ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

KidneyNews

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Study Reveals Deadly Effects of Inactivity for Kidney Transplant Recipients

By Tracy Hampton

A new study indicates that not getting enough exercise can be fatal for kidney transplant patients.

"From our research we can conclude that a low level of physical activity is a new—and modifiable—risk factor for cardiovascular and all cause mortality in these patients," said Dorien Zelle, of the University Medical Center Groningen, in the Netherlands, lead author of the *Clinical Journal of the American Society of Nephrology (CJASN)* study.

Intervention trials are needed to investigate whether increasing physical activity levels may improve outcomes after transplantation, she added.

The price of inactivity

Patients with advanced chronic kidney disease, particularly those receiving dialysis, tend to get little exercise. Most increase their physical activity after receiving a kidney transplant, but only slightly. Studies in the general population have shown that low levels of physical activity increase individuals' risk for cardiovascular disease and premature death. Zelle and her colleagues looked to see whether the same holds true for kidney transplant recipients.

Maintaining heart health is particularly important for these patients, given that kidney transplant recipients have a fourfold to sixfold increased risk of dying of heart-related causes than do individuals in the general population.

"Partly this is due to clustering of several risk factors. High cholesterol, high blood pressure, and obesity are often seen after transplantation and create a 'bad' risk profile," said Zelle.

To study whether low exercise levels are linked to cardiovascular disease and premature death in kidney transplant recipients, Zelle and her team studied the health of 540 kidney transplant recipients between 2001 and 2003, assessing physical activity through questionnaires and recording deaths until August 2007. With regard to the guidelines for minimum requirements

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Research Sheds Light on Racial and Ethnic Disparities in Kidney Transplantation

Persistent inequities in accessing kidney transplants have been described for most racial and ethnic groups in the United States, and now investigators have uncovered some of the reasons behind them (Hall Y, et al. Racial and Ethnic Differences in Rates and Determinants of Deceased Donor Kidney Transplantation. *J Am Soc Nephrol*, April 2011). The findings indicate that greater efforts are needed to overcome the varied hurdles faced by different racial and ethnic minorities in obtaining organs.

"Our research is important in that it provides a structural framework to address shared as well as race- or ethnicity-specific barriers in accessing kidney transplantation," said lead author Yoshio Hall, MD, of the University of Washington in Seattle.

Unequal access

Numerous studies have investigated inequities in kidney transplantation, but none have examined race-specific factors that contribute to diminished access to, or delayed completion of, deceased donor kidney transplantation among all major racial and ethnic groups. Therefore, despite the increasing diversity of patients receiving dialysis who need kidney transplants, the effects of factors such as histocompatibility, health insurance coverage, poverty, and other socioeconomic factors on transplantation rates remain poorly understood.

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Inside

“OUR PATIENTS’ KIDNEYS ARE FAILING THEM. WE WON’T.”

— **Heather Dean and Janice MacKay**
Kidney Marchers, 2010 and 2011

A BELIEF IN TRIUMPH, 100 KILOMETRES LONG

Inspirational Kidney March Story, #483 Registered Nurses in the Southern Alberta Renal Program for years and renal activists in Calgary, Heather Dean and Janice MacKay know that chronic kidney disease is irreversible, but they won’t surrender. They work on tirelessly, in the belief that the human spirit can strengthen the life force in any patient. They walk on tirelessly, too: This September at the breathtaking, three-day Kidney March, they will be joined by a thousand kindred spirits in what will surely be a peak experience — literally: a heroic trek right through Kananaskis Country!

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Deadly Effects of Inactivity

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of physical activity, 260 (48 percent) of patients were not meeting the criteria, and 79 (14.6 percent) were completely inactive.

During the study period, 81 patients died, 37 of whom succumbed to cardiovascular ailments. Those with lower levels of physical activity experienced higher rates of death. Cardiovascular deaths occurred in 11.7 percent of patients considered inactive, 7.2 percent of those considered moderately active, and 1.7 percent of those who were active. Deaths resulting from any cause occurred at rates of 24.4 percent, 15.0 percent, and 5.6 percent in these respective groups.

Kidney specialists not involved with the research said that the findings provide valuable information for physicians and patients.

"There seems to be relatively little attention devoted to self-care among kidney transplant recipients besides issues of medication adherence, and there does not seem to be enough scientific research on patient-related modifiable factors influencing graft or patient survival," said Elisa Gordon, PhD, MPH, of the Northwestern University Transplant Outcomes Research Collaborative in Chicago. "Thus, this paper makes a very nice contribution toward clearly showing the significant association of the patient-related factor of physical activity with patient survival."

Gordon also noted that the study suggests a direct effect of exercise on kidney health.

"The authors found that physical activity levels are related to creatinine clearance. In my own research, I similarly found that physical activity levels are related to estimated glomerular filtration rates, suggesting that graft function is affected by physical activity," she said. (Gordon EJ et al., *Transpl Int* 2009; 22:990–998).

Jamie MacDonald, PhD, of Bangor University's School of Sport, Health and Exercise Sciences and the Renal Unit at Gwynedd Hospital in the United Kingdom, added that the study's finding of a linear dose–response effect between physical activity and risk reduction is of particular note.

"Previous studies in patients with chronic kidney disease have shown reverse epidemiology between certain risk factors and outcome—such as body mass index—or a ceiling effect with the highest levels of physical activity not necessarily inferring greater benefit for survival," MacDonald said.

Interventions needed

Zelle noted that there may be several reasons why kidney transplant recipients have low levels of physical activity. Exercise capacity is approximately 30 percent lower in these patients than in control individuals, and patients often have low muscle mass before transplantation as a consequence of their chronic kidney disease and dialysis treatments.

"A lack of physical activity after transplantation can adversely affect muscle mass; so it's obvious that to restore and maintain muscle mass after transplantation, regular physical activity is required," said Zelle.

Zelle noted that it has become a habit for kidney transplant recipients to be inactive. "Before transplantation most patients had very low levels of physical activity mainly because of the burden of being a dialysis patient," she said.

Although this study did not assess the causes of low physical activity levels in kidney transplant recipients, Gordon's work has indicated that patients' psychosocial factors are involved and that patients reported that transplant professionals inconsistently communicated to them about engaging in physical activity (Gordon EJ et al., *Clin Transplant* 2010; 24:E69–81; Gordon EJ et al., *Chronic Illn* 2009; 5:75–91).

Zelle and her coauthors, in collaboration with researchers at the University Medical Center Maastricht, plan to design a randomized controlled lifestyle intervention study to determine whether increased physical activity can improve the health and prolong the lives of transplant recipients. Patients will take part in a supervised exercise program and receive individual counseling to promote exercise and a healthy diet.

"It is often hard to change habits, and we hope that our intervention program will provide help in this," said Zelle.

MacDonald offered some recommendations for other types of studies that should be conducted. "Researchers should consider further epidemiologi-

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Racial and Ethnic Disparities

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Hall and his colleagues looked into the issue by examining historical data extracted from the U.S. Renal Data System, a national data registry of patients with end stage kidney disease. The data they analyzed included the rates and determinants of waitlisting and deceased donor kidney transplantation among 503,090 nonelderly adults of different racial and ethnic groups who began receiving dialysis between 1995 and 2006. They followed up the patients through 2008.

The annual rates of deceased donor transplantation from the time dialysis was begun were lowest in American Indians/Alaska Natives (2.4 percent) and blacks (2.8 percent), intermediate in Pacific Islanders (3.1 percent) and Hispanics (3.2 percent), and highest in whites (5.9 percent) and Asians (6.4 percent).

The investigators noted that lower rates of deceased donor transplantation among most racial and ethnic minority groups appeared primarily to reflect differences in time from waitlisting to transplantation, but this was not the result of higher rates of waitlist inactivity or removal from the waitlist. Determinants of delays in time to transplantation differed substantially by racial or ethnic group, and the fraction of the reduced transplant rates attributable to demographic, clinical, socioeconomic, linguistic, and geographic factors varied from 14 percent in blacks to 43 percent in American Indians/Alaska Natives compared with whites.

"Blacks, American Indians, and Alaska Natives face continued difficulty in accessing the transplant waitlist, primarily due to socioeconomic factors," Hall said, "while Hispanics, Asians, and Pacific Islanders encounter delays from the waitlist, which may be adversely influenced by regional organ availability, linguistic isolation, and perhaps cultural isolation."

Compared with whites, the disparity in transplant rates attributed to adjustment for health insurance coverage and local poverty rate were 18 percent in blacks, 15 percent in Hispanics, and and 23 percent in American Indians/Alaska Natives. Among Hispanics and Pacific Islanders, disparity was mostly attributed to geographic variation in organ availability (14 percent and 19 percent, respectively) and to difficulty with English among all household members (7 percent and 6 percent, respectively). By contrast, the latter accounted for little to none of the reduced rate of transplantation among blacks and American Indians/Alaska Natives.

"This paper is an important first step in examining racial-ethnic disparities in kidney transplantation," said Devin Eckhoff, MD, who was not involved with the work and is a professor in the department of surgery at the University of Alabama at Birmingham. "The authors have identified several factors that contribute to this disparity, from difficulty accessing the transplant list secondary to socioeconomic factors, to delays to transplantation which may be adversely influenced by regional organ availability, and to linguistic and perhaps cultural isolation."

Looking forward

According to the authors, the findings suggest that current kidney allocation algorithms need to be re-evaluated to reduce persistent racial and ethnic disparities. Recent efforts to reduce disparities in kidney transplantation have focused on improving access to the transplant waitlist. Although efforts such as expanding health insurance coverage will likely improve transplant access for some groups, effective interventions to increase deceased donor transplant rates once patients are waitlisted are more likely to have more consistent benefits in reducing waiting times for all racial and ethnic minority groups, the investigators said.

The results also indicate that region- and center-level efforts targeted to address specific racial and ethnic delays in accessing transplantation may also be important.

"Looking forward, our study suggests that interventions to address local population-specific barriers to transplantation may help to reduce overall racial, ethnic, and socioeconomic disparities in kidney transplantation," Hall said.

In cases where waitlisted minorities encounter delays in receiving a deceased donor transplant because they live in an area where English is not the first language, the authors suggest that increasing provider awareness and providing training to better identify patients with limited English proficiency or inadequate health literacy might allow more efficient use of interpreters and culturally appropriate educational materials regarding kidney transplantation.

Eckhoff noted that region- and center-level efforts targeted to address local racial and ethnic minority delays in accessing transplantation may help reduce disparities in kidney transplantation.

"However, the real tragedy is the limited organ supply," he said. "All racial and ethnic groups, despite differences in the annual rate of deceased donor transplantation, are waiting too long. The take-home message should be that we need to redouble our efforts to increase the organ supply."

Study coauthors include Ping Xu, Ann O'Hare, MD (University of Washington, Seattle); Andy Choi, MD (University of California San Francisco); and Glenn Chertow, MD (Stanford University). The study is dedicated to Dr. Andy Choi, who died unexpectedly during final modification of the study manuscript. His coauthors noted that Dr. Choi was an extremely talented, dedicated, and passionate physician scientist whose primary clinical and research goal was to improve the prevention and treatment of kidney disease among traditionally underserved populations. His expertise in biostatistics and epidemiologic methods were critical to the success of the study. They are

deeply saddened by his untimely death.

Disclosures: Dr. Ann O'Hare reported receiving royalties from UpToDate, Inc. All other authors reported no financial disclosures.

Deadly Effects of Inactivity

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cal studies, perhaps using time-lagged analyses to provide stronger evidence of cause and effect. Funding bodies can also have greater confidence to support experimental exercise intervention studies," he said. "These types of studies will not only strengthen the evidence base for physical activity, but by elucidating mechanisms may also identify further targets for intervention. For example, does a lack of physical activity cause low muscle mass or the other way around?"

Gordon suggested some immediate steps that can be taken. "In my opinion, these findings underscore the need for transplant health care providers and nephrologists to routinely recommend engaging in physical activity and specify required amounts and types of exercise, emphasize the importance of engaging in physical activity, and address any barriers that patients may have such as limited self-efficacy. Also, transplant or health care centers should promote a chronic care model approach to support kidney transplant recipients such as through the provision of rehabilitation centers."

Study coauthors include Eva Corpeleijn, PhD, Ronald Stolk, MD, Mathieu de Greef, PhD, Reinold Gans, MD, Gerjan Navis, MD, and Stephan Bakker, MD, PhD (University Medical Center Groningen, the Netherlands).

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Letters

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Practice Pointers

RAAS Blockade: A Two-Edged Sword?

This month, Kidney News *interviews Laurence Carroll MD, FASN, with the ASN Practicing Nephrologists Advisory Group.*

What is "renoprotection"? When was it coined or first used?

"Renoprotection" is the concept of limiting or reversing progressive kidney injury via maneuvers such as proteinuria or blood pressure reductions. Clinical evidence of possible benefit was shown in diabetic nephropathy by C.E. Mogenson in 1976 (*Scand J Clin Lab Invest* 36; 1976:383–388), who used the term "renoprevention" in a subsequent paper (*Clin Invest Med* 14; 1991:642–651).

Of course, the concept of glomerular hypertension and hyperfiltration kidney injury had been formulated in the 1980s by Neuringer and Brenner (*Am J Kid Dis* 1993; 22:98–104) and then applied with renin–angiotensin–aldosterone system (RAAS) blockade (angiotensin-converting enzyme [ACE] inhibitors) in 1993 first with type I diabetics (Lewis et al., *N Engl J Med* 1993; 329:1456–1462). Later type II diabetics (vide infra) and nondiabetic proteinurics were shown to benefit in additional studies of RAAS blockade (e.g., angiotensin receptor blockers [ARBs]-vide infra), leading one editorialist to ponder: "Renoprotective therapy: how good can it get?" (Hebert, *Kidney Int* 2000; 57:343–344).

Recently, M. A. Onuigbo used the term "renoprevention" to define efforts to avoid progressive chronic kidney disease (CKD) by avoiding nonsteroidal anti-inflammatory drugs, radiocontrast exposure, and volume depletion (Onuigbo, *QJM* 2009; 102:155–167) as well as stopping RAAS blockade to allow stabilization in stage 4 CKD and more time for dialysis access creation and preemptive kidney transplant (Ahmed et al., *NDT* 2010; 25:3977–82).

What is LORFFAB (late onset renal failure from angiotensin blockade)?

Late Onset Renal Failure from Angiotensin Blockade (LORFFAB) was described by M. Onuigbo in a series of publications beginning in 2008. He followed a group of older patients who demonstrated significant worsening with angiotensin blockade (>25 percent increase in serum creatinine). Off such therapy, most showed subsequent improvement and stabilization in kidney function (*Int Urol Nephrol* 2008; 40:233–239). Whether these changes represent a true change in the progression of their CKD or a transient hemodynamic phenomenon awaits further study and confirmation.

What is SORO-ESRD (syndrome of rapid onset end stage renal disease), and how is it different from classic ESRD?

The term "SORO-ESRD" (syndrome of rapid onset end stage renal disease) also comes from Onuigbo's 100-patient cohort described above. When Onuigbo looked at the 17 patients who did not improve off angiotensin blockade, 88 percent had an acute kidney injury (AKI) event before ESRD. The role of AKI in progressive CKD is increasingly recognized (Venkatachalam et al., *Am J Physiol Renal Physiol* 2010; 298:F1078–F1094) and adds a new perspective on the well-accepted model of hyperfiltration-mediated progressive kidney injury.

Please comment on the ONTARGET (Renal Outcomes with Telmisartan, Ramipril, or both, in people at high vascular risk) study, whereby dual RAAS blockade was shown to be effective in reducing albuminuria, but was also associated with a doubling of creatinine and need for dialysis.

The ONTARGET study was performed in a population with relatively preserved kidney function (GFR 50–70 mL/min) and showed higher risk of hyperkalemia and no benefit with combined ACE inhibitor/ARB therapy. Whether other combinations (with aldosterone blockade or renin inhibitor) will prove to be better remains to be seen. Until more information is available, we remain in a quandary, as shown in two recent minireviews by Weir et al. (*Kidney Int* 2010; 78:539–545) and Bakris (*Kidney Int* 2010; 78:546–549).

Should RAAS blockade be discontinued prior to coronary artery bypass graft surgery? Contrast requiring procedures? Is there any literature to support this at this time?

Since my first experience with Captopril, I, like most clinicians, have found that volume depletion situations are aggravated by RAAS blockade and have sought to counsel my patients about discontinuing those drugs during times of gastrointestinal upset or poor intake. Other situations in which RAAS blockade may need to be withheld include aggressive diuresis, surgery, or contrast exposure. Ongoing ACE inhibitor/ARB therapy use has been associated with a >25 percent risk of AKI in cardiac surgery (Arora et al., *Clin J Am Soc Nephrol* 2008; 5:1266–1273), and RAAS blockade has also been associated with a threefold increase of contrast-induced nephropathy.

Is there a particular subset of CKD patients who should not be subjected to RAAS blockade?

We all have seen warnings that bilateral renal artery stenosis and unilateral stenosis in a solitary kidney could result in acute renal failure with RAAS blockade. Based on the above discussion, RAAS blockade use in the elderly and in volume-stressed scenarios (e.g., chronic diarrhea) requires close follow-up. I think another way to ask this question would be "When should we stop RAAS blockade?" (e.g., in stage 4 CKD to allow time for access placement and transplant workup).

Over the past several years, numerous trials have been published proving the beneficial effects of RAAS blockade. Is there any literature to suggest that these agents are more detrimental?

In addition to what I've already discussed, a Canadian study performed in a cohort of over 6000 diabetic patients showed that ACE inhibitor use did not decrease the long-term risk of ESRD and might actually increase it, reporting a relative risk of 4.2 after three years (Suissa et al., *Kidney Int* 2006; 69:913–919).

In 2009, the Canadian Hypertension Education Program recommended against the use of dual RAAS blockade therapy. As a member of the ASN Practicing Nephrologist Advisory Group (PNAG), do you think that this will be a precedent?

I think the role of combined ACE inhibitor/ARB therapy needs to be circumscribed to at least high-grade proteinuria. With the risks of hyperkalemia, I'm concerned that I see that such treatment is used in primary care situations for essential hypertension.

At the same time, I've found that low-dose aldosterone blockade is often a helpful step in treating persistent proteinuria or refractory hypertension when adding it to an ACE inhibitor or ARB (Mehdi et al., *J Am Soc Nephrol* 2009; 20:2641–2650).

We (i.e., PNAG and other advisory groups) should advise caution but not make any blanket statement against dual RAAS blockade.

In light of all that's been published for and against the use of RAAS blockade therapy, do you have any final practice pointers?

I've found it useful in my own practice to always use a diuretic in patients with CKD and ACE inhibitor/ARB therapy to promote kaliuresis. Before CKD staging, this would include women with serum creatinine levels of ≥1.5 mg and men with levels ≥2.0 mg; today, this would translate with an estimated GFR of 30–60 cc/min (stage 3 CKD) and usually means a loop diuretic. It also would potentiate the antiproteinuric effect of RAAS blockade.

Policy Update

CMS Proposes Maintaining Current ESA Coverage Policy

By Rachel Shaffer

Nephrologists would maintain current flexibility in prescribing erythropoiesis stimulating agents (ESAs) to patients on dialysis and to those with chronic kidney disease (CKD) who are not on dialysis under a Centers for Medicare and Medicaid Services (CMS) proposed memorandum.

If the proposal not to issue a National Coverage Decision (NCD) for ESAs is finalized, the current policy for ESA coverage would remain in place with no changes.

The March 16 release of the proposed memorandum marks the end of an approximately yearlong CMS examination of the evidence regarding the effects of ESAs on health outcomes for patients with CKD, both those receiving and those not receiving dialysis, known as a National Coverage Analysis (NCA). Based on the findings of an NCA, CMS often issues a National Coverage Determination (NCD), which specifies the exact indications for which CMS will provide reimbursement for the drug. CMS concluded that the evidence gathered in the NCA on ESAs did not generate sufficient evidence to warrant a policy change.

CMS' proposal not to issue an NCD at this time is widely viewed in the renal community as a positive outcome. Prior to the release of the proposed memorandum, concern existed that CMS might issue an NCD that would permit reimbursement for ESA administration only to patients with certain hemoglobin levels—specifically, to patients with hemoglobin levels below the 10–12 g/dL range specified by the ESRD Quality Improvement Program (QIP), which takes effect on January 1, 2012. The discrepancy between reimbursement policy and the QIP quality measures would have almost certainly posed a challenge for nephrologists and providers, with potential effects on patient care.

"I am generally pleased that CMS has proposed not to issue an NCD for ESAs at this time," commented ASN Public Policy Board Chair Thomas Hostetter. "CMS clearly took into account the comments and testimony ASN submitted to CMS regarding the NCA on ESAs. If finalized, I believe this will enable patients and their nephrologists to continue to make individualized decisions about ESAs and at least has avoided a potential conflict with the recently introduced QIP for care of anemia in ESRD."

The potential lack of any NCD has for some, however, raised questions about what could happen at the local level in terms of ESA coverage. Technically, when no NCD exists, regional Medicare contractors have the option to consider instituting a Local Coverage Decision (LCD) for products and services. However, it is highly unlikely that a regional contractor would choose to attempt to change the current policy of reimbursing ESA administration for three reasons.

First, because no NCD for ESAs existed in the past, regional contractors have long had the potential to conduct an LCD but have historically chosen not to do so. If CMS decides to finalize its proposal not to issue an NCD, it does not create any opportunities for regional contractors to consider LCDs that did not previously exist. Second, the U.S. Food and Drug Administration did not recommend any changes to current labeling for patients either on dialysis or not on dialysis at its most recent meeting examining the safety and efficacy of ESAs. Third, because CMS was unable to generate sufficient evidence to warrant a change in ESA coverage at the national level, it is unlikely that a regional contractor would be able to do so.

CMS is accepting public comments on its proposal not to issue an NCD until April 15, 2011, and expects to issue a final memorandum in mid-June 2011.

To learn more about ASN's advocacy efforts with CMS regarding the NCA, please visit the ASN patient care public policy webpage at www.asn-online.org/policy_and_public_affairs.

ASN Advocates on World Kidney Day 2011

In honor of World Kidney Day 2011, ASN ascended Capitol Hill to advocate on behalf of patients with kidney disease and the nephrologists who treat them. World Kidney Day, a global kidney disease awareness day, this year highlighted the theme "Protect Your Kidneys and Save Your Heart," emphasizing the important links between kidney disease and cardiovascular disease.

ASN President Joseph Bonventre, MD, PhD, FASN, and ASN Public Policy Board Chair Thomas Hostetter, MD, visited five congressional offices on World Kidney Day in March.

"It is essential that we help the public and lawmakers recognize the importance of research in understanding the link between kidney disease and cardiovascular disease," Bonventre said. "World Kidney Day is a prime opportunity for the kidney community to raise awareness about improving the health of millions of kidney and heart patients."

Besides raising awareness of the relationship between kidney disease and heart disease, Bonventre and Hostetter emphasized the vital importance of supporting kidney research at the National Institutes of Health (NIH) and other federally funded agencies.

"It's clear that this is a really crucial time for the kinds of things that we're interested in. NIH is under lots of pressure, even pressure to be cut," Hostetter said. "Research is really critical for patient care and alleviating the kind of suffering we know happens with kidney patients. But there are other issues that people on the Hill need to know about."

Hostetter and Bonventre also advocated for extending lifetime coverage for immunosuppressive drugs for kidney transplant recipients, and explained the necessity of maintaining access to medications and services for all patients with kidney disease as CMS implements new policies such as the End-Stage Renal Disease Quality Improvement Program and considers decisions about national coverage for erythropoiesis-stimulating agents (ESAs).

Further, Hostetter said, "Part of our job on the Hill is not just to advocate for these three specific messages, but to raise members' and staffers' awareness of kidney disease issues in general, and let them know that there are people like us who care about these issues not only for ourselves but for the patients we take care of."

Other ASN World Kidney Day awareness efforts included the Public Policy Board's publication of an editorial in *JASN*; working with the NIDDK Director's office to draft a World Kidney Day announcement distributed on the NIH listserve; and attending the World Kidney Day congressional reception.

ASN Launches First Annual Hill Day

On May 4–5, 2011, ASN will launch the first annual ASN Hill Day to raise awareness of kidney disease in the halls of Congress and among federal agencies. ASN will meet with Congressional members, key legislative staff members, and administrators in federal agencies including CMS, the Department of Veterans Affairs (VA), and the Agency for Healthcare Research and Quality.

"By organizing the first annual ASN Hill Day, ASN continues to show leadership advocating on behalf of patients with kidney disease by engaging the nation's decision-makers on the issues most important to our community," said Thomas Hostetter, MD, chair of the ASN Public Policy Board.

In addition to ASN staff, members of the ASN Council, Public Policy Board, and Board of Advisors will participate in advocacy visits on Hill day. Visits will focus on three main advocacy priorities: sustained, robust funding for medical research; increasing the success rate of transplants through the availability of immunosuppressive drugs; and ensuring quality and access for patients in new care delivery systems.

To make ASN Hill Day a success, ASN encourages all ASN members to actively engage their Congressional representatives. In May, ASN will reach out to the membership to contact Congress in support of the society's advocacy priorities and the dedicated efforts of the participants in ASN Hill Day 2011.

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- **ASN Kidney Week 2011** remains the world's premier gathering of kidney professionals presenting advances in treatment, research, and education.

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- Experience as a specialist in kidney disease and related conditions.

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Journal View

Rise in Creatinine After Heart Surgery Linked to CKD and Mortality Rates

Patients with greater increases in creatinine after cardiac surgery are at higher risk of incident chronic kidney disease (CKD), progressive CKD, and death, reports the *Archives of Internal Medicine*.

The study included data on 29,388 patients undergoing cardiac surgery at Veterans Affairs hospitals between 1999 and 2005. For each patient, the postoperative increase in creatinine was determined and classified as no change, a peak postoperative increase of 1 percent to 24 percent (class I), increase of 25 percent to 49 percent (class II), increase of 50 percent to 99 percent (class III), or increase of 100 percent or greater (class IV). Rates of postoperative CKD, progressive CKD, and death were compared between groups.

Rates of all three outcomes increased in monotonic fashion along with the magnitude of change in creatinine. At three months' follow-up, hazard ratios (HRs) for incident CKD were 2.1 for patients in class I, 4.0 in class II, 5.8 in class III, and 6.6 in class IV. Hazard ratios for CKD progression were 2.5, 3.8, 4.4, and 8.0; whereas HRs for long-term mortality were 1.4, 1.9, 2.8, and 5.0, respectively.

The associations were strongest in the immediate postoperative period, becoming weaker with longer follow-up. However, even at five years, most associations remained significant—for all outcomes, patients in class IV had approximately a twofold increase in risk.

Acute kidney injury (AKI) is common among hospitalized patients, particularly those undergoing cardiac surgery. Recent studies have challenged the assumption that as long as patients survive the episode, there are no long-term sequelae of AKI.

This study shows increased long-term risks of CKD and death among cardiac surgical patients with AKI. These risks increase along with the magnitude of the postoperative increase in creatinine. Although the risks are greatest between 3 and 24 months after cardiac surgery, they remain significant even at five years' follow-up [Ishani A, et al. The magnitude of acute serum creatinine increase after cardiac surgery and the risk of chronic kidney disease, progression of kidney disease, and death. *Arch Intern Med* 2011; 171:226–233].

Tamoxifen Reduces Mortality in Encapsulating Peritoneal Sclerosis

For peritoneal dialysis patients with encapsulating peritoneal sclerosis (EPS), treatment with tamoxifen is associated with a lower risk of death, according to a study in *Nephrology Dialysis Transplantation*.

The retrospective study included 63 patients with severe EPS from eight Dutch centers. All had severe intestinal obstruction leading to persistent clinical problems, requiring surgery, immunosuppressive therapy, and/or total parenteral nutrition. Enrolled between 1996 and 2007, patients were followed up until 2008. Survival was compared for 24 patients treated with tamoxifen versus 39 patients not receiving tamoxifen; the two groups had similar clinical and demographic characteristics.

Overall mortality was 45.8 percent in patients treated with tamoxifen versus 74.4 percent in those not receiving tamoxifen. On multivariate adjustment for a wide range of factors—including presence of a functioning kidney transplant, concomitant prednisolone, and total parenteral nutrition—there was a trend toward improved survival in the tamoxifen group. (The associated hazard ratio was 0.39, although the difference did not achieve significance.)

Encapsulating peritoneal sclerosis is a serious complication of peritoneal dialysis, with high morbidity and mortality. In the absence of data on efficacy, there is no uniform treatment approach. Through its effects on the profibrotic cytokine transforming growth factor-β, tamoxifen may be effective in fibrotic diseases such as EPS.

This multicenter experience shows lower mortality with tamoxifen treatment in patients with severe EPS. A trend toward improved survival was independent of other potentially beneficial treatments. Added to supportive therapy, tamoxifen may improve outcomes for patients with this life-threatening condition [Korte MR, et al. Tamoxifen is associated with lower mortality of encapsulating peritoneal sclerosis: results of the Dutch Multicentre EPS Study. *Nephrol Dial Transplant* 2010; 26:691–697].

Immediate Catheter Removal "Mandatory" in Fungal Peritonitis

For peritoneal dialysis patients who develop fungal peritonitis (FP), mortality is dramatically lower if the catheter is removed within 24 hours, reports a study in *Peritoneal Dialysis International*.

The retrospective analysis included data on 94 cases of FP (in 92 patients) occurring among 1926 peritoneal dialysis patients in a Japanese university health system between 1992 and 2008. The FP cases accounted for 4.0 percent of all peritonitis episodes and 4.8 percent of patients. The researchers analyzed risk factors associated with mortality from FP, including the impact of immediate catheter removal.

Turbid dialysate was the most common presenting symptom, followed by abdominal pain and fever. Three-fourths of FP cases were caused by candidal species, most commonly *Candida albicans*. Catheter removal was immediate (within 24 hours) in 41.5 percent of episodes and delayed (between 2 and 9 days) in 44.7 percent. Overall mortality from FP was 28.7 percent. A switch to hemodialysis was necessary in 62.8 percent of patients, although 8.5 percent were able to resume peritoneal dialysis.

Mortality was 12.8 percent in patients with immediate catheter removal, compared with 31.7 percent in those with delayed removal. On multivariate analysis, delayed removal was a strong risk factor for death, odds ratio 13.73. Intestinal obstruction and elevated white blood cell counts in peripheral blood and peritoneal dialysis effluent were also independent predictors of mortality.

Fungal infection is a relatively uncommon but potentially life-threatening complication of peritoneal dialysis. Recent recommendations suggest prompt catheter removal immediately after fungi are identified.

This study shows a sharply increased risk of death in patients with FP when catheter removal is delayed by more than 24 hours. On the basis of their findings, the researchers concluded that immediate catheter removal is "mandatory" after a diagnosis of FP in peritoneal dialysis patients [Chang TI, et al. Early catheter removal improves patient survival in peritoneal dialysis patients with fungal peritonitis: results of ninety-four episodes of fungal peritonitis at a single center. *Perit Dial Int* 2010; 31:60–66]

Nephron-Sparing Surgery for Larger Renal Tumors

In elderly as well as younger patients with renal tumors larger than 4 cm, nephron-sparing surgery (NSS) provides superior long-term kidney function, according to a study in the urology journal *British Journal of Urology International*.

The research analyzed outcomes data from 829 patients with renal tumors measuring larger than 4 cm treated between 1981 and 2007. After exclusion of patients with imperative indications and metastases, the analysis included 81 patients younger than 55 years and 85 elderly patients (older than 65). Nephron-sparing surgery was performed in 36 of the younger patients and 33 of the elderly patients. The remaining patients (45 younger and 52 elderly) underwent radical nephrectomy (RN). Complication rates and outcomes, including risk of long-term chronic kidney disease (CKD), were compared between groups.

The younger patients had significantly larger tumors: median 6 cm, compared with 5 cm in the elderly group. There was no difference in complication rates between the two age groups, or between NSS patients and RN patients in either age group.

At a median follow-up of 5.5 years, rates of CKD (defined as a GFR less than 60 mL/min/1.73 m^2) were significantly lower after NSS. In the younger group, CKD occurred in 15.5 percent of NSS patients versus 31.1 percent of RN patients. In the elderly group, the rates were 50.9 percent versus 24.2 percent, respectively. Within age groups, there was no significant difference in overall survival between patients undergoing NSS and those undergoing RN.

The incidence of renal tumors is increasing, particularly among patients in their 70s and 80s. Nephron-sparing surgery is recommended for patients with tumors measuring 4 cm or smaller, but it is often withheld from older patients.

This study showed better long-term maintenance of renal function with NSS for tumors larger than 4 cm in younger patients and in carefully selected elderly patients. In both age groups, the risk of CKD is higher after RN than with elective NSS. On the basis of these results, NSS provides a better functional outcome without compromising oncologic control [Chang TI, et al. Perioperative morbidity and renal function in young and elderly patients undergoing elective nephron-sparing surgery or radical nephrectomy for renal tumors larger than 4 cm. *BJUI* 2011; 107:554–561].

Risk Alleles for Idiopathic Membranous Nephropathy Identified

A genomewide association study identifies two risk alleles for idiopathic membranous nephropathy, suggesting an autoimmune cause of this condition, reports the *New England Journal of Medicine*.

The researchers performed independent genomewide association studies of patients with biopsy-confirmed idiopathic membranous nephropathy from three cohorts of white ancestry. The cohorts included 75 French, 146 Dutch, and 335 British patients. On joint data analysis, alleles at two loci were identified as significantly associated with idiopathic membranous nephropathy. One was the gene encoding the M-type phospholipase A_2 receptor (PLA_2R1) (rs4664308), previously reported as the target of an autoimmune response.

The other allele was the gene encoding HLA complex class II HLA-DQ α chain 1 (HLA-DQA1) (SNP rs2187668) on chromosome 6p21. The latter association was significant in all three study cohorts. Odds ratios for idiopathic membranous nephropathy among homozygous subjects were 20.2 for the HLA-DQA1 risk allele, 4.2 for the PLA2R1 allele, and 78.5 for both alleles.

Despite its importance as a cause of nephrotic syndrome in adults, the etiologic factors behind idiopathic membranous nephropathy remain unclear. The observation of familial cases suggests a genetic contribution.

This study identified two risk alleles associated with idiopathic membranous nephropathy in white populations. The HLA-DQA1 risk allele may facilitate autoimmune responses, with the variant PLA2R1 being among the possible targets [Stanescu HC, et al. Risk HLA-DQA1 and PLA2R1 alleles in idiopathic membranous nephropathy. *N Engl J Med* 2010; 364:616–626].

Belatacept Shows BENEFITs in Kidney Transplantation

Two-year results from the Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression" (BENEFIT) studies show better renal function with belataceptt-based versus cyclosporine A (CsA)-based immunosuppression in kidney transplant recipients, reports a study in *Transplantation*.

The analysis included 666 patients enrolled in BENEFIT and 347 in the BENEFIT-EXTended criteria donors (BENEFIT-EXT) study. Patients were randomly assigned to more intensive or less intensive belatacept-based immunosuppression, or to a CsA-based regimen. As previously reported, the belatacept groups had better renal function and an improved cardiovascular/metabolic risk profile at one year, with similar patient and graft survival. There was evidence of a higher acute rejection rate and posttransplant lymphoproliferative disorder (PTLD)-particularly of the central nervous system-with belatacept.

At two years, rates of patient survival with a functioning graft were similar in both groups: over 90 percent in BENEFIT and over 80 percent in BENEFIT-EXT. The belatacept groups continued to have better renal function than the CsA group: calculated glomerular filtration rate was 6 to 17 mL/min higher in BENEFIT and 8 to 10 mL/min higher in BENEFIT-EXT. Few new acute rejection events occurred in the second year.

The PTLD rate was highest in patients negative for Epstein-Barr virus (EBV). On efficacy analysis of EBV-positive patients, the results were consistent with the overall study population. Two cases of PTLD (previously reported) developed in the belatacept groups in each study between one and two years. The overall balance of safety to efficacy favored the less intensive belatacept regimen.

Through two years, belatacept-based immunosuppression provides better renal function, with similar patient and graft survival, compared to a CsA-based regimen. The results are similar in EBV-positive patients, and no new safety problems have emerged in the second year of follow-up. Three-year outcome studies are planned [Larsen CP, et al. Belatacept-based regimens versus a cyclosporine A-based regimen in kidney transplant recipients: 2-year results from the BENEFIT and BENEFIT-EXT studies. *Transplantation* 2010; 90: 1528-1535].

rt-PA Prevents Dialysis Catheter Problems

Once-weekly use of recombinant tissue plasminogen activator (rt-PA) for catheter locking reduces the rate of central venous catheter problems in patients receiving long-term hemodialysis, reports a trial in the *New England Journal of Medicine*.

The multicenter "Prevention of dialysis catheter lumen occlusion with rt-PA versus heparin" (PreCLOT) trial included 225 long-term hemodialysis patients with a newly inserted central venous catheter. One group received a standard catheter-locking regimen, consisting of heparin 5000 U/mL used three times weekly. In the other group, rt-PA, 1 mg in each lumen, was used in place of heparin at one of the three weekly sessions. After six weeks, rates of catheter malfunction and catheter-related bacteremia were compared between groups.

Standard thrice-weekly heparin was associated with a 34.8 percent rate of catheter malfunction, compared with 20.0 percent with once-weekly rt-PA, hazard ratio 1.91. Catheter-related bacteremia was also more frequent in the heparin group: 13.0 percent versus 4.5 percent, hazard ratio 3.30. Despite the high cost of rt-PA, the incremental cost of care per episode of catheter-related bacteremia prevented was much lower in the rt-PA group. Bleeding and other adverse events were similar between groups.

Central venous catheters used for vascular access in hemodialysis patients are associated with high failure rates, most often related to thrombosis. Catheter-locking regimens are used to prevent thrombosis and may also lower the risk of catheter-related infection. Heparin is most commonly used, but one recent study reported better outcomes with rt-PA.

Substituting rt-PA for heparin at one of three weekly sessions reduces the risk of catheter malfunction and bacteremia, the PreCLOT findings suggest. The results were similar in patients with initial and replacement central venous catheters. Study limitations included a low number of malfunctions requiring catheter removal [Hemmelgarn BR, et al. Prevention of dialysis catheter malfunction with recombinant tissue plasminogen activator. *N Engl J Med* 2010; 364:303–312].

Early Initiation of Dialysis Linked to Higher Mortality

As more patients start dialysis at earlier stages, those with a higher estimated glomerular filtration rate (GFR) at dialysis initiation appear to be at increased risk of death, reports a study in *Canadian Medical Association Journal*.

The analysis included Canadian Organ Replacement Register data on 25,910 adult patients starting dialysis between 2001 and 2007. Cases with an estimated GFR above 10.5 mL/min per 1.73 m^2 at the start of dialysis were defined as early initiators. Trends in GFR at the start of dialysis were assessed, and the risk of death was compared for patients with early versus late initiation of dialysis.

Mean estimated GFR at the start of dialysis increased during the period studied: from 9.3 mL/min per 1.73 m^2 in 2007 to 10.2 mL/min per 1.73 m^2 in 2007. Meanwhile, the percentage of patients with early initiation increased from 28 percent to 36 percent. Mean GFR was 15.5 mL/min per 1.73 m^2 among early initiators versus 7.1 mL/min per 1.73 m^2 for late initiators.

Early initiators were at increased risk of death: unadjusted hazard ratio (HR) 1.48. The association was weakened but still significant, HR 1.18, after adjustment for demographic factors, serum albumin level, cause of end stage renal disease, type of vascular access, late referral, and transplant status. The difference in mortality between early and late initiators narrowed after one year. However, the gap started to widen again at 24 months, and remained significant at 30 and 36 months.

In Canada and elsewhere, dialysis is being initiated in patients with higher estimated GFRs. In contrast to the belief that early initiation of dialysis may lead to some advantage in patient outcomes, recent studies have found no survival benefit of starting dialysis at a higher GFR.

The new report provides evidence that patients starting dialysis at a higher GFR are at higher risk of death than those with later initiation of dialysis. The association is attenuated, but remains significant after adjustment for baseline characteristics. Rigorous studies are needed to develop evidence-based guidelines for the optimal timing of dialysis initiation [Clark WF, et al. Association between estimated glomerular filtration rate at initiation of dialysis and mortality. *CMA* 2011; 183:47–53].

Letters

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Fellows Corner

The Nephrology Match Experience for Foreign Medical Graduates: *An IMG's Perspective*

By Fahad Saeed

According to 2009 National Resident Matching Program (NRMP) statistics, international medical graduates (IMGs) comprise more than half—52 percent—of the fellowship applicants matching in nephrology. Here I describe my personal experiences as an IMG on an H1-B visa applying for a nephrology fellowship. I have also applied for fellowships through the couples match program as my wife is pursuing fellowship training in infectious diseases. Although I present my own personal experiences throughout the match process, it is important to keep in mind that these experiences are not in any way unique. Most of my colleagues have encountered many of the same obstacles. Based on my experiences, I suggest mechanisms for improving future nephrology match experiences for other IMGs.

My passion for nephrology was always discouraged by my colleagues. It is commonly believed that acceptance into a nephrology fellowship on an H1-B visa is extremely difficult. Senior residents who had applied for nephrology fellowships in previous years told me to secure my visa status first and then apply for fellowship. Unfortunately, there is no reliable official source of information on this issue.

As an intern, I participated in the American Society of Nephrology (ASN) Resident Program. ASN provides travel support grants to internal medicine residents from across the United States who are interested in nephrology to attend the ASN Annual Meeting. The resident program includes a reception for residents and fellowship program directors. At this reception I had the opportunity to meet nephrology program directors from all regions of the country. Through this event I learned that only a few programs sponsor H1-B visa-holding fellows. In addition, fellows on H1-B visas who are interested in pursuing additional research training as part of fellowship will likely have significant issues with funding while on this visa and may not be afforded opportunities for additional research training. The ASN resident program provided me with the most important information on available fellowship opportunities. Efforts to publicize and promote this program would be helpful to IMG applicants for nephrology fellowships.

In early October 2009, I started sending emails to fellowship programs asking if they would sponsor an H1-B visa applicant. I sent emails to 141 programs listed on the Fellowship and Residency Electronic Interactive Database Access (FRIEDA). By November, I received replies from almost 85 programs—only 35 sponsored fellows on H1-B visas. I applied to all of these programs in early December. A few weeks after applying, I received rejections from three programs because they decided not to sponsor H1-B exist visa applicants that year.

Because nephrology is new in the match, multiple opportunities exist for improving the process for programs and for candidates.

One program later denied me an interview because "they only accept domestic candidates." Later in the interview process, a few more programs that had previously reported sponsorship of H1-B visa holders sent me rejection letters because of a reversal in their visa acceptance policy. Confusion could be prevented if programs would simply and clearly mention their policy toward fellowship opportunities for H1-B visa holders on FRIEDA or their own websites.

In early January 2010, I received my first interview call and ultimately had 15 interviews by the end of March. To my surprise, although I had clearly mentioned on my electronic application that I was applying for a nephrology fellowship through the couples match in which my wife was applying for an infectious disease fellowship, not a single nephrology program coordinated with the infectious disease programs to which my wife had applied. I sent emails to the various infectious disease divisions myself in an attempt to coordinate interview schedules with limited success.

Interview season for infectious disease fellowship positions started somewhat later than nephrology, but the infectious disease program directors coordinated more proactively with nephrology divisions for our interviews. In despair, with fears of not matching at the same institution, my wife and I began making plans for hospitalist positions or possibly even living apart for our fellowship years. Since nephrology is new to the match process, it may be that program directors have limited knowledge about the couples match. Perhaps if the NRMP educated training programs about the couples match process, better coordination between specialties could be achieved and couples would be invited for interviews as a couple, rather than as individuals. Residency training programs have operated with a couples match for years. There is no reason fellowship programs cannot do the same.

Throughout the interview process and in speaking with peers, I also noticed what may be a geographical bias in interviewing fellowship candidates. For example, programs from the East Coast tended to interview only candidates with East Coast addresses on their electronic application. This presumptive bias to select fellows in part based on geographic residence might be reasonable for U.S. graduates but does not hold true for most of the IMGs. Most IMGs do not have families in the United States and their choice of fellowship programs is already limited by visa issues. Thus,

many IMGs do not have geographic constraints for fellowship. During the interview, I sometimes found it very difficult to convince the program director that I did not have a geographical preference for fellowship training. In my opinion, programs need to be mindful of this issue and realize IMGs may be quite willing to move long distances for fellowship training.

I started interviewing in early February and would like to highlight a few of my interview experiences in the hope that my experience may lead to improvements in the process, especially for IMGs. Generally speaking, the expense of one interview is $350 to $400 or even higher. I personally took each interview very seriously. I went to a program in the Midwest through a snowstorm and, to my disappointment, the program director had not even reviewed my application. He glanced through my application during my interview and remarked, "Oh, I did not know that you are on an H1-B visa." My time and the expense of this interview could have been saved since that program was not interested in candidates with H1-B visas.

Some training programs seemed to have a good interview philosophy and process; these program directors seemed genuinely interested and had actually reviewed my entire application. Clearly, interviewers have different styles, but displaying an interest in the fellowship candidates and candidly offering opinions on the strengths and weaknesses of one's training programs are valuable to applicants. Having other fellows available to speak with applicants on the interview day is helpful. Fellow satisfaction was an important consideration for me in making my rank order list.

There are multiple pressures on the candidate during the whole interviewing and matching process. One pressure is to show the program that you are genuinely interested. Most programs seem to want to hear that you are going to rank them first, which obviously is not possible. Clearly both the program and the applicant would like to know each other's probable ranking, but the match was designed to eliminate this issue from the interviewing process. There should be enough respect among the parties to avoid asking this question.

Many programs asked me to name other programs in which I interviewed. This violates NRMP rules. Although it is understandable (an assessment of geographic preference, clinical or research predilection, etc., may be gained by the answer to this question), interviewers should be educated about the need to avoid this inquiry. Some program directors clearly told me to "keep in touch, as this really affects our ranking." However, no specific instruction about how or when to "keep in touch" was provided. One of the program directors spoke to the candidates at the end of the interview and told us not to feel pressured about sending follow-up "thank you" before submission of the NRMP rank list because this would not affect their ranking of us. This small gesture was deeply appreciated by all the candidates at the interview.

My story has a happy ending—my wife and I matched together. Because nephrology is new in the match, multiple opportunities exist for improving the process for programs and for candidates. Programs should clearly state their policy on visa sponsorship. Couples should be considered together during the application process. Interviewing should be a pleasant, informative, and pressure-free experience both for the candidates and the programs. Implementing these simple guidelines will create a positive impression of fellowship programs and provide candidates with a sense of fairness and satisfaction throughout the match process.

Acknowledgments: I thank Jean Holley, MD, and Nehal Patel, PhD, for their review of and suggestions for this article.

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A Training Program Director's Perspective

By Donald Kohan

The nephrology subspecialty, both at the fellow and practitioner level, has a greater percentage of international medical graduates (IMGs) than any other internal medicine subspecialty with the exception of geriatrics. As such, the contributions of IMGs to our field are tremendously important and we must work to continue to make nephrology an attractive career choice for them.

There are a number of challenges relating specifically to potential IMG fellows. Since J-1 and H1-B visa holders are not eligible for funding through the NIH, their options are substantially limited if they are interested in research training. Owing to limitations imposed by many states, obtaining waivers for H1-B holders is difficult if not impossible for many programs. Programs have a wide variety of approaches to J-1 and H1-B visa holders, so getting specific information from individual programs is required. To facilitate this, ASN could develop a list of programs that accept H1-B and J-1 visa holders. The ASN residents program is also a valuable source of information for all prospective nephrology fellows. This program is advertised on the ASN website and through direct communication with all nephrology training program directors (TPDs). The nephrology TPD contacts the internal medicine or pediatric TPD in order to advertise the residents program. ASN is aware of the challenges in recruiting nephrologists and is actively working on long-term plans to increase the visibility and attractiveness of our subspecialty to undergraduates, medical students, and residents.

Dr. Saeed did an excellent job of identifying appropriate programs and still ran into difficulties on the interview trail. Many of the problems he encountered are readily avoidable with a little extra attention to detail by the TPD. Clearly, TPDs must familiarize themselves with local policies toward visa holders and be very careful about which visa holders they select to interview. Posting an institution's policies toward visa holders on its website is an excellent idea—it would help prospective fellows and would also help remind TPDs of the importance of this issue.

Other issues that Dr. Saeed raises apply to all applicants, regardless of nationality. First, the couples match is well known to nephrology TPDs, having been part of residency program recruitment for many years. While it does complicate planning, it is readily addressable with a little extra time spent in coordinating interviews. This is not a National Registry Matching Program (NRMP) issue and simply requires TPDs to alert the person doing the interview scheduling to discuss coordination of interviews with the applicant.

Secondly, I question the geographical bias of training programs. With the exception of some programs that predominantly take applicants within the immediate area, TPDs are generally looking for the best applicants, regardless of their location. I would be very surprised if an excellent candidate was not interviewed because of his or her location.

A third issue relates to adhering to NRMP guidelines. It is unequivocally stated by the NRMP that it is not permissible to ask applicants about ranking preferences or other interviews. Such infractions can be reported to the NRMP, and programs can risk being excluded from the match.

Nephrology is relatively new to the Electronic Registry Application Service and the match and, while having made substantial strides, still has adjustments to make. Standards for conducting interviews have been established by the NRMP, and all TPDs should be closely adhere to them. ERAS provides more applicants per program, and more applications per applicant (particularly with regard to IMGs), than in the pre-ERAS era. Programs need to be aware of these application trends and work to facilitate the process of matching the right applicant with the right program with as little stress to either as possible.

Donald Kohan, MD, PhD, FASN, is chair of the ASN Training Program Directors Executive Committee. He is with the University of Utah Medical Center in Salt Lake City,

Fellows Corner

Communication Skills: Part of the ABCs of Nephrology Fellowship Training

By Jane Schell and James Tulsky

"Mrs. S, has anyone discussed moving toward comfort measures?"

I can still remember the question leaving my lips, followed by the look of surprise and discomfort on Mrs. S's face. I was a first-year fellow caring for her husband, Mr. S, a dialysis patient whom I had admitted numerous times that year. This time he had been brought unresponsive into the emergency room, and he had been lying in bed for a week, receiving pressors and ventilator support but with no signs of neurologic recovery. As I sat with Mrs. S I felt helpless. How could I begin to explain to this devastated wife that her husband was dying?

I imagine I am not alone when I share these sentiments. As a third-year nephrology fellow at Duke University, I have frequently joined in many cafeteria lunch conversations with other nephrology fellows, discussing difficult situations similar to this one. Although many of us feel equipped to treat patients with advanced kidney disease, we often lack skills in delivering bad news.

We care for a sick, complex patient population. These patients are often burdened with numerous comorbidities, which affect their experience of illness, quality of life, and functional status. When approaching the care of these patients, we face difficult conversations that range from diagnosis to treatment options to end-of-life decisions. Although prognostic tools can assist nephrologists in predicting patients who are at risk for poor outcomes, effective communication of this message remains a challenge. The quality of a physician's communication affects how patients respond to their illness and plan for the future.

Good communication is often seen as a bonus to the care we provide. However, communication is fundamental to the care we deliver. Good communication includes a set of learned skills that can be polished with practice. It includes the ability to recognize and respond to a patient's concerns and need for information, along with the physician's ability to recognize and attend to these concerns and needs in a way that is both therapeutic and supportive. Furthermore, it involves the delivery of sensitive information, balancing reality while maintaining hope.

Recognizing the need for communication education, the Duke Nephrology Division has developed a communication workshop specifically designed for nephrology fellows. This annual workshop has been led by Dr. James Tulsky, an experienced communication expert, director of the Duke Center for Palliative Care and coinvestigator in OncoTalk, a national oncology communication workshop funded by the National Institutes of Health. OncoTalk is dedicated to teaching oncology fellows how to communicate effectively with seriously ill patients, and it has expanded to include OncoTalk Teach, which teaches oncology faculty the skills for teaching communication to oncology fellows.

The Duke Nephrology Communication Workshop (NephroTalk) applies the OncoTalk communication skills training to clinical scenarios commonly encountered in nephrology. The workshop begins with a didactic session, which is followed by a role-play opportunity with scripted case scenarios using simulated patients. These cases are specifically written to represent scenarios frequently experienced by nephrology fellows.

The fellows surveyed thought that the workshop was helpful and relevant to their work. Most importantly, all fellows surveyed agreed that the workshop will change the way they practice. One fellow stated, "These techniques are a good foundation of tools, but one's effectiveness in this can only come with experience and practice. I think I'll try using many of the techniques we talked about and eventually learn which ones work best for me." Regarding specific techniques taught, one fellow wrote, "The 'Ask-Tell-Ask' approach was particularly helpful in thinking about how to broach these discussions as well."

Fellowship training is an intense time, full of learning opportunities. Reflecting on my own experience with Mrs. S, I wish I had been equipped with the communication skills necessary to attend to her emotional needs and, moving forward, to assist with care planning goals for her husband. Echoing the words of one Duke fellow workshop participant, a communication workshop "should be part of every nephrology training program." With that goal in mind, the next step is to implement formal communication skill training nationally in fellowship programs and annual meetings.

Jane Schell, MD, is a nephrology fellow at Duke University Hospital, and James Tulsky, MD, is director of the Duke Center for Palliative Care at Duke University Hospital.

Interventional Nephrology: A Fellow's Perspective

The chair of ASN's Interventional Nephrology Advisory Group, Jack Work, MD, interviews the advisory group's newest member, fellow Ammar Almemhi, MD, about his interest in and possible future directions for interventional nephrology.

Work: **What sparked your interest in interventional nephrology?**

Ahlmemhi: During my internal medicine residency at West Virginia University–Charleston, I was heavily involved in establishing a database for renal artery disease and the role of interventions in treating it. What struck me the most was the high cardiovascular mortality in the CKD population, and this generated an immense interest in exploring the link between cardiovascular and chronic kidney diseases.

This interest was the driving force behind my effort to establish a large database for patients with coronary artery disease who underwent percutaneous coronary interventions and had CKD. We initially investigated the relationship between angina at presentation and balloon-induced angina. Interestingly, we found that a good fraction of coronary artery disease patients experienced no chest pain during balloon inflation—mainly those patients with CKD.

This means that CKD patients experience more silent ischemia (defined as the absence of chest pain in response to balloon inflation). This finding led us to hypothesize that silent ischemia could explain the cardiovascular mortality in the CKD population. We showed this during my nephrology fellowship years at Kansas University Medical Center, during which we looked at 10-year mortality in both patients with normal kidney function and those with low glomerular filtration rate. We demonstrated that, indeed, silent ischemia is more prevalent in patients with compromised renal function and is associated with worse 10-year survival. This work was supported in part by T32-NIH and National Kidney Foundation (NKF) research fellowship grants and was presented in part at NKF and ASN meetings.

In short, I was neither an outsider to the field of vascular interventions nor to the nephrology world. Interventional nephrology offers the opportunity to better understand the cross-talk between these two fields.

Work: **What prompted your interest in joining the ASN advisory group? What unique perspectives do you see yourself bringing to INAG?**

Ahlmemhi: Traditionally, advisory groups of any scientific society or organization consist of faculty members, usually seniors, who have been in their respective fields for years.

Being on the ASN advisory group is meant to bridge the trans-generational gap between traditionally trained physicians and those who are trained or getting trained in the era of many protocols and electronic medical records. My job is to be the voice of my co-fellows, who are trained in a more technology- driven medicine that is based on many protocols and quality indices and are constantly faced with more stringent rules (HIPPA, work hours, or documentation) and with a complicated medical–legal system.

The set-up of nephrology training leaves no spare time for current fellows to understand and appreciate the importance of vascular access for dialysis patients. We fellows in training are struggling to finish our four monthly notes in order to be compliant with CMS rules and regulations. This type of practice spares no time for fellows to spend with patients during dialysis—where they can assess the vascular access in real time. Moreover, owing to financial constraints, faculty members must work longer hours to generate their income through seeing more patients or by struggling for limited ever-competitive grants. This situation translates into limited interaction between mentors and fellows.

Work: **What are goals for projects for INAG?**

Ahlmemhi: Interventional nephrology, as a young field, needs to be introduced to all nephrology training programs and to be a part of their core curriculum. Our responsibility as an advisory group is to facilitate the teaching process by working closely with the American Board of Internal Medicine, ASN, and the American Society of Diagnostic and Interventional Nephrology.

It is very cost effective and time saving to learn from other fields (with a special reference to interventional cardiology) that have come a long way in establishing their societies. For example, we might market interventional nephrology through mechanisms such as online teaching models accessible to all programs, creating an exam model intended to help fellows preparing for their board exam, and establishing more academic interventional nephrology fellowship programs

Likewise, it is well acknowledged that the strength and reputation of any subspecialty comes from standardizing its practice according to evidence-based medicine. This would require more rigorous investigations in interventional nephrology that include multicenter randomized clinical trials and large cohort studies.

Work: **What are the most pressing issues for trainees in interventional nephrology?**

Ahlmemhi: The most pressing issues include limited proper academic training programs in interventional nephrology, lack of standardization in training, and limited full exposure to different aspects of interventional nephrology (including surgical and radiologic experience).

Work: **What aspects of interventional nephrology are compelling to you?**

Ahlmemhi: It is a fascinating young field that deals with a growing population. It involves a wide spectrum of endovascular interventions that prepare stage 4 or 5 CKD patients prior to dialysis. It decreases the hospitalization rate and contributes to cost savings. It is a joint venture between medical, radiological, and surgical fields.

Work: **Are you involved in research?**

Ahlmemhi: Research is an essential component of contemporary medicine, and our practice for the most part relies on ongoing research. I am involved in several research projects in general nephrology and interventional nephrology. We are looking at the role of interventional nephrologists in creating arteriovenous fistulas. In another project, we are analyzing the role of surgical interventions in treating cephalic arch lesions.

Jack Work, MD, is a professor of medicine in the Renal Division of the Department of Medicine at Emory University and chair of the ASN Interventional Nephrology Advisory Group. Ammar Almemhi, MD, is an interventional nephrology fellow at the University of Arizona in Phoenix and a member of the ASN Interventional Nephrology Advisory Group, He did his nephrology fellowship training at the Kansas University Medical Center in Kansas City.

Detective Nephron

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

Ms. Curious Tubule enters the room along with L.O. Henle to present a case.

Nephron My apprentice, what do you have for me? And I see we have our medical student back… good!

Henle I have a calcium level of 16 mg/dL in a 40-year-old male.

Nephron Well, then, let's begin… it's always fun to discuss hypercalcemia. Symptomatic or not?

Tubule Symptomatic, but aggressive treatment with hydration has been started. The cause is uncertain.

Nephron That's always the problem. Figuring out the cause is important, but for now you have to just put out the fire.

Henle Broadly speaking, I usually categorize hypercalcemia into hormonal causes: malignancy, medications, infections, or other rare causes.

Nephron That's a good place to start. But what do I also want to hear about when I hear calcium levels?

Tubule Phosphorus levels?

Nephron Good! And…?

Tubule I thought you could do this with just one value. Why do you need the phosphate level?

Nephron It may give me an idea about what the patient might have ingested. Let's take this case from an "inpatient admissions" standpoint. The most common cause of hypercalcemia in the inpatient setting is primary hyperparathyroidism, followed by hypercalcemia of malignancy and then calcium or milk alkali syndrome. What is the phosphorus level?

Tubule It was 3.0 mg/dL, which is normal.

Henle Primary hyperparathyroidism might cause a low normal phosphorus level, but ingestion of calcium tablets that could be binders, such as Tums, or calcium alkali syndrome could also result in low levels of phosphorus. However, we can't rule out primary hyperparathyroidism or malignancy yet.

Nephron Good thinking. Since you've started, let's complete the hormones. What other hormones can result in elevated calcium?

Tubule Elevated vitamin D in some cases of lymphoma, thyrotoxicosis, and adrenal insufficiency are a few that come to mind.

Nephron Good. In cases of lymphoma, there is an increased amount of the enzyme that converts 25-OH vitamin D to 1,25-OH vitamin D, resulting in hypercalcemia. In thyrotoxicosis, bone resorption causes hypercalcemia. The reasons are a little more complex for adrenal insufficiency—it could be increased calcium resorption by the kidneys due to hypovolemia or increased release of calcium from the bone. I don't think this patient has that.

Tubule His vitals were normal except for a fever of 101°F. He had no clinical signs of adrenal insufficiency. His parathyroid hormone level, cortisol level, both 25-OH and 1,25-OH vitamin D levels, and thyroid-stimulating hormone level were all normal.

Henle I would consider medications a potential culprit. The patient is relatively young and may have ingested Tums.

Tubule Dr. Henle, we went over this already. His phosphorus level is normal, so it's unlikely he ingested any Tums tablets. Besides, I took a complete history, and he denies ingestion of Tums, lithium, or any thiazide diuretics. No theophylline, either.

Nephron (smiling) Nice work, Tubule. That's a good working list.

Tubule Also, a thiazide screen was negative.

Nephron You really didn't need that. What are the other electrolytes showing?

Tubule Normal potassium, normal sodium, and a slight increase in serum creatinine to 1.5 mg/dL.

Henle (smiling) No other signs of thiazide toxicity. No hypotension, either.

Nephron Tubule, I'm curious… what did you do next?

Henle (jumping in) She ordered an angiotensin-converting enzyme test, and it was normal.

Nephron (confused) What is his race?

Tubule He's black, but I don't know where he's from originally.

Henle He's from the West Indies.

Nephron I see…

Tubule A normal angiotensin-converting enzyme level and a normal chest x-ray put a disease like sarcoidosis lower down on my list of causes in his case…

Henle (interrupting) …a tuberculin (ppd) test was also normal.

Nephron I already had a diagnosis when you told me his country of origin. Take 15 minutes and see what else you can come up with.

Henle and Tubule leave the room.

Henle (to himself) Tubule isn't even a full MD yet, but she's trying to jump in with impressive answers. Why is she being so competitive?

Tubule (to herself) I think I can come up with this diagnosis faster than Henle can.

Henle and Tubule pace back and forth, reading books and checking Google, and go back in after 15 minutes.

Henle (jumping right in) I think we should go step-by-step in the next category: malignancy.

Tubule Yes, malignancy can cause hypercalcemia via several mechanisms, including increased parathyroid hormonal production, production of parathyroid hormone like peptide, bone resorption, and interleukin-6 production.

Nephron (smiling) Good start!

Nephron (to himself) I'm enjoying this passionate discussion between my two apprentices. It makes them think and learn!

Henle Could he have a malignancy? He did have an enlarged parotid gland.

Tubule Serum-free light chains and serum immunofixation were normal, ruling out myeloma. Lactate dehydrogenase is elevated, but I don't know what to make of that.

Nephron (interrupting) Has his hypercalcemia corrected?

Henle It corrects down to 10–12 mg/dL after hydration and furosemide but returns quickly back to 15–16 mg/dL. In desperation, steroids and bisphosphonates were begun.

Tubule Infectious work-up revealed a negative HIV test and a negative bronchoscopy to rule out granulomatous infection, although his ppd was negative. His parathyroid hormone–like peptide was mildly elevated. Might he have cancer? A full body scan didn't reveal anything.

Nephron (stopping both of them) Where is he from again?

Henle The West Indies.

Nephron Go ask him for a thorough history of his recent travels, sexual activity, and transfusions. I need a good history and physical exam!

Henle and Tubule return in a few hours.

Tubule He was in the West Indies last year for four to five months for work-related purposes. While there, he had a blood transfusion during an urgent orthopedic procedure after a fall.

Henle Might he have a human T lymphotropic virus type 1 (HTLV-1) infection?

Nephron Bingo!

Henle …and perhaps even an acute T cell leukemia/lymphoma?

Nephron Yes and yes! My advice is to get him tested quickly and conduct a bone marrow biopsy.

Three days later…

Nephron (curious) So, what was it?

Henle His HTLV-1 polymerase chain reaction test was positive, and a bone marrow test confirmed smoldering T cell leukemia. He was started on zidovudine and interferon and is planning to undergo high-dose chemotherapy as well.

Nephron So… as the "kidney police," what would you have to monitor in this individual in terms of renal disease?

Tubule Both interferon and HTLV-1 have been associated with collapsing focal segmental glomerulosclerosis, so it might not be a bad idea to check his urine protein to creatinine ratio once every few weeks to monitor for development of this entity.

Nephron Acute T cell leukemia/lymphoma can be smoldering, acute, or chronic and can occur in this age group. One of the causes is HTLV-1. Smoldering T cell leukemia rarely causes hypercalcemia, though it can happen sometimes. High calcium and lactate dehydrogenase are poor prognostic factors. HTLV-1 has a high prevalence in Jamaican patients—mostly women, but men have it, too. It's transmitted in the same manner as HIV, and can be spread via blood donation. Hypercalcemia occurs in 50 percent of patients with HTLV-1–induced adult T cell leukemia. The mechanism is not clear, but it is likely mediated by parathyroid hormone–like peptide and possibly interleukin-6. No one knows!

Once again, from a single entity of hypercalcemia, you diagnosed a life-threatening cancer from a strange virus. Remember, in addition to laboratory data and clinical acumen, you need a good history and physical exam—neither of these tools can ever be replaced. No online tool or laboratory test will ever give you as much information as the patient can.

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

Industry Spotlight

More Dialysis Merger News

On the heels of a big dialysis merger between privately held Renal Advantage and Liberty Dialysis to form the number three provider of dialysis services in the United States, DaVita has announced it will buy DSI Renal, Inc., for about $690 million. With this deal, Da Vita can expand its geographic range.

Reuters reports that the deal will bring the 106 dialysis centers under the DSI family and help DaVita expand in Midwestern, Southern, and some Western states.

The DSI locations generate annual revenue of about $360 million, Reuters said. DSI currently serves approximately 8000 patients, according to the February DaVita announcement.

Before the merger, DaVita ran or provided administrative services at nearly 1600 dialysis facilities, serving about 124,000 patients, according to Dow Jones Newswires.

DaVita stock has risen 25 percent in the past year, Dow Jones Newswires reported.

"This acquisition introduces us to several new geographies and makes us a more effective competitor in selected areas," said Kent Thiry, DaVita chairman and chief executive. "Through this acquisition, we will be able to bring the broader line of DaVita chronic kidney disease services to DSI patients."

The deal is expected to close in the second or third quarter of this year. According to Zacks Investment Research, DaVita will require the Hart-Scott-Rodino antitrust clearance to complete the deal. The company may have to divest some of its centers as a condition of completing the transaction, Zacks reported.

Detecting Inpatient Kidney Damage

On March 6, FlowSense Medical, Ltd., announced that a clinical trial of its URINFO 2000 device detected early-stage acute kidney damage, according to the business news site Globes.

A 25-patient trial was conducted at the San Bortolo Hospital in Vicenza, Italy.

The URINFO 2000 continuously collects data and displays real-time information about urine flow. FlowSense's technology processes patient urine into drops of uniform size and then counts them optically as they drip into a bag.

The product is currently on sale in Israel and has been installed alongside 100 beds.

The device is not approved for use in the United States by the Food and Drug Administration.

"The product does not require U.S. Food and Drug Administration approval, because it does not come into contact with the body," said FlowSense's Robert Bash. "It does not need to be recognized by insurance companies because it is intended for use in accident and emergency rooms and on intensive care wards, where the insurance refund is received by the hospital per patient, according to his or her injury or illness, and not as a refund for specific procedures."

According to FlowSense, about 5 percent of patients in hospitals and 30 percent of patients specifically in intensive care units have acute kidney damage, which increases morbidity rates, cost of care, and length of stay.

Globes reported in January that the company raised NIS 5.2 million (about $1.3 million) in a private placement, at NIS 0.338 per share. (NIS is the Israeli money unit, Israeli New Shekel, which runs roughly four to the U.S. dollar.)

The main shareholders in the company are investment and consultancy company Trendlines; the Zitelman Group, Inc.; a private investor, Shraga Karpfen; and Zeev Bronfeld, who has a previous investment history with Trendlines.

Year-End Roundup

Dialysis-related industries

Rockwell Medical, a publicly traded biopharmaceutical company offering products and services that target ESRD, chronic kidney disease, and iron deficiency anemia, reported fourth-quarter sales of $14.3 million—a 3 percent decrease compared with the fourth quarter of 2009. For the year, it had sales of $59.6 million—an increase of $4.8 million, or 8.8 percent, compared with 2009. In 2010, it had a net loss of $2.7 million, compared with a net loss of $5.5 million in 2009.

"We moved our SFP (soluble ferric pyrophosphate, an antianemia drug) clinical development significantly forward and we expect to begin enrolling patients into our Phase III CRUISE studies this quarter," said Robert L. Chioini, chairman and chief executive officer. "Moving into 2011, we look forward to continuing to build both our operating and drug businesses, progressing SFP through Phase III and closer to commercialization."

AMAG Pharmaceuticals, Inc., a publicly traded biopharmaceutical company, is focused on the development and commercialization of a therapeutic iron compound to treat iron deficiency anemia. AMAG reported total revenues for the year of $66.2 million, of which $59.3 million were net product revenues from Feraheme (ferumoxytol) Injection for intravenous use. For the fourth quarter, total revenues were $17.2 million, of which $15.2 million were Feraheme net product revenues.

Over the course of 2010, the company stated, demand by providers shifted from primarily dialysis in the first quarter to primarily nondialysis in the fourth quarter, largely because of purchasing decisions by dialysis providers in response to the January 1, 2011, bundling payment system. In February, the U.S. Department of Justice informed AMAG that it had closed its investigation of the company and that no further investigation was warranted.

In its 2010 annual report, Polypore International had sales in the fourth quarter for its Separations Media segment, Healthcare Products, of $30.0 million—an increase of $2.6 million, or 10 percent. For the year, sales were $107.4 million—an increase of $5.3 million, or 5 percent. Sales in both periods were driven by solid demand in hemodialysis and blood oxygenation applications.

Said Robert B. Toth, Polypore president and chief executive officer: "We are very pleased with the growing and accelerating demand trends in our business (including separations media, such as that used in dialysis equipment). Long-term demand drivers remain positive, and we will continue to make the necessary investments to ensure sustainable growth over the long term."

All sectors of the company, including dialysis products, embarked on "significant capacity expansions," he said.

Dialysis providers

The big two publicly traded dialysis providers in the United States—Fresenius North America (FNA), and DaVita—shared their fourth-quarter and year-end 2010 results. In the dialysis industry overall, the new Medicare prospective payment system, which bundled pharmaceuticals as part of a single payment, is putting pressure on companies' financials.

For the last quarter of 2010, FNA revenue increased by 3 percent to $2.072 billion total, including dialysis services and pharmaceutical treatments. The services sector reported that although reimbursement increases were favorable, this was offset by reduced use of pharmaceuticals. Dialysis product revenue decreased by 1 percent to $210 million.

Overall, Fresenius operated a network of 2757 dialysis clinics (up 8 percent year over year) around the world, by the end of the fourth quarter of 2010, according to the company. Fresenius provided dialysis treatment to 214,648 patients, which marked a 10 percent increase in treatments worldwide over the calendar year 2010.

Looking ahead in 2011, the Fresenius parent company expects revenue to grow to between $12.8 billion and $13.0 billion, corresponding to a growth rate of 6 to 8 percent.

DaVita announced that revenues from its dialysis and related laboratory services segment for the quarter were $1.55 billion, compared with $1.48 billion in the prior-year quarter, Zacks reported.

Ancillary services and strategic initiatives generated revenues of $105 million in the 2010 fourth quarter, compared with $85 million in the year-ago quarter. The segment suffered an operating loss of $2 million in the reported quarter as against the loss of $5 million in the year-ago quarter.

By December 31, 2010, DaVita operated or provided administrative services at 1612 outpatient dialysis centers serving approximately 125,000 patients (1580 centers are consolidated in DaVita's financial statements). Total DaVita treatments for the fourth quarter of 2010 were 4,657,498, or 58,956 treatments per day, the equivalent of a per-day increase of 6.8 percent over the fourth quarter of 2009.

DaVita declined to offer official guidance on its 2011 operating income range. Apart from the impact of the recently announced acquisition of DSI Renal Inc., DaVita said its current projections indicate that 2011 operating income will be flat or modestly down in comparison with 2010.

Top10 reasons to join ASN

ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

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