonly affecting the proximal femur, it typically requires surgical intervention, and has been linked to early steroid dosage in kidney transplantation (13).

Bone fractures are surprisingly common in kidney transplantation after long-term follow-up (14). In the Astellas trial, posthoc analysis found that the combined rate of bone fracture and avascular necrosis was higher in the steroid maintenance group (11.3 percent) compared with the steroid withdrawal group (5.2 percent, P = 0.04). This finding was likely observed due to the prolonged five-year follow-up of this trial and illustrates the significance of bone complications that manifest after years of steroid therapy.

Given the current clinical data, it is feasible to argue for steroid avoidance in kidney transplantation. The majority of patients will enjoy stable renal function with no overt rejection in the absence of steroid therapy. The challenge is to identify the small minority of high-risk patients for whom steroid withdrawal will lead to detrimental outcomes.

Identifying patients at risk for complications from steroid withdrawal

Patients with moderate to high levels of antibody sensitization were not included in recent randomized trials, and the Astellas trial excluded patients with delayed graft function, a known correlate of acute rejection (15). It may therefore be prudent to continue steroids in these higher risk subgroups. New immune monitoring techniques should ultimately allow for more precise identification of high-risk patients. For example, patients with donor reactive cellular immunity at the time of transplant may particularly benefit from maintenance steroid therapy (16).

In the meantime, all patients must be counseled on the small increased risk of acute rejection with steroid withdrawal. Close monitoring of renal function is mandatory, and protocol biopsies may be useful in identifying subclinical rejection after steroid elimination. Early steroid withdrawal may be favorable to a late steroid taper because most transplant centers obtain frequent bloodwork early posttransplantation, and patients may be reluctant to follow as closely with increased time from transplantation. The prognosis for early rejection is superior to that for late rejection, likely due to increased monitoring and patient compliance (17). After rejection, it is prudent to reintroduce maintenance steroid therapy, based on a recent report of a high rate of recurrent rejection in the absence of steroid therapy (18).

Induction therapy important in early steroid withdrawal

Induction therapy appears critical to the success of early steroid withdrawal. In the ATLAS study, 151 European renal transplant recipients received TAC and MMF with no induction therapy and steroid elimination after a single 500-mg dose of solumedrol (19). At six months, the incidence of biopsy-proven acute rejection in this cohort was 30.5 percent and three times the rate in a cohort on maintenance steroids. Renal function was also inferior in the steroid elimination cohort at six months posttransplantation.

Rejection rates were much lower in the Astellas trial, and polyclonal antibody therapy appeared to offer a further advantage over anti-IL-2 receptor antibody therapy. Acute rejection at five years occurred in 24.2 percent of steroid-free patients who received an anti-IL-2 receptor antibody and in 14.4 percent of patients who received rabbit-antithymocyte globulin (ATG) (P = 0.09), despite a greater percentage of deceased donors in the ATG group (7).

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…But Not All Patients Should be Steroid-Free Posttransplant

By Vikas Dharnidharka

Glucocorticoids (more commonly referred to as steroids) have been a key component of posttransplant immunosuppression and rejection treatment since the 1960s, the very early days of solid organ transplantation. At the time, steroids, in combination with azathioprine (Aza) or other mercaptopurine analogs, were the most common oral maintenance immunosuppressive agents used. Graft survival was not great, but in the absence of steroids, graft rejection and loss were almost assured.

Over the next few decades, many newer and more potent immunosuppressive agents were developed, leading to remarkable declines in early acute rejection (AR) rates and some improvements, to a lesser degree, in graft survival. With these results, many investigators justifiably questioned the time-honored belief that steroids were still needed. Initial studies focused on steroid "withdrawal," i.e., the phased removal of steroids at some point after transplant, in a select group of patients who were considered "low-risk" (usually those without prior AR episodes). Many of these studies showed an unacceptably high rate of AR postwithdrawal (1, 2), leading to the belief that patients developed an immunological dependency on steroids once they began receiving this class of drugs.

Are steroids necessary with modern immunosuppressants?

Because these studies occurred in the cyclosporine (CsA)-Aza era, prior to introduction of tacrolimus and mycophenolate, the question remained as to whether steroids were needed with modern immunosuppression drugs. Steroid withdrawal at time points at or beyond three months posttransplant in a CsA-mycophenolate–based regimen was associated with more AR episodes (3, 4). But the metabolic benefits included less hypertension and less hyperlipidemia, two major cardiovascular risk factors.

In order to get around the "dependency" phenomenon, regimens were devised that eliminated steroids completely (avoidance) or exposed patients to steroids only for a brief period posttransplant, in most cases less than a week (minimization). Prospective limited center studies with historical controls suggested no detriment in terms of AR increase or worse graft survival (5–9). In fact, many perceived benefits were noted, such as reduced incidence of hypertension, better linear growth in children, better cosmetic appearance, and better compliance with medications.

Yet the gold standard for evidence-based medicine remains the randomized controlled trial. Initial results were promising in terms of steroid withdrawal with modern immunosuppression. Vincenti et al. found that addition of the induction antibody basiliximab and a change from Aza to mycophenolate allowed for safe early steroid withdrawal or minimization (10). The incidence of biopsy-proven AR at 12 months was not significantly different between the steroid withdrawal group (20 percent) and the standard treatment group (16 percent). Allograft function and incidence of adverse events and infections were similar between the two groups. Now the question was whether steroid avoidance was better than minimization.

While steroid avoidance might be a suitable strategy for a select group of patients, a significant number will not qualify.

Avoidance versus minimization

The FREEDOM study was a large prospective randomized controlled trial that compared three groups head to head: steroid maintenance, early steroid withdrawal by day seven, and steroid avoidance (11). The results of the study were very clear: a graded increase in one-year AR incidence going from 19 percent in the maintenance group to 29 percent in the withdrawal group to 36 percent in the avoidance group. Mean glomerular filtration rate (GFR) at one year was identical in all three groups, as was short-term graft survival. Hypertension incidence was slightly lower in the avoidance group. In short, from the authors' perspective, the randomized prospective trial showed some detriment and some benefit to avoiding steroids, in contrast to prior historically controlled studies, which showed only benefits.

In an editorial accompanying the FREEDOM study, Meier-Kriesche et al. pointed out that the steroid avoidance group had a greater percentage of living donors, generally associated with better outcomes (12). The study was open-label. In the intent-to-treat analysis, the incidence of biopsy-proven acute rejection was statistically higher in both the steroid avoidance (31.5 percent) and the steroid withdrawal (26.1 percent) arms compared with the steroid maintenance group (14.7 percent).

Hricik has provided further insight into this study's results (13). The graft survival rates were similar among the three groups, but the study was not powered to detect differences in graft survival. The metabolic benefits observed were modest (fewer antihyperglycemic medications in the steroid-free group and less frequent lipid-lowering agents in the steroid withdrawal group), but actual incidences of diabetes mellitus were the same in all groups. Lipid levels were not measured. Less weight gain was seen only in the steroid withdrawal group, not in the avoidance group.

The groups did not remain as they were initially assigned: 12 percent of steroid maintenance subjects were not on steroids at 12 months, and a substantial minority of steroid-sparing subjects started steroids through the course of the study. The patient population was set up to be standard immune risk, but only 1.2 percent of participants were African Americans, a traditionally high-risk group. To these comments, I would add that the study was designed with basiliximab, CsA, and enteric-coated mycophenolate as concomitant medications, a combination of drugs all manufactured by one company but not commonly used clinically in the United States.

Another recently published trial by Woodle et al. looked at early (within seven days) withdrawal (minimization) versus long-term steroid maintenance in prospective randomized cohorts receiving tacrolimus and mycophenolate mofetil (14). Complete steroid avoidance was not tested in this trial, but blinding was maintained for five years.

In the Woodle study, 386 subjects were divided into two groups. The early withdrawal group had a significantly higher biopsy-proven AR rate of 17.8 percent versus 10.8 percent ($P = 0.04$) for the long-term steroid maintenance group. Graft survival and kidney allograft function at five years posttransplant were similar. Five-year death-censored graft loss was 5.8 percent with early withdrawal and 3.6 percent with maintenance. Cockroft-Gault GFR was 58.6 mL/min in the early withdrawal group and 59.8 mL/min in the maintenance group. Once again, metabolic benefits were modest. Serum triglycerides were better with steroid early withdrawal at earlier time points, but no different between groups at the study end point of five years. Newly onset diabetes requiring treatment was also no different (early withdrawal, 20.5 percent; long-term steroid maintenance, 20.9 percent), although the percentage of patients who needed insulin was less in the early steroid withdrawal group.

Steroids in children

The NIH-funded SNS01 prospective randomized controlled trial of steroid avoidance versus maintained steroids in children is nearing completion. Analysis of 12-month clinical end points was presented by Minnie Sarwal, MD, PhD, at the American Transplant Congress in 2008. The incidence of AR and graft loss were identical in both groups, as were the improvements in linear height and incidence of hypertension. Thus, the primary end point, a significant difference in delta height Z-score, was not met. Among the exclusion criteria for steroid avoidance were subjects with percent reactive antibody (PRA) > 20 percent, repeat transplants, those needing steroids for primary disease, and presence of delayed graft function.

The only steroid late withdrawal trial conducted in children was the NIH-funded SW01 trial conducted between 1999 and 2004, before the SNS01 trial. These children all received basiliximab, tacrolimus, sirolimus, and prednisone until month six. If no ARs had occurred and the six-month protocol biopsy was free of subclinical rejection, then those children were randomized to wean off steroids or stay on. The trial enrolled 276 children but was stopped six months prior to expected completion due to a high incidence of posttransplant lymphoproliferative disorder in both study arms (15). What is notable is that the steroid withdrawal group was doing better in terms of graft survival and graft function than the maintained group. The difference did not quite reach statisti-

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Avoiding Steroids

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Most transplant centers in the United States are using induction therapy along with calcineurin inhibitors and MMF. In this setting, steroid withdrawal has already become an accepted practice in the transplant community.

Data from the most recent report of the Scientific Registry for Transplant Recipients indicate that as of 2006, more than 30 percent of patients receiving kidney transplants in the United States are discharged from their initial hospitalization without maintenance steroid therapy.

The push for steroid elimination has been driven by patient preference and patient demand. In our center's experience, patients remain eager to avoid steroids, despite the increased risk of acute rejection. We routinely encounter patients who refuse to initiate oral steroids or who independently taper prednisone after transplantation. Use of corticosteroid therapy will likely diminish further over time as immunosuppressive therapies become more targeted and less toxic. Even with the current immunosuppressive arsenal, steroid avoidance is now a reasonable and successful strategy in kidney transplantation.

Joshua Augustine, MD, is assistant professor in the department of medicine at University Hospitals Case Medical Center in Cleveland, Ohio.

References

1. Cole E, Landsberg D, Russell D, et al.: A pilot study of steroid-free immunosuppression in the prevention of acute rejection in renal allograft recipients. *Transpl* 2001; 72:845–850.
2. Birkeland SA: Steroid-free immunosuppression after kidney transplantation with antithymocyte globulin induction and cyclosporine and mycophenolate maintenance therapy. *Transpl* 1998; 66:1207–1210.
3. Matas AJ, Kandaswamy R, Gillingham KJ, et al.: Prednisone-free maintenance immunosuppression: A 5-year experience. *Am J Transpl* 2005; 5:2473–2478.
4. Kaufman DB, Leventhal JR, Axelrod D, et al.: Alemtuzumab induction and prednisone-free maintenance immunotherapy in kidney transplantation: comparison with basiliximab induction—long-term results, *Am J Transpl* 2005; 5:2539–2548.
5. Opelz G, Dohler B, Laux G: Long-term prospective study of steroid withdrawal in kidney and heart transplant recipients. *Am J Transpl* 2005; 5:720–728.
6. Luan FL, Steffick DE, Gadegbeku C, Norman SP, Wolfe R, Ojo AO: Graft and patient survival in kidney transplant recipients selected for de novo steroid-free maintenance immunosuppression. *Am J Transpl*, 2009; 9:160–168.
7. Woodle ES, First MR, Pirsch J, et al.: A prospective, randomized, double-blind, placebo controlled multicenter trial comparing early (7 day) corticosteroid cessation versus long-term low-dose corticosteroid therapy. *Ann Surg* 2008; 248: 564–577.
8. Hricik DE, O'Toole MA, Schulak JA, Herson J: Steroid-free immunosuppression in cyclosporine-treated renal transplant recipients: a meta-analysis. *J Am Soc Nephrol* 1993; 4:1300–1305.
9. Sinclair NR: Low-dose steroid therapy in cyclosporine-treated renal transplant recipients with well-functioning grafts. The Canadian Multicentre Transplant Study Group. *CMAJ* 1992; 147:645–657.
10. Adams PL: Long-term patient survival: strategies to improve overall health. *Am J Kidney Dis* 2006; 47 (4 Suppl 2): S65-S85.
11. Pascual J, Zamora J, Galeano C, et al.: Steroid avoidance or withdrawal for kidney transplant recipients. *Cochrane Database Syst Rev* 2009; 1: CD005632.
12. Rostaing L, Cantarovich D, Mourad G, et al.: Corticosteroid-free immunosuppression with tacrolimus, mycophenolate mofetil, and daclizumab induction in renal transplantation. *Transpl* 2005; 79:807–814.
13. Shibatani M, Fujioka M, Arai Y, et al.: Degree of corticosteroid treatment within the first 2 months of renal transplantation has a strong influence on the incidence of osteonecrosis of the femoral head. *Acta Orthop* 2008; 79:631–636.
14. O'Shaughnessy EA, Dahl DC, Smith CL, Kasiske BL: Risk factors for fractures in kidney transplantation. *Transpl* 2002; 74:362–366.
15. Gaber LW, Gaber AO, Hathaway DK, Vera SR, Shokouh-Amiri MH: Routine early biopsy of allografts with delayed function: correlation of histopathology and transplant outcome. *Clin Transpl* 1996; 10:629-634.
16. Augustine JJ, Siu DS, Clemente MJ, et al.: Pre-transplant IFN-gamma ELISPOTs are associated with posttransplant renal function in African American renal transplant recipients. *Am J Transplant* 2005; 5:1971–1975.
17. Basadonna GP, Matas AJ, Gillingham KJ, et al.: Early versus late acute renal allograft rejection: impact on chronic rejection. *Transpl* 1993; 55:993-995.
18. Humar A, Gillingham K, Kandaswamy R, Payne W, Matas A: Steroid avoidance regimens: a comparison of outcomes with maintenance steroids versus continued steroid avoidance in recipients having an acute rejection episode. *Am J Transpl* 2007; 7:1948–1953.
19. Vítko S, Klinger M, Salmela K, et al.: Two corticosteroid-free regimens—tacrolimus monotherapy after basiliximab administration and tacrolimus/mycophenolate mofetil—in comparison with a standard triple regimen in renal transplantation: results of the Atlas study. *Transpl* 2005; 80:1734–1741.

Disparities

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at hand.

Neither the classic conservative ideology of "blaming the victim" by ascribing limited access to low donation rates (in African Americans) and poorer graft survival to recipient noncompliance, nor the paternalistic liberal position of ascribing all problems to systemic racism, cultural bias, and a "somewhat different" and recalcitrant immunobiology in African Americans offers a promising or productive guide on how best to address these thorny issues.

Role of research and future directions

No adequately powered multicenter prospective study of medical adherence behavior has been conducted in kidney transplantation, let alone convincingly documented that African Americans are less compliant with immunosuppressive regimens, yet this explanation is confidently offered as an important cause of diminished allograft survival in African Americans. It is also a fact that no evidence shows that overt racism or cultural bias play any role in allocation of donor organs to the detriment of African American transplant candidates. Some organized professionals continue to massage the allocation system at great effort to accomplish marginal interracial redistribution of deceased donor organs as a way of redressing racial imbalance.

Given the significance of this issue, it is lamentable that we have yet to conduct an adequately powered multicenter clinical trial to address the question of optimal immunosuppression in African Americans. Not one such study has been sponsored either by the National Institutes of Health (NIH) or the pharmaceutical industry. Instead, posthoc analysis of completed clinical trials and single center retrospective studies have been the main sources of data on how African American kidney transplant recipients should be managed.

The key problem may be that very few individuals and, worse yet, no governmental entity or representative of the pharmaceutical industry is seriously committed to tackling the problems presented by racial disparities in organ transplantation, at least not as can be judged by demonstrable interest in sponsoring or organizing research projects to address the problems. This lack of commitment is not evident from public pronouncements, advertisements, or the medical literature. Symbolic gestures and politically correct attentiveness to racial disparity issues abound ad nauseum.

Given the inadequacy of current approaches, the way forward requires that a number of questions should be tackled with the utmost urgency. What is the most promising package to stimulate an increase in live kidney donation from which African Americans stand to benefit? Should there be a systematic testing through demonstration projects of radical ideas such as significant financial compensation for both deceased and live kidney donation? Which of the immunosuppressive drugs under development confer benefits in African Americans, rather than just giving larger doses to African Americans in phase four clinical trials? What is the optimal posttransplant management scheme that will improve long-term outcomes in African Americans? Should amply reimbursed capitated posttransplant management schemes be tested through private-public partnerships to assess the potential impact of intensive and well-coordinated posttransplant follow-up?

It is time to establish a consortium of committed professionals to conduct research studies and develop guidelines on racial issues in kidney transplantation just as there are consortia for interventional cardiology, AIDS, type 1 diabetes mellitus, breast cancer, and other diseases. The understandable risk aversion of pharmaceutical companies to offer new drugs in development to African American recipients can be addressed by establishing an active collaboration between relevant agencies within NIH, FDA, and the pharmaceutical industry.

One way to start the ball moving toward tangible goals today is for professional societies to assemble the many individuals who have championed these issues to develop a roadmap to advance the agenda of improving access and outcomes of kidney transplantation in African Americans and other minorities. Unless a new course is charted and vigorously traveled, the next generation will lament the same appalling statistics and revisit an even greater magnitude of unnecessary human suffering, ill health, and

Not for All

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cal significance, but the likelihood that the steroid withdrawal group was worse is extremely remote.

Another highly rated form of evidence-based medicine is the Cochrane review system. Pascual et al. recently published a systematic review of steroid avoidance or withdrawal, evaluating 30 studies containing 5949 patients (16). Patients on any steroid-sparing strategy showed a higher risk of graft loss (excluding death) than those with conventional steroid use [relative risk (RR), 1.23; 95 percent confidence interval (CI), 1.00 to 1.52]. Acute rejection was also more frequent (RR, 1.27; 95 percent CI, 1.14 to 1.40).

Sarwal will argue that steroid avoidance is not inferior and may remove one drug from a long list of medications that transplant patients need to take daily. Although steroid avoidance certainly may be feasible for some recipients, the following groups may not be candidates for steroid avoidance: patients with high PRA levels or the need for steroids for primary renal disease (such as lupus nephritis) and those with delayed graft function (DGF). DGF, as defined by need for dialysis in the first week posttransplant, currently occurs in 24 percent of all deceased donor kidney transplants in the United States. Milder degrees of kidney injury, called slow graft function by some, are much more frequent.

Steroid avoidance and acute rejection

What about those patients on steroid avoidance in whom an AR occurs? Are these patients at risk for worse outcomes if they stay steroid-free? There are no rigorous data at present. However, Humar et al. provided some indication of possible outcomes in a retrospective uncontrolled analysis (17). They looked at 842 adult kidney transplant recipients on a steroid minimization protocol. Of these, 17.7 percent, or 149, had at least one AR episode. Thirty-four percent of these patients restarted maintenance steroids; the other 66 percent remained steroid-free. The choice was not randomized; physician preference and concomitant diabetes played a significant role. Not restarting steroids after the first AR resulted in a borderline increase in risk for a second AR episode (RR = 2.1; $P = 0.07$). The study suggested that some patients might be worse off if steroids were not restarted, although graft survival was not different between the two retrospective groups.

An analysis of the Scientific Registry of Transplant Recipients (SRTR), to be presented by Santos et al. at the American Transplant Congress this month, supports this view. This study looked at all solitary kidney transplants performed between 2002 and 2006. By 12 months posttransplant, 34 percent of recipients who were reported as steroid-free at initial discharge were now on steroids. The patients who restarted were predictable: African Americans, retransplants, those with high PRAs, and those who received expanded criteria kidneys. Patients newly started on steroids had a 20 percent increased risk of graft loss compared to those maintained on steroids from the start.

In summary, while steroid avoidance might be a suitable strategy for a select group of patients, a significant number will not qualify. Patients with high PRAs or a prior transplant comprise an ever-increasing proportion of the transplant population. Furthermore, published studies did not enroll African Americans to a significant extent, yet this group is known to be at higher immunologic risk. DGF occurs in a quarter of all deceased donor kidney transplant recipients. A significant minority of such recipients will have a greater propensity to immunologic events requiring steroid use pretransplant.

Potential side benefits of steroid avoidance or minimization have been much more modest in the recently reported randomized controlled trials than in prior series. Whether steroid minimization is better than avoidance when DGF is present is unknown. Furthermore, late steroid withdrawal may not be as bad as previously thought, with the switch from CsA-Aza to tacrolimus-mycophenolate mofetil–based maintenance immunosuppression.

Vikas Dharnidharka, MD, is associate professor of pediatrics at the University of Florida College of Medicine.

References

1. Kasiske BL, Chakkera HA, Louis TA, Ma JZ: A meta-analysis of immunosuppression withdrawal trials in renal transplantation. *J Am Soc Nephrol* 2000; 11(10):1910–7.
2. Pascual J, Quereda C, Zamora J, Hernandez D: Steroid withdrawal in renal transplant patients on triple therapy with a calcineurin inhibitor and mycophenolate mofetil: a meta-analysis of randomized, controlled trials. *Transpl* 2004; 78(10):1548–56.
3. Ahsan N, Hricik D, Matas A, Rose S, Tomlanovich S, Wilkinson A, et al.: Prednisone withdrawal in kidney transplant recipients on cyclosporine and mycophenolate mofetil—a prospective randomized study. Steroid Withdrawal Study Group. *Transpl* 1999; 68(12):1865–74.
4. Vanrenterghem Y, Lebranchu Y, Hene R, Oppenheimer F, Ekberg H: Double-blind comparison of two corticosteroid regimens plus mycophenolate mofetil and cyclosporine for prevention of acute renal allograft rejection. *Transpl* 2000; 70(9):1352–9.
5. Cole E, Landsberg D, Russell D, Zaltzman J, Kiberd B, Caravaggio C, et al.: A pilot study of steroid-free immunosuppression in the prevention of acute rejection in renal allograft recipients. *Transpl* 2001; 72(5):845–50.
6. Elias TJ, Bannister KM, Clarkson AR, Russ GR, Mathew TH, Barratt LJ, et al.: Excellent long-term graft survival in low risk, primary renal allografts treated with prednisolone-avoidance immunosuppression. *Clin Transpl* 2000; 14(2):157-61.
7. Sarwal MM, Vidhun JR, Alexander SR, Satterwhite T, Millan M, Salvatierra O, Jr.: Continued superior outcomes with modification and lengthened follow-up of a steroid-avoidance pilot with extended daclizumab induction in pediatric renal transplantation. *Transpl* 2003; 76(9):1331-9.
8. Shapiro R, Ellis D, Tan HP, Moritz ML, Basu A, Vats AN, et al.: Antilymphoid antibody preconditioning and tacrolimus monotherapy for pediatric kidney transplantation. *J Pediatr* 2006; 148(6):813–8.
9. Matas AJ, Kandaswamy R, Gillingham KJ, McHugh L, Ibrahim H, Kasiske B, et al.: Prednisone-free maintenance immunosuppression—a 5-year experience. *Am J Transpl* 2005; 5(10):2473–8.
10. Vincenti F, Monaco A, Grinyo J, Kinkhabwala M, Roza A: Multicenter randomized prospective trial of steroid withdrawal in renal transplant recipients receiving basiliximab, cyclosporine microemulsion and mycophenolate mofetil. *Am J Transpl* 2003; 3(3):306–11.
11. Vincenti F, Schena FP, Paraskevas S, Hauser IA, Walker RG, Grinyo J: A randomized, multicenter study of steroid avoidance, early steroid withdrawal or standard steroid therapy in kidney transplant recipients. *Am J Transpl* 2008; 8(2):307–16.
12. Meier-Kriesche HU, Magee JC, Kaplan B. Trials and tribulations of steroid withdrawal after kidney transplantation. *Am J Transpl* 2008; 8(2):265–6.
13. Hricik DE. Comparing early withdrawal or avoidance of steroids with standard steroid therapy in kidney transplant recipients. *Nat Clin Pract Nephrol* 2008; 4(7):360–1.
14. Woodle ES, First MR, Pirsch J, Shihab F, Gaber AO, Van Veldhuisen P: A prospective, randomized, double-blind, placebo-controlled multicenter trial comparing early (7 day) corticosteroid cessation versus long-term, low-dose corticosteroid therapy. *Ann Surg* 2008; 248(4):564–77.
15. McDonald RA, Smith JM, Ho M, Lindblad R, Ikle D, Grimm P, et al.: Incidence of PTLD in pediatric renal transplant recipients receiving basiliximab, calcineurin inhibitor, sirolimus and steroids. *Am J Transpl* 2008; 8(5):984–9.
16. Pascual J, Zamora J, Galeano C, Royuela A, Quereda C: Steroid avoidance or withdrawal for kidney transplant recipients. Cochrane Database Syst Rev 2009; (1):CD005632.
17. Humar A, Gillingham K, Kandaswamy R, Payne W, Matas A: Steroid avoidance regimens: a comparison of outcomes with maintenance steroids versus continued steroid avoidance in recipients having an acute rejection episode. *Am J Transpl* 2007; 7(8):1948–53.

Disparities

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premature deaths of untold number of those with end stage kidney disease.

Akinlolu Ojo, MD, PhD, is Florence E. Bingham Research Professor of Nephrology in the department of internal medicine at the University of Michigan in Ann Arbor.

References

1. Opelz G, Mickey MR, Terasaki PI: Influence of race on kidney transplant survival. *Transpl Proceedings* 1977; 9:137–42.
2. Relman AS. Race and end-stage renal disease [editorial]. *New Engl J Med* 1982; 306:1290–1.
3. Shapiro R, McCauley J, Scantlebury V, et al: Effect of recipient race on waiting time for renal transplantation at the University of Pittsburgh. *Transpl Proceedings* 1993; 25:2458–9.
4. McDonald JC: Issues related to race in transplantation. *Transpl Proceedings* 1989; 21:3411–2; discussion 3–8.
5. Koyama H, Cecka JM: Race effects. *Clin Transplants* 1991; 269–80.
6. Geiger HJ: Race and health care—an American dilemma? *N Engl J Med* 1996; 335:815–16.
7. Held PJ, Pauly MV, Bovbjerg RR, Newmann J, Salvatierra O, Jr.: Access to kidney transplantation. Has the United States eliminated income and racial differences? *Arch Intern Med* 1988; 148:2594–600.
8. Levinsky NG, Rettig RA: The Medicare end-stage renal disease program. A report from the Institute of Medicine. *N Engl J Med* 1991; 324:1143–8.
9. Rettig AR, Levinsky GN: Kidney failure and the federal government. Committee for the Study of the Medicare ESRD Program, Division of Health Care Services, Institute of Medicine: National Academy of Sciences; 1991.
10. Gaber AO, First MR, Tesi RJ, et al.: Results of the double-blind, randomized, multicenter, phase III clinical trial of Thymoglobulin versus Atgam in the treatment of acute graft rejection episodes after renal transplantation. *Transpl* 1998; 66:29–37.

Living Donors—An Expanding Spectrum of Quality

By David Foley

Kidney transplantation remains the standard of care for patients with end stage renal disease (ESRD). Owing to the significant shortage of donor organs, transplant centers continue to expand the criteria for suitable kidney donors. As a result, there has been a progressive change in the spectrum of quality of kidney donors.

The increased use of transplanted kidneys recovered from expanded criteria deceased donors (ECD) and donation after cardiac death (DCD) both contribute to the change in the quality of kidney donors. Between 1997 and 2006, the number of standard criteria donor (SCD), ECD, and DCD kidney transplants increased by 22 percent, 59 percent, and 684 percent, respectively. In addition, between 2005 and 2006, there was a 7.4 percent increase in deceased donor kidney transplants and a 2 percent decrease in living donor (LD) kidney transplants, according to the 2007 OPTN/SRTR (Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients) Annual Report.

Despite the recent decreases in kidney transplants involving living donors, such donors continue to play a significant role in kidney transplantation. Contributing to the demand for LD kidney transplants are the minimal long-term risk to the donor and superior outcomes in the recipient compared with deceased donor kidney transplants.

Expanding the donor base

Transplant centers are expanding the acceptance criteria for living kidney donors. Recent data show an increased use of older living kidney donors. According to the 2007 OPTN/SRTR Annual Report, from 1997 to 2006, there was a 5.9 percent decrease in living donors 18–34 years old and a concomitant 5.4 percent increase in living donors 50–64 years old. The percentage of living donors 35–49 and those over age 65 has remained essentially unchanged.

This trend is also illustrated in studies looking at practice patterns at transplant centers in the United States. Mandelbrot et al. performed a survey of U.S. transplant centers that looked at the medical evaluation of living kidney donors. When they compared their 2007 survey to a survey published in 1995, they found that most programs no longer have an upper age limit to be eligible for kidney donation (1). The percentage of programs in 2007 with no upper age limit (59 percent) nearly doubled from that identified in the 1995 survey (27 percent) (2).

To assess the influence of using more "marginal" or "high-risk" living kidney donors, one must look at the impact on both donors and recipients after donation. Ibrahim et al. recently studied long-term risk to the kidney donor in an analysis of 3698 kidney donors who had previously donated kidneys between 1963 and 2007.

The authors ascertained the vital status and lifetime risk of ESRD in these donors and assessed glomerular filtration rate (GFR), urinary albumin excretion, prevalence of hypertension, general health status, and quality of life in 255 donors. These measurements were compared to those of matched controls from the National Health and Nutrition Examination Survey. The authors found that survival and the risk of ESRD in carefully screened kidney donors appeared to be similar to those of the general population. Most donors who were studied had preserved GFR, normal albumin excretion, and an excellent quality of life (3). However, these outcomes were likely limited to the healthiest donors and did not address those donors who may be considered marginal or high-risk.

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Risk factors that contribute to the classification of a marginal or high-risk kidney donor include obesity, age, presence of hypertension, and low GFR at the time of donation. Recent data show that more individuals with these pre-existing conditions are being accepted as kidney donors. Reese et al. defined living donors with hypertension, obesity, or low GFR as "medically complex donors." Among the 9319 kidney donors he analyzed between July 2004 and December 2005, 2254 (24.2 percent) were complex: 1194 (12.8 percent) were obese, 956 (10.3 percent) were hypertensive, and 392 (4.2 percent) had low GFR (4).

Short-term outcomes for living kidney donors

Despite the increased use of medically complex kidney donors, the literature on outcomes for these select donors remains limited. Some data exist on the follow-up of kidney donors with obesity at the time of donation and renal function after nephrectomy. In a single center study, Heimbach et al. retrospectively evaluated 553 consecutive living kidney donors and studied the effects of body mass index (BMI) on postnephrectomy renal function. At six to 12 months after donation, renal function and microalbuminuria did not differ across BMI (5).

In contrast, Rook et al. studied the impact of donor age and BMI on the renal functional reserve capacity of kidney donors before and after donor nephrectomy. Reserve capacity was assessed by GFR increase to dopamine infusion. The dopamine-induced GFR increase of 11 ± 10 percent prior to donation was reduced to 5 ± 7 percent after donor nephrectomy ($P < 0.001$). Before donor nephrectomy, older age and higher BMI did not affect reserve capacity. However, after donor nephrectomy, the response of GFR to dopamine independently and negatively correlated with older age and higher BMI. Despite these findings, it remains unclear whether the impairment of renal reserve capacity after donor nephrectomy is prognostic of an increased risk for loss of renal function (6).

Outcomes for hypertensive kidney donors have also been studied. In a single center study, Textor et al. studied detailed measurements of blood pressure and clinical and renal characteristics in 148 living kidney donors before and six to 12 months after nephrectomy. Twenty-four patients were hypertensive before donation. Hypertensive donors were older and had lower GFR after kidney donation. However, after correcting for age, the investigators found no independent effect of blood pressure for predicting GFR either before or after nephrectomy.

The authors concluded that white patients with moderate essential hypertension and normal kidney function do not experience adverse effects on blood pressure, GFR, and urinary protein excretion during the first year after living kidney donation (7). These data on short-term outcomes demonstrate no significant differences between carefully selected hypertensive donors and nonhypertensive controls. However, long-term outcomes remain unknown.

Long-term outcomes for living kidney donors

The scarcity of adequate data assessing the long-term outcomes of living kidney donors with isolated medical abnormalities (IMAs) was recently studied in a literature review. Young et al. systematically reviewed studies with three or more living kidney donors with preexisting IMAs. They identified 22 studies on older donors (n = 484), six studies on hypertensive donors, four studies on donors with nephrolithiasis, two studies on donors with microscopic hematuria, and one study each on donors with proteinuria or reduced GFR.

Few studies reported longer-term (> 1 year) rates of hypertension, proteinuria, or renal function. Owing to the variability among the studies and methodological limitations, the authors concluded that uncertainties remain regarding long-term medical outcomes for IMA donors (8).

Recipient outcomes

As use of older kidney donors for transplants expands, questions arise regarding recipient outcomes. In a recent analysis of data from the OPTN and United Network for Organ Sharing (UNOS), Gill et al. studied all first-kidney-only transplants in the United States between 1995 and 2003 and assessed outcomes of living donor transplantation as a function of donor age.

GFR one year after transplantation decreased with increasing donor age. In multivariate analysis, the relative risk of graft loss of kidney transplants from living donors > 55 years was significantly greater than that with younger living donors (YLD), those ≤ 55 years. In comparison to transplants with deceased donors < 55 years, the risk of graft loss with living donors 55–64 years was similar, while recipients from living donors 65 years and older had a higher relative risk of graft loss (9).

In a separate prospective cohort study of 739 first-time LD transplantations, Oien et al. studied the effects of donor age on short- and long-term recipient outcomes. Graft survival was unaffected by donor age > 50 years as long as the recipients did not experience an early acute rejection episode. In the absence of acute rejection episodes, there was

no difference in graft survival [relative risk, 1.55; 95% confidence interval (CI), 0.67–3.60, $P = 0.31$]). Donor age > 65 years was a risk factor for early acute rejection episodes (10).

Gill et al. performed another analysis in 2008 using the OPTN/UNOS database and analyzed outcomes of kidney transplantation from 1996 to 2005 from older living donors (OLD = age > 55 years) to older recipients (> 60 years). OLD transplantations were associated with slightly inferior four-year graft survival rates (77.7 percent), and patient survival rates (82.4 percent) compared with YLD (four-year graft survival, 80.7 percent; patient survival, 84.2 percent). But OLD transplantations had superior graft survival compared with all deceased donor options.

Recipients of ECD transplants had inferior outcomes. Four-year overall allograft and patient survival rates were 57.1 percent and 67.5 percent, respectively. On univariate analysis and when compared to OLD transplantations, ECD transplantations were associated with a greater risk of graft loss (hazard ratio, 2.36; 95% CI, 1.18–4.74) (11). Although the outcomes of OLD are inferior to YLD kidney transplants in this study, there is a significant survival benefit conferred to the recipient receiving an OLD kidney compared to an ECD kidney. However, it remains unclear whether transplantation of an OLD kidney is better than waiting for an SCD kidney (12).

In summary, over the past several years there has been a steady increase in the use of "medically complex" or "high-risk" living kidney donors, including those who are older, obese, have hypertension, or have low GFR. Despite the limited long-term data evaluating the outcomes in these patients, up to one-quarter of transplant centers are approving these donors (4). Recipients clearly sustain a life-saving benefit from receiving a living donor kidney from an older or medically complex donor compared with dialysis. The data also suggest that outcomes are significantly better than receiving an ECD kidney. Whether there is a true benefit over waiting for an SCD donor remains to be determined.

In these instances, short- and long-term safety to the donor should take precedence over recipient needs for a kidney transplant. Although informed consent remains a critical component to the LD evaluation process, one may argue that true informed consent is limited in this group of donors owing to the lack of long-term follow-up. These donors need to be made aware that the long-term consequences of kidney donation for patients defined as medically complex or older are unknown, and the transplant community needs to proceed cautiously when approving these kidney donors.

It is essential that future studies include close follow-up of both medically complex and older living donors. It is also critical to study the long-term benefits to recipients of receiving one of these kidneys compared with SCD deceased donor transplantation. This will allow for true risk-benefit analyses when considering the use of these donors in the future.

David Foley, MD, is with the division of organ transplantation, department of surgery, at the University of Wisconsin School of Medicine and Public Health in Madison.

References

1. Bia MJ, Ramos EL, Danovitch GM, et al.: Evaluation of living renal donors. The current practice of U.S. transplant centers. *Transpl* 1995; 60(4):322–7.
2. Mandelbrot DA, Pavlakis M, Danovitch GM, et al.: The medical evaluation of living kidney donors: a survey of U.S. transplant centers. *Am J Transpl* 2007; 7(10):2333–43.
3. Ibrahim HN, Foley R, Tan L, et al.: Long-term consequences of kidney donation. *N Engl J Med* 2009; 360(5):459–69.
4. Reese PP, Feldman HI, McBride MA, et al.: Substantial variation in the acceptance of medically complex live kidney donors across U.S. renal transplant centers. *Am J Transpl* 2008; 8(10):2062–70.
5. Heimbach JK, Taler SJ, Prieto M, et al.: Obesity in living kidney donors: clinical characteristics and outcomes in the era of laparoscopic donor nephrectomy. *Am J Transpl* 2005; 5(5):1057–64.
6. Rook M, Bosma RJ, van Son WJ, et al.: Nephrectomy elicits impact of age and BMI on renal hemodynamics: lower postdonation reserve capacity in older or overweight kidney donors. *Am J Transpl* 2008; 8(10):2077–85.
7. Textor SC, Taler SJ, Driscoll N, et al.: Blood pressure and renal function after kidney donation from hypertensive living donors. *Transpl* 2004; 78(2):276–82.
8. Young A, Storsley L, Garg AX, et al.: Health outcomes for living kidney donors with isolated medical abnormalities: a systematic review. *Am J Transpl* 2008; 8(9):1878–90.
9. Gill JS, Gill J, Rose C, et al.: The older living kidney donor: part of the solution to the organ shortage. *Transpl* 2006; 82(12):1662–66.
10. Oien CM, Reisaeter AV, Leivestad T, et al.: Living donor kidney transplantation: the effects of donor age and gender on short- and long-term outcomes. *Transpl* 2007; 83(5):600-6.
11. Gill JS, Bunnapradist S, Danovitch GM, et al.: Outcomes of kidney transplantation from older living donors to older recipients. *Am J Kidney Dis* 2008; 52(3):541–52.
12. Nanovic L, Kaplan B. The advantage of live-donor kidney transplantation in older recipients. *Nat Clin Pract Nephrol* 2009; 5(1):18–19.

Practice Pointers

Nonadherence in Kidney Care

Thomas Nevins

In this month's issue, ASN Kidney News *editorial board member Edgar Lerma interviewed Thomas Nevins, professor of pediatrics at the University of Minnesota Amplatz Children's Hospital in Minneapolis, about nonadherence among patients—and care providers—in transplantation, dialysis, and kidney care in general.*

What does the term nonadherence mean in nephrology?

In the broadest sense, nonadherence describes the failure to follow specific recommendations concerning a patient's health care. Nonadherence is usually thought of in a single dimension—that the patient fails to take a medication as prescribed. Upon further reflection, nonadherence is obviously multidimensional and includes a whole range of behaviors in addition to the patient's medication adherence. It may even be expanded to include the health-care worker's behavior in terms of following widely accepted guidelines and protocols defining a patient's care.

In nephrology, therapies are often quite complex and, correspondingly, so is adherence. Patients are regularly asked to take numerous medications, follow a defined diet, and engage in other follow-up activities, such as clinic and laboratory visits or dialysis sessions. A variety of more specific behaviors may also be required based on each patient's unique clinical status. Nephrology professionals also have a number of guidelines (e.g., JNC7 and KDOQI) and specific protocols they are expected to follow while directing patient care.

Is nonadherence synonymous with noncompliance?

In medical use and in the behavioral literature, several words—compliance, adherence, concordance, and persistence—have all been used interchangeably but with a focus on underlying assumptions implicit with each word. Historically, "noncompliance" was the term first used and remains useful, since even outside health care, everyone generally understands what is meant.

But in the interpersonal environment of patient care, many are concerned that the term "compliance" is too authoritarian, emphasizing the asymmetry of power that exists between physicians and patients.

"Adherence" then is intended to suggest that the recommendations are the result of a dialogue between the health-care professional and the patient. In Great Britain, extending this concept, the synonym "concordance" (or "consensual prescribing") is meant to describe an agreement between a patient and a health-care professional about whether, when, and how medications will be taken. Finally, "persistence" has been defined as the actual duration of time a patient takes a specific medication or otherwise follows a health recommendation.

What is the Physicians' Health Study?

The Physicians' Health Study is a randomized, double-blind, placebo-controlled clinical trial initiated in 1982 by researchers at Harvard University. The research was designed to examine the efficacy of aspirin and beta-carotene in respectively reducing cardiovascular mortality and new malignancies. The study recruited a cohort of U.S. male physicians (n=33,223; age 40–84 yrs). To be eligible for this study and deemed "compliant," physicians had to report taking at least two-thirds of their pills over a specified time.

An unintended consequence of the study's 18-week "run-in" observation period was to highlight the self-reported noncompliance of physician volunteers (25 to 30 percent) with the daily drug regimen prescribed. In December 1987, the aspirin limb of the study was halted early due to the increased frequency of cardiovascular events in physicians receiving placebo. A later analysis of physicians in the aspirin group even demonstrated a further association between regimen noncompliance and an increased rate of cardiovascular events.

Thus, in a volunteer, motivated, and educated population taking a single daily drug dose, the frequency of self-reported noncompliance was more than one in four. The report highlights that we are all human and despite our best intentions we do not always do what we intend or promise. Recognizing this simple fact should help us avoid "blaming" patients and move us closer to working with our patients to minimize this problem.

Nonadherence is obviously multidimensional and includes a whole range of behaviors in addition to the patient's medication adherence.

The theme for this issue is kidney transplantation. What is the impact of nonadherence on renal transplants?

Given today's effective and potent immunosuppressive drugs, medication adherence is now central to the success of any solid organ transplant. It is profoundly counterintuitive that competent adult transplant recipients would fail to take the very medications needed to preserve their graft function. Despite that simple analysis, many renal transplant patients regularly miss some of their medication doses.

In our studies of azathioprine adherence after renal transplant, nearly 20 percent of patients missed more than 10 percent of their drug doses during the first posttransplant month. This pattern was monotonously repeated during each of the first six months. Not surprisingly, the group missing the most doses of azathioprine also experienced the highest rate of acute rejection episodes. In later follow-up, this group also experienced the highest rate of graft loss. Recently, we demonstrated a similar frequency and pattern of medication nonadherence in current transplant recipients taking either mycophenolate or sirolimus.

In addition, long-term renal transplant survivors often experience hypertension, hyperlipidemia, increased weight gain, and an increased frequency of cardiovascular events. Successful prevention or treatment of these complications requires adherence to lifestyle changes and medical therapy. However, there is no evidence that transplant patients will be any more adherent with these additional prescriptions. Following technically successful renal transplantation, medication adherence is one of the most important factors impacting both near-term and later outcomes.

Wherein lies the problem? Is it the health-care system per se? Is it the provider? Or is it the patient?

Perhaps the most fundamental aspect of the "noncompliance problem" is simply recognizing it! Medication nonadherence is ubiquitous, and it appears early posttransplant. However, except for patients with florid rejection, who admit they have discontinued their medications, physicians are slow to recognize noncompliance. Instead, when the observed clinical response is subpar, we often just increase the prescribed medication dose. So the first step with every patient is to ask, "How often do you miss medication doses?"

Because the etiologies of nonadherence are multifactorial, the underlying causes will be as many and diverse as our individual patients and their associated health-care systems. Again, focusing on renal transplantation, the "system" isn't usually the central problem. Indeed, nonadherence is found in every culture and health-care delivery system where it has been carefully sought. Certainly, patients can't take drugs they don't have. So a lack of insurance, restrictive formularies, or high co-payments may all be significant barriers to medication adherence. However, even in the context of national health insurance (Canada and European countries) medication nonadherence is a significant posttransplant problem regularly impairing outcomes. Even in homogenous subspecialty clinics, and in cultures acknowledged for their attention to protocol and detail, nonadherence remains a central issue.

Besides recognizing nonadherence, what is the role of health-care providers? Studies in other chronic diseases (e.g.,

AIDS) have emphasized the importance of the patient's belief that their physician knows what to do and that they care about their patients. Simply put, patients are more likely to follow the recommendations of health-care providers with whom they feel a connection. During posttransplant care, in addition to transplant physicians, nurses, coordinators, social workers, and dietitians all contribute in varying degrees to a patient's perception about the concern and care they receive.

From the provider's perspective, a good start is to adapt medication schedules and protocols to suit individual patients' needs and to select drugs with lower side-effect profiles and longer half-lives. Then, discussing with patients how they are doing with their drugs, discovering barriers to adherence (literacy, low vision, travel, work schedules, etc.), and finding out what number of doses are missed each week, are activities that both improve adherence and build the patient's perception that their doctor is knowledgeable and cares about them.

Finally, although our patients are all individuals, some group characteristics are more often associated with medication nonadherence. The first is age. Beginning in adolescence, younger patients as a group are more likely to be noncompliant. The reasons for this are unclear. Perhaps young patients are less able to concretely envision the adverse effects of nonadherence, or perhaps they aspire to the "normal life" of their peers. Also, younger patients typically have lives that are simply less organized and therefore less readily adapted to scheduled medications.

Patients with psychological problems (personality disorders, posttraumatic stress disorder, drug use, and depression) are generally at increased risk for nonadherence. When identified, they may benefit from specific therapy prior to renal transplantation. Patients without established, strong psychosocial supports (family, spouse, etc.) are also more often nonadherent.

Conversely, characteristics that we might expect to impact adherence do not seem to consistently apply. This includes donor source (live versus deceased), with the possible exception of spousal donation. Gender doesn't predictably impact adherence nor do chronic co-morbidities such as diabetes.

What is your advice on how to solve the problem of nonadherence?

Because the issue of medication nonadherence is so complicated, there are no simple "solutions." However, there are approaches that will reduce medication nonadherence. While recognizing that we really can't choose our patients or alter their behavior, it is clear that the one behavior we can reliably change is ours. In that regard, there are several important areas that the nephrologist can address to improve medication adherence:

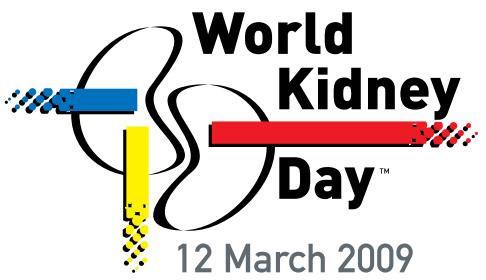
- **Medication regimen**
  - Prescribe drugs with lower side-effect profiles.
  - Prescribe "forgiving" drugs—those with long half-lives and simpler schedules.
  - Early on, simplify the dosing schedule by eliminating unnecessary drugs.
- **Education**
  - Ensure patients know all of their medications and each drug's purpose.
  - Document the patient's adherence with their regimen (drug levels, prescription refill records).
- **Discussion**
  - At each clinic visit, proactively review medication adherence.
  - Discuss any patient concerns about their medications and any side effects.
  - Inquire about the use of nonprescription or herbal therapies.
- **Solutions**
  - Encourage the use of medication boxes and other reminder systems.
  - Identify and use robust daily habits as cues to remember medications.
  - Help the patient to "problem-solve," overcoming adherence barriers.
  - Be aware of failed appointments (lab or clinic), and missed prescription refills—these may be markers for declining adherence.

In the end, nonadherence is a simple fact of life, a reflection of our shared humanity. Our task as nephrologists is to recognize nonadherence and then help blunt its impact on our patients and their lives.

ASN News

ASN Participates in World Kidney Day 2009

ASN President Thomas Coffman and The Sopranos actor Vincent Curatola.



In honor of World Kidney Day 2009, more than 20 ASN members and staff and dozens of patients and representatives from the National Kidney Foundation, Dialysis Patient Citizens, and the American Society of Pediatric Nephrology visited more than 100 congressional offices on March 12 to urge sustained funding for kidney disease research and greater support for programs that improve treatment outcomes for patients suffering from kidney disease.

World Kidney Day (celebrated every year on the second Thursday of March) is a global campaign focused on publicizing the importance of kidney health and reducing the frequency and impact of kidney disease and its associated health problems.

This year, ASN member physicians urged their members of Congress to expand coverage of life-saving medications needed to reduce the likelihood of organ rejection among transplant recipients. Patient advocates explained that Medicare coverage for immunosuppressive drugs expires after 36 months even though they must take the drugs for their entire lives if they are to reduce the risk of rejection. The immunosuppressive drug protocol is significantly cheaper than the alternative. The drugs cost $11,000 per year, while Medicare must pay $81,000 per patient for graft failure and $71,000 per year for dialysis. Participants asked their senators and representatives to support bills introduced in both chambers of Congress to amend title XVIII of the Social Security Act to provide continued entitlement in coverage for these drugs.

ASN members also encouraged support for robust research funding via the National Institutes of Health (NIH). While appreciative of the $10 billion increase provided to NIH under the economic stimulus package, ASN advocates reminded their representatives that increases over the newly established base are essential to prevent a hard landing in fiscal year 2011 that might stall discovery and innovation. ASN members also highlighted the need for additional basic and clinical research on the relationship between kidney disease and diabetes, hypertension, and obesity, and urged continued support to maintain the pipeline of investigators dedicated to studying the disease.

Advocates also discussed the importance of addressing health-care disparities in future legislation. Armed with disconcerting statistics, ASN members educated their representatives on the disparate health outcomes among their African American and Hispanic patients compared to Caucasian patients.

The evening before World Kidney Day, more than 200 guests joined the co-chairs of the Congressional Kidney Caucus, Reps. Mark Kirk (R-IL) and Jim McDermott (D-WA), as well as Reps. Shelley Berkley (D-NV), Steve Kagen (D-WI), Gene Green (D-TX), and special celebrity guests Vince Curatola of HBO's The Sopranos and the Washington Redskins' Reed Doughty, to celebrate the launch of World Kidney Day with a congressional reception.

On Friday, March 13, ASN members encouraged support for kidney disease research at the National Institute of Diabetes and Digestive and Kidney Diseases, the National Heart, Lung, and Blood Institute, and the National Institute on Aging. ASN representatives discussed with NIH officials the importance of interdisciplinary trials and of improving communication regarding the use of the $10 billion stimulus funding.

Additional World Kidney Day celebrations around the world included:

- The launch of the Rediscovering Food & Flavours Cookbook by renowned TV chef Lawrence Keogh, from BBC One's Saturday Kitchen and Roast restaurant in London's Borough Market (developed in conjunction with Shire).
- A lecture at Benhah University in Benhah, Egypt, on how to prevent and screen a high-risk population for CKD; how to prevent and manage high blood pressure; and the role of environmental pollutants, a cause of CKD in the region.
- An educational symposium held by the Japan Association of Chronic Kidney Disease Initiative and The Kidney Foundation, Japan.
- A presentation and recipe contest to encourage healthy, kidney-friendly meals in Vancouver, British Columbia.
- A cultural event in Nagpur, India, with songs, dance, drama, and more, with dialysis technicians and nurses providing some of the entertainment.
- In Yangon, Myanmar, a 20-minute television broadcast on CKD.
- A march with the public, local celebrities, health leaders, and professionals to promote World Kidney Day in Casablanca, Morocco.
- A bicycle ride by three nephrologists in Cardiff, U.K., to raise money for dialysis centers.

For more information on how you can participate in ASN advocacy, please contact ASN Director of Policy and Public Affairs Paul Smedberg at (202) 416-0646 or psmedberg@asn-online.org.

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- **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]

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- 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, Fan Q. A comparison of sevelamer and calcium-based phosphate binders on mortality, hospitalization, and morbidity in hemodialysis: a secondary analysis of the dialysis clinical outcomes revisited (DCOR) randomized trial using claims data. Am J Kidney Dis. 2008;51:445-454. **5.** PhosLo® [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):S17-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

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