ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

KidneyNews

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Removing a Kidney after Failed Transplant Can Yield Benefits

By Tracy Hampton

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Nephrectomy following failed kidney transplant can yield significant benefits for some patients.

Kidney transplants can be life-savers for many patients with chronic kidney disease. Still, a significant number of transplanted kidneys are rejected or do not function properly over time. Physicians have been reluctant to remove these organs, but a recent study indicates that such a transplant nephrectomy can offer significant survival benefits for patients (Ayus JC, et al. *J Am Soc Nephrol* 2010; 21:374–380). While additional studies are needed, the results indicate that clinicians should rethink how they treat patients with failed kidney allografts.

"Our results raise questions about the current clinical paradigm and suggest that routine allograft nephrectomy in stable dialysis patients with a failed renal allograft should be evaluated against current management strategies in a randomized trial as a possible strategy for improving outcomes among this growing population of high-risk patients with end stage renal disease," the authors wrote.

Options after allograft failure

Patients with chronic kidney disease often must wait years for a suitable kidney transplant (and some die while on the waiting list), but their return to health is not ensured once they receive a donor kidney. A growing number of patients are returning instead to dialysis after a failed kidney transplant, where they face an increased risk of complications and premature death. The problem will likely become more widespread, as the prevalence and incidence of end stage renal disease are projected to increase substantially in the United States over the next several decades.

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Researchers Discover Gene for Devastating Kidney Disease

Finding Could Lead to Better Diagnosis and Treatment of Patients with FSGS

A recent genetic discovery may provide clues to the mysteries behind focal segmental glomerulosclerosis (FSGS), the second leading cause of kidney failure in children and the most prevalent acquired kidney disease leading to transplantation among pediatric patients (Brown E, et al. *Nature Genet* 2010; 42:72–76). Investigators have found that mutations in the *INF2* gene occur in a large numbers of families with affected members and may be relevant for understanding how the disease originates.

"We are hopeful these new findings will impact future clinical studies and patient care," said Henry Brehm, executive director of the nonprofit NephCure Foundation, which helped fund the study.

These latest research findings could not come soon enough, as prevention and treatment options for patients with FSGS are sorely needed. Patients today are treated with steroids, must undergo dialysis, and often require a kidney transplant. In 20 percent to 50 percent of transplant cases, the disease recurs in the transplanted kidney, sometimes within hours. Over half of the patients with recurrent FSGS in their transplant will lose their kidney within five years.

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

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Failed Transplant

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Physicians have wrestled with whether to remove failed kidney allografts in these patients, not knowing how such an extensive surgery would affect the health and survival of individuals receiving chronic dialysis. Many have assumed that the operation would be too risky and would increase patients' immunoreactivity—presumably due to increased exposure to foreign antigens during the nephrectomy operation. The thought is that this increased immunoreactivity would decrease these patients' chances of receiving a future transplant.

Others have questioned this rationale, however, and say that the benefits of nephrectomy outweigh its risks. They point to studies showing that a failed kidney allograft acts as a focal point of immunoreactivity that can perpetuate chronic inflammation, which is a major risk factor for cardiovascular death in patients receiving chronic dialysis.

Outcomes following nephrectomy

To investigate the costs and benefits of transplant nephrectomy in patients with failed kidney allografts, Juan Carlos Ayus, MD, FASN, director of clinical research at Renal Consultants of Houston, and his colleagues studied information from all adults who underwent a single kidney transplant or two nonsequential kidney transplants and returned to chronic dialysis after kidney allograft failure between January 1994 and December 2004. Data were obtained from the U.S. Renal Data System (USRDS). The researchers excluded patients in whom the kidney allograft did not survive at least three months, as well as those who died within less than one day after kidney allograft failure, those who did not have Medicare fee-for-service insurance after the first 90 days following the return to dialysis, and those without confirmed sequential transplants.

The primary outcome was death from any cause through December 31, 2004, which was identified from USRDS files. The mean follow-up was 2.93 ± 2.26 years.

Among 10,951 transplant recipients who returned to chronic dialysis, 3451 (31.5 percent) received an allograft nephrectomy during follow-up. These patients returned to dialysis at a median time of 1.66 years (interquartile range: 0.73 to 3.02 years). The investigators found that 34.6 percent of these patients died during follow-up.

Receiving an allograft nephrectomy was associated with a 32 percent lower risk for death from all causes after adjusting for sociodemographic characteristics, comorbidity burden, donor characteristics, interim clinical conditions associated with receiving allograft nephrectomy, and propensity to receive an allograft nephrectomy. Even after Ayus and his team performed six additional sensitivity analyses including or excluding specific patient subgroups, there were no clinically relevant differences in the estimated benefits associated with the nephrectomy. For patients who underwent a transplant nephrectomy, the rate of death within 30 days of the surgery was only 1.5 percent (53 deaths).

The investigators also found that patients receiving a transplant nephrectomy were more than twice as likely to receive a second transplant during the follow-up period than those who did not undergo a nephrectomy of the initial failed allograft (10 percent versus 4.1 percent, $p < 0.001$). It is unclear why patients who received a transplant nephrectomy had an increased rate of repeat transplantation. The researchers suspect the increased transplantation rate may reflect better health in the nephrectomy group through either lower comorbidity or improved health status following nephrectomy due to reduced chronic inflammation.

The investigators made several postulations after analyzing their findings. They suspect that patients with failed transplants experience higher death rates due to chronic inflammation. In addition, patients who retain a failed renal allograft routinely use low-dose immunosuppressive therapies after returning to dialysis, which may delay the need for ultimate nephrectomy and contribute to an increased risk of cardiovascular and infectious complications.

Nephrectomy "spares the patients unnecessary immunosuppressive therapy and more importantly removes a source of chronic inflammation that predisposes to morbidity and mortality on dialysis," said William Bennett, MD, who was not involved with the research. Bennett is medical director of kidney transplantation at Legacy Good Samaritan Hospital in Portland, Oregon.

According to Ayus, this is the first study to use a very sophisticated and large

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Kidney News

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Gene Discovered

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Importance of the INF2 Gene

Patients with FSGS excrete abnormally large amounts of protein in their urine and may develop low blood protein levels as well as edema, especially in the feet and legs. Despite years of research and the discovery of several genes that play a role in the development of some cases of FSGS, investigators have failed to uncover the disease's underlying mechanisms or come up with effective treatments for patients.

Many patients with familial FSGS do not have mutations in the known FSGS-causing genes. To look closely at the heritability of FSGS, researchers led by Elizabeth Brown, MD, and Marin Pollak, MD, performed a genetic linkage analysis in two large families affected by the disease. The study was designed to identify new FSGS-causing genes in family members with autosomal dominant disease who were negative for all known FSGS-causing gene mutations. Brown is associate physician in medicine in the division of nephrology at Children's Hospital, in Boston, and Pollak is assistant professor in medicine at Brigham and Women's Hospital and associate professor in medicine at Harvard Medical School, also in Boston.

The researchers' analysis revealed that mutations in a region of chromosome 14q were common in affected individuals. By sequencing the genes in this region, the investigators detected various mutations, all of them in a gene called *INF2*. Next, they sequenced the *INF2* gene in 91 additional families and uncovered nine different *INF2* mutations in 11 of the 93 total families. *INF2* gene mutations were found in more families than either of the previously identified autosomal dominant disease-associated genes, *actinin-4* and *TRPC6*. The *INF2* gene mutations caused substitutions in highly conserved amino acids in the *INF2* protein (a formin protein), and the mutations segregated with disease within the affected families. None of the gene mutations were found in healthy controls. In addition, the *INF2* gene mutations were all located in the same region, which encodes a domain that is thought to be involved in the regulation of the INF2 protein.

The formin protein encoded by the *INF2* gene regulates actin. Abundant in the podocytes of the kidney, actin is important for creating and maintaining the cells' architecture, namely their cytoskeleton. The researchers believe that mutations in the *INF2* protein in podocytes compromise the cells' structure and, hence, their ability to filter toxins. "This is the second actin binding protein described that, when mutated, can cause FSGS," said Brown. "Both of these proteins are ubiquitous; however, the kidney appears to be the primary organ affected by the genetic mutations, reinforcing the importance of the podocyte architecture in the development of FSGS."

The research makes several contributions to basic and clinical research, Pollak said: "It adds to the complexity of the genetic basis of FSGS, identifies a new gene and pathway as critical to the biology of the podocyte, and adds to the ability to make a correct etiologic diagnosis."

The findings could have important clinical implications beyond diagnosis. "Understanding the function of *INF2* and the pathways in which it is involved in the cell will hopefully lead to better targets for the prevention and treatment of FSGS," Brown said.

There is still much to learn about the function of the *INF2* gene and the precise mechanism by which actin behavior is disrupted in the presence of *INF2* alterations. "Studying the way in which mutations in *INF2* disrupt normal cell function can help us understand the role of *INF2* in the podocyte. In addition, studying patients with *INF2* mutations can help us better stratify patients with FSGS for more personalized treatment options," said Brown.

Other researchers not involved with the work also anticipate that the findings could have a considerable impact on FSGS research and treatment. "The report by Brown *et al.* is yet another step forward in our understanding the complexity of the genetics of podoctyes in health and disease," said Frederick Kaskel, MD, PhD, chief of the nephrology section at Children's Hospital at Montefiore, in Bronx, NY. "The fact that the newly identified mutations are associated with proteins that maintain the stability of the podocyte cytoskeleton opens the doors for further investigations aimed at targeting these mutations in health and disease in an attempt to halt the progression of the podocytopathy." Kaskel noted that it will be interesting to search other familial FSGS databases to confirm the latest findings.

Need for new treatments

According to the NephCure Foundation, more than 20,000 people currently live with end stage renal disease due to FSGS. Chronic kidney disease sufferers in various stages of FSGS number in the tens of thousands, at the least. More people in the United States suffer from FSGS than from cystic fibrosis, according to NephCure. The organization estimates that 1117 kidney transplants were performed on FSGS patients in 2007 alone. In addition, young African American males are diagnosed with FSGS five times more frequently than young Caucasian males.

"FSGS is a very serious condition and one that affects thousands worldwide. There are few effective treatments for FSGS and its recurrence posttransplant is devastating to patients and families," said the NephCure Foundation's Brehm. He hopes that the Pollak team's findings will encourage other FSGS investigators to step up the pace of their research. "This is the kind of tangible progress that creates the kind of momentum we need. The most exciting part is that the research is just getting started," he said.

Failed Transplant

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database to suggest a significant survival advantage with transplant nephrectomy and a very low mortality with this type of operation.

"More importantly, the study has dispelled the notion that transplant nephrectomy reduces the chance for re-transplantation when in fact our study shows for the first time that in the group of patients who underwent transplant nephrectomy, the rate of re-transplantation was significantly higher compared with the non-nephrectomy group," he said. This finding argues against withholding a transplant nephrectomy due to a presumed reduced chance of repeat transplantation, the authors wrote.

The research results challenge the traditional practice of retaining kidney allografts after transplant failure. "This is indeed an important article addressing a difficult management point in transplantation management," Bennett said. "The paper gives us clear guidance on the preferability of allograft nephrectomy for failed grafts."

While this study is the largest and most rigorous thus far, it is not a randomized clinical trial, which is the gold standard in epidemiology, Ayus said. "Our study only indicates a very strong association between transplant nephrectomy and increased survival," he said. "Until the randomized study is done (if ever), this information is the strongest evidence that physicians could use to improve survival in patients who return to dialysis with a failed allograft."

Ayus said he hopes that additional rigorous studies are performed to provide more definitive information on the value of transplant nephrectomy following failed kidney allografts.

ASN News

New Archives Effort Will Document ASN and Nephrology History

In honor of ASN's 50th anniversary in 2016, the society is developing an archives program to document important milestones in the history of ASN and nephrology.

ASN seeks volunteers to assist the society in identifying pivotal moments in ASN history and the most important advances in kidney treatment and research. Please let us know if you are interested in participating and contributing to our archiving efforts.

One way you may wish to contribute is by sharing materials you have from ASN meetings, publications, or other activities. If you have material you think may be of interest, please contact Shari Leventhal at archives@asn-online.org or call her at 202-416-0658 to discuss your potential contributions.

ASN will underwrite the costs of copying and shipping material that we do not already possess and that needs to be added to the archives.

We have included some images of ASN attendees during past Renal Week meetings and encourage you to guess who they are. You will find the key on page 23 to help you find out if you were right.

ASN invites our members to contribute to this exciting endeavor. As we look toward the future with the arrival of 2010, let us celebrate the past by building our archives program!

Guess the Nephrologist

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B.

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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.

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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.

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Acute Kidney Injury: The Road to Recovery

Richard Lafayette

Acute renal failure, increasingly being called acute kidney injury (AKI), is a devastating event, most typically occurring in hospitalized patients. While we teach our students to look for easily reversible causes such as pre-renal and obstructive causes of AKI, or treatable interstitial nephritis or glomerulonephritis, it often follows a progressive course.

Patients with AKI, presently recognized by increasing serum creatinine values or oliguria, have unacceptably high rates of complications demonstrated by increased costs, prolonged ICU stays, and hospitalization, as well as the frequent need for dialysis support. Most notably, hospital mortality rates range from 30 to 80 percent for sustained, dialysis-dependent AKI, depending on the setting (1,2). Recently, there has been increased attention to the fact that survivors of AKI continue to suffer long-term adverse events, including progression to renal failure and increased mortality (3).

In our hospitals, the incidence of AKI is increasing, reaching rates as high as 7 percent of all admissions (4). This is associated with an aging population, sicker inpatients, and more aggressive care for serious illnesses, including cardiovascular disease and cancer. The community-based risk of AKI is also apparently growing, now as high as 5.2 cases per 1000 patient-years (5).

There are some indications that overall outcomes may be improving slightly either due to better reporting of cases or to true improvements in overall supportive care (6). It is also encouraging that there are clear efforts at getting better definitions of disease and of the measures of outcome to set the stage for future discovery (7,8). Unfortunately, to date, most studies of specific therapies and interventions have failed to show any benefit on the course of this disease.

Presently, there is great uncertainty as to how best to diagnose this process or to get an early and full appreciation of risk. Furthermore, once identified, there is no clear intervention to help the kidney recover more quickly or completely or to assure that the patient suffers fewer complications. We continue to be uncertain of the appropriate time to intervene with dialysis or with which modality or intensity to supply renal replacement therapy (2).

In this special issue of *ASN Kidney News*, we are fortunate to have the viewpoints of several leaders in the field of acute kidney injury. They provide evidence that nephrology is trying to develop better, more effective ways to deal with the diagnosis, treatment, and support of patients with AKI. Ranging from efforts to verify novel biomarkers of injury through enhanced basic science understanding of pathophysiology, to specific issues in patient care in terms of fluid support and nondialytic and dialytic treatment in the hospital, these insights should pave the way to new avenues of investigation and clinical care. We certainly must hope for improvement in the care and outcome of this very devastating event.

Richard Lafayette, MD, is clinical chief, nephrology, and associate professor of medicine at Stanford University Medical Center.

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Fluid Administration in Pediatric AKI: When Is a Patient Being Overdosed?

By Stuart Goldstein

Recent and important advances in acute kidney injury (AKI) research have focused primarily on: (i) derivation and validation of multidimensional AKI definitions and classification systems, e.g., RIFLE (Risk, Injury, and Failure (1), pRIFLE (2), or the Acute Kidney Injury Network (AKIN) (3) definitions; (ii) demonstrating that even small serum creatinine increases (e.g., > 0.3 mg/dL) can be associated with increased patient mortality (4); and (iii) discovery and validation of novel urinary biomarkers that can detect AKI earlier than serum creatinine changes with the hope that earlier detection may provide clinicians with the opportunity to intervene to prevent or at least mitigate the effects of AKI (5–7). Although these advances will undoubtedly lead to improved patient care by prompting clinicians to be vigilant for early AKI development, they may provide little benefit once patients have already developed AKI.

Care for the critically ill patient with sepsis and AKI is further complicated by the need to manage multiorgan system failure, often requiring complex supportive measures of fluid resuscitation, vasoactive medication administration, and decisions as to timing of renal replacement therapy (RRT).

Clinical research in adults with sepsis and acute respiratory distress syndrome has also focused primarily on the benefits of early and aggressive goal-directed fluid resuscitation to restore end-organ provision. Recently attention has been given to conservative late fluid management strategies to limit fluid administration (8–9). However, it has been pediatric studies that have examined the concept of fluid accumulation in the critically ill child with AKI.

Children with AKI provide an informative population for study, as their care is usually not complicated by comorbidities found in adults such as atherosclerotic heart disease, diabetes, or chronic obstructive pulmonary disease. The purpose of this article is to introduce the concept of "fluid overdose" in the critically ill patient with AKI based on pediatric studies from the past decade.

Can fluid be a toxic medication?

All physicians are taught about fluid and electrolyte homeostasis in medical school and early in postgraduate training, with an emphasis on how to respond to pathological homeostatic disorders such as SIADH or diabetes insipidus. In these instances, physicians become quite adept at managing fluid composition and volume rates to correct or minimize the electrolyte derangements that accompany these syndromes. In fact, much controversy has arisen recently regarding the potential dangers of prescribing hypotonic solutions to any hospitalized patient (10–12). Clearly the concept that certain fluid compositions in particular settings may be toxic is not new.

In the setting of AKI, physicians are very cognizant to limit the dose of potentially harmful electrolytes (potassium, phosphorus) provided in exogenous fluids, but the concept of a fluid volume dose has been limited for the most part to an acute dose to treat hypotension (e.g., 10 mL/kg of normal saline). Yet the concept of a deleterious degree of positive fluid accumulation, or fluid overdose, has received no systemic evaluation and certainly has not been defined. For example, neither of the two most recent, comprehensive, randomized, and controlled trials comparing small solute dose of RRT has reported to date the positive fluid balance in their patient cohorts at the time of RRT initiation (12–14). Given that these patients had oligoanuric AKI and that disordered fluid homeostasis is a primary indication to initiate RRT, our collective ignorance regarding the fluid balance status in patients with AKI is perplexing.

Why has cumulative fluid balance received such short shrift? I suggest that we and AKI investigators have assumed that patients are getting the amount of fluid they need (and maybe too little, but rarely too much), and since it is usually of a relatively isotonic composition (e.g., normal saline or Ringer's lactate) and can be removed by RRT, fluid can't really be overdosed. However, lessons from the pediatric AKI literature challenge these assumptions.

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Fluid Administration

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Lessons from the pediatric intensive care unit

The lessons from pediatric nephrologists and intensivists emanate from two practice perspectives ingrained into pediatricians—disease prevention and medication dosing based on patient size. I am not suggesting that these perspectives are unique to pediatrics and absent in internal medicine, but they are more common in pediatric training and everyday practice.

In the area of pediatric AKI and RRT, a concept of relative fluid accumulation (percent fluid overload) based on ICU admission weight and timing of renal replacement based on percent fluid overload and not BUN concentration has driven extensive pediatric research in the past decade.

Critically ill children often require aggressive fluid and inotropic support to maintain adequate perfusion. Substantial single-center and multicenter pediatric study over this past decade demonstrates that increasing degrees of relative fluid accumulation, or percent fluid overload, at the time of RRT initiation in children with AKI is independently associated with mortality (Table 1) (15–19). Percent fluid overload is calculated by totaling fluid volumes from ICU admission to RRT initiation using the following equation:

%FO = [(Fluid Input (L) – Fluid Output (L)) / Patient ICU admission weight (kg)]

In all of these studies, estimated GFR, patient age and size, urine output, diuretic use, and severity of illness did not differ between survivors and nonsurvivors. Analysis of different percent thresholds from these studies suggests mortality increases from 40 percent to 60 percent in children with >10–20 percent fluid overload at RRT initiation, independent of patient severity of illness (Table 1). Thus, the pediatric community now has data from over 400 children in five studies that consistently show a potential fluid overdose threshold at >20 percent positive accumulation from ICU admission to CRRT initiation.

The Prospective Pediatric Continuous Renal Replacement Therapy (ppCRRT) Registry Group recently conducted an analysis of its entire 340-patient cohort using a tripartite classification for percent fluid overload (FO) at CRRT initiation: < 10 percent FO, 10–20 percent FO, and > 20 percent FO (Sutherland S. et al, accepted for publication in *Am J Kidney Dis*).

One could still potentially argue that the patients actually "needed" the fluids they received. However, in a published multicenter study from the ppCRRT, the mean central venous pressure (CVP) for survivors was 16.5 ± 6.1 mm H_2O versus 21.2 ± 6.6 mm H_2O for nonsurvivors (18). Current recommendations for early goal-directed fluid resuscitation advocate fluid administration until a CVP of 8. Since the mean CVP was two- to threefold above target recommendations, it is difficult to support the notion that patients received only the fluid volumes they needed and not an excess amount of fluid.

Limitations and potential rationale

The observational and focused nature of the studies mentioned above cannot be overemphasized. These studies just highlight a potential association between fluid overdose and mortality, yet do not prove causality. In addition, the studies only included children who ultimately received CRRT at the discretion of the local physician; CRRT initiation was not directed by a protocol in any of these studies. Finally, since these studies involved only CRRT cohorts, the ability to generalize the findings to patients without AKI who don't need RRT is hampered.

Nonetheless, the observations generate some potential provocative hypotheses to explain the associations. For instance, in pediatric practice, almost all medications are prescribed to patient size, in terms of body weight or surface area. One can imagine a scenario in which a child with gram negative sepsis treated with a third-generation cephalosporin dosed on ICU admit weight or historical dry weight is actually underdosed as a result of a severely increased volume of drug distribution from excessive fluid accumulation. In this example, it is possible that the antibiotic concentration is below the pharmacodynamic profile to eradicate the organism. Another obvious potential hypothesis would posit an association between excessive fluid accumulation and impaired oxygenation or other pulmonary mechanics, especially in patients with capillary leak syndromes such as sepsis.

Final thoughts

This article promotes a concept of fluid overdose in critically ill children with AKI. Inherent in this concept is the importance of regarding fluid as a medication with respect to both composition and volume (dose). Future investigation will require prospective evaluation of different fluid dosing strategies beyond the initial resuscitation effort to optimize care for all critically ill patients.

Stuart Goldstein, MD, is associate professor of pediatrics at Baylor College of Medicine and medical director, Renal Dialysis Unit and Pheresis Service, Texas Children's Hospital. He is also founder and principal investigator of the Prospective Pediatric Continuous Renal Replacement Therapy (ppCRRT) Registry in Houston, Texas.

Table 1

Author	Cohort (n)	Outcome	p
Goldstein	Single center (22)	Survivors 16% FO Nonsurvivors 34% FO	0.03
Gillespie	Single center (77)	% FO>10% with OR death 3.02	0.002
Foland	Single center (113)	3 organ MODS patients Survivors 9% FO Nonsurvivors 16% FO 1.78 OR death for each 10% FO increase	0.01
Goldstein	Multicenter (116)	2+ organ MODS patients Survivors 14% FO Nonsurvivors 25% FO <20% FO: 58% survival >20% FO: 40% survival	0.002
Hayes	Single center (76)	Survivors 7% FO Nonsurvivors 22% FO OR death 6.1>20% FO	0.001

Data from over 400 critically ill children demonstrate increased risk of mortality at > 10% fluid overload (FO) at CRRT initiation

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Optimizing Therapeutic Options in Acute Renal Failure—An Ever Elusive Goal

By Orfeas Liangos and Bertrand Jaber

The main therapeutic intervention for treatment of acute renal failure (ARF), extracorporeal renal replacement therapy (RRT) was introduced over half a century ago. RRT has changed the natural history of this disorder from a devastating condition that almost invariably led to the patient's demise, to a manageable complication. Unfortunately, further improvement in survival rates among patients with ARF have at best been incremental, with mortality rates remaining unacceptably high (1–3).

Optimization of RRT carries the promise of improving clinical outcomes. Several treatment characteristics have been the subject of clinical investigations, including RRT intensity and type of modality. Two recently published trials addressed dialysis intensity and were unprecedented in scale and quality to any previously published work related to ARF (4,5). Unfortunately, the results of these trials were negative, finding no improvement in survival with higher treatment intensity. Previous, smaller scale trials addressing questions of modality and timing were similarly unrevealing. In addition to understanding the reasons why these characteristics of RRT seemingly have no effect on the survival of patients with ARF, this brief review raises the question of timing of dialysis as a new frontier with the potential for substantially improving the outcome of patients with ARF and for advancing the field of critical care nephrology further.

Intensity of RRT

It is logical to assume that increasing the intensity or dose of therapy would improve outcome in patients with ARF, i.e., the more therapy is administered, the better the correction of electrolyte and acid base disturbances, as well as the control of extracellular fluid volume and removal of uremic retention solutes, which in turn, leads to improved outcomes. However, it has been difficult, if not impossible, to demonstrate such a cause-and-effect relationship.

Several small, single-center studies on this topic have reported conflicting results and great heterogeneity of patient population, RRT modality, and design (6–11). Moreover, to date, there are no well-established and validated methods to measure intensity of RRT in ARF. Clearly, well designed and executed, adequately powered multicenter, randomized controlled trials have been lacking until two such trials were recently published demonstrating no measurable benefit in the higher intensity treatment arms (4,5). Despite these negative results, it has recently been argued that tools for quality assurance and performance improvement should be adopted for RRT rendered to patients with ARF, to ensure that the therapy delivered is at least as intensive as that provided in the lower-intensity groups of these two trials (12). It is important to note, however, that the minimal effective dose of RRT required to optimize survival in ARF is not yet known.

Continuous RRT (CRRT) versus intermittent RRT (IRRT)

The importance of CRRT as a modality for the treatment of critically ill patients with ARF is presented in detail by Tolwani in this issue. (see page 12). CRRT has become popular among nephrologists and intensivists due to its superior tolerability and capacity for volume and solute control, especially in critically ill patients with circulatory compromise. CRRT requires high resource and personnel utilization and there is a high mortality in patients chosen to receive CRRT. Comparing in a controlled fashion the effects of CRRT versus IRRT on mortality in ARF would be helpful. This question of course, as simple as it may seem, has been difficult to answer, because patients who typically require CRRT, and therefore are set to benefit most from it, are those who cannot tolerate IRRT, namely the hemodynamically unstable, making it impossible to randomize such patients to IRRT. On the other hand, patients who

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Therapeutic Options

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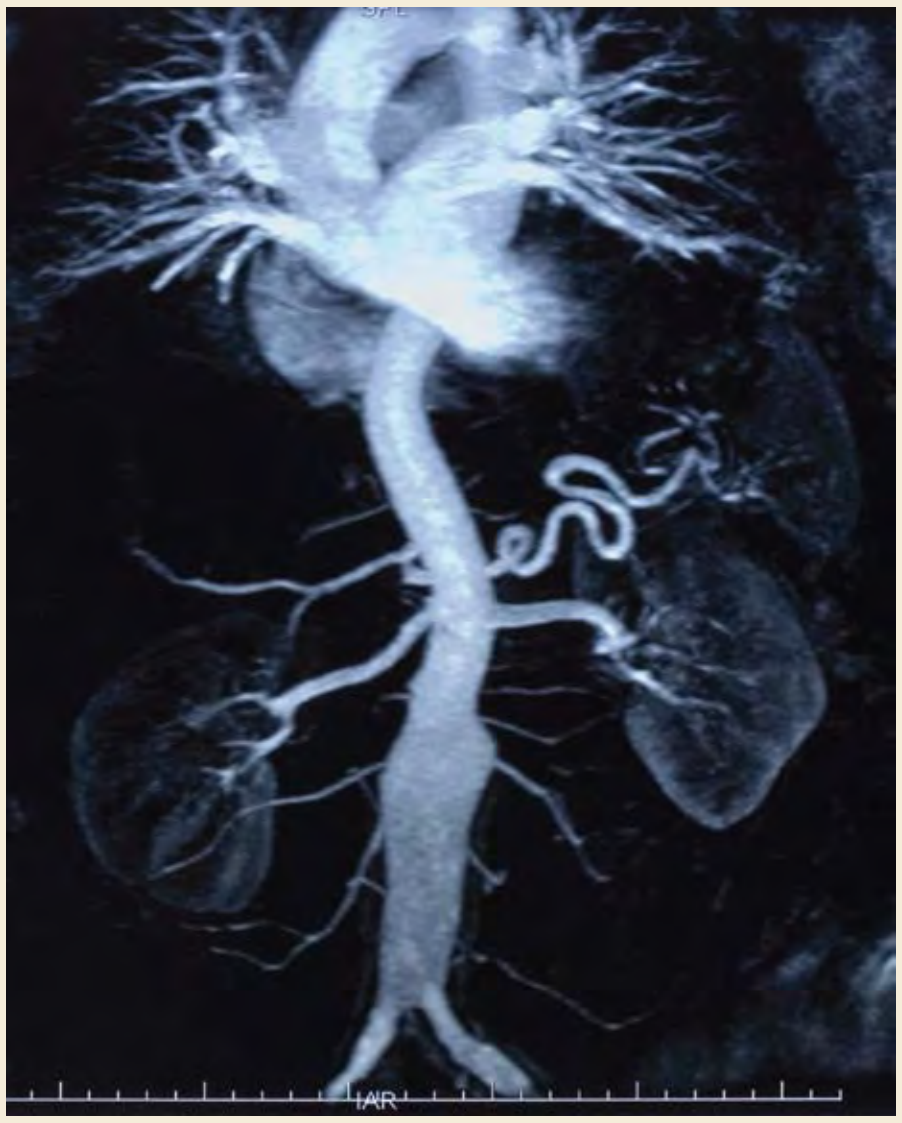
are able to tolerate either of the modalities, and thus would be good candidates for randomization, are not likely to benefit from CRRT, which is more invasive and more prone to untoward effects than IRRT. This dilemma is underscored by the lack of a mortality benefit for CRRT compared with IRRT in prospective randomized controlled trials as discussed by Tolwani in this issue.

In summary, CRRT, once a promising new method that allowed for the first time the administration of effective RRT and correction of metabolic and volume derangements in the most severely ill, did not prove superior to IRRT in direct comparison. However, CRRT will continue to have an important place in the treatment armamentarium for critically ill patients in whom IRRT is not an option.

Timing of RRT

Timely institution of RRT in ARF is fundamental to achieving treatment goals, namely solute clearance and fluid balance, while awaiting recovery of kidney function. Currently indisputable indications for RRT include persistent hyperkalemia, severe metabolic acidosis, and hypervolemia unresponsive to conservative measures; uremic serositis; bleeding diathesis; and severe encephalopathy (13). Beyond these indications and when azotemia is the sole abnormality, it is unclear when RRT should be started. "Early" or "prophylactic" RRT historically described the initiation of dialysis therapy before nitrogenous waste products reached some arbitrary predefined "critical" blood value, regardless of other indications. Older reports suggested that early initiation of RRT might improve survival (14,15), but this has not been confirmed in recent years.

We performed a comprehensive review of all available data on this topic by conducting a systematic review and meta-analysis to examine the effect of early initiation of RRT on survival (16). Again, the heterogeneity of the individual studies was formidable. They included randomized controlled trials, trials with sequential treatment assignment, and prospective and retrospective comparative cohort studies. In addition, the studies spanned more than four decades. In the primary analysis, which included four randomized controlled trials and one quasi-randomized controlled trial totaling 270 patients, early RRT was associated with a 36 percent mortality risk reduction (relative risk = 0.64; 95% confidence interval = 0.40, 1.05; p = 0.08). In a secondary, more inclusive analysis comprising 18 comparative cohort studies and totaling 2108 patients, early RRT was associated with a 28 percent mortality risk reduction (relative risk = 0.72; 95% confidence interval = 0.64, 0.82; p < 0.001).



This systematic review suggested that early institution of RRT might have a beneficial effect on survival of patients with ARF. Besides the design and methodological concerns of the studies included, the most commonly used criterion for "early" versus "late" initiation of RRT was an arbitrary cutoff of blood levels of retention solutes, rather than an objective time variable from onset of renal failure to RRT. This represents a fundamental design flaw since not only the time, but also the velocity of uremic retention solute accumulation such as urea, related in part to the degree of protein catabolism, determine its blood level.

Overall, these findings require confirmation by a large multicenter randomized controlled trial primarily designed to assess the effect of timing of RRT on survival in ARF. A trial designed to answer this question should be adequately powered. If one conservatively assumes an overall hospital mortality rate of 25 percent in patients with ARF regardless of dialysis requirement (3,17) and a hypothesized 36 percent mortality risk reduction derived from the aforementioned meta-analysis (16), a sample size of approximately 1100 would be required to achieve 90 percent power, which is a feasible goal. Much more thought and deliberation, however, must be spent on selecting the appropriate patient population and entry criteria. Clearly, an arbitrary cutoff value for urea or similar retention solutes will not suffice. Other measures—including novel urinary or blood markers conferring prognostic discrimination toward a prospective need for RRT—might be more valid inclusion criteria.

Finally, a large observational study to further characterize practice patterns and variation in RRT care internationally might help identify more robust criteria for timing of RRT, which in turn, might possibly help develop best practices of care. In summary, after completion and publication of two definitive, large-scale clinical trials addressing RRT intensity and modality in ARF, a case is made for the next "RRT frontier" that might promise improvement in outcomes, i.e., the timing of RRT initiation. Based on the results of a recent systematic review, we argue in favor of designing and carrying out a large-scale, definitive clinical trial on timing of RTT initiation in ARF, while avoiding potential pitfalls and study design flaws.

Orfeas Liangos, MD, FASN, and Bertrand Jaber, MD, FASN, are with the Department of Medicine, Division of Nephrology, St. Elizabeth's Medical Center, in Boston. Liangos is also with the Division of Nephrology, Klinikum Coburg, Coburg, Germany.

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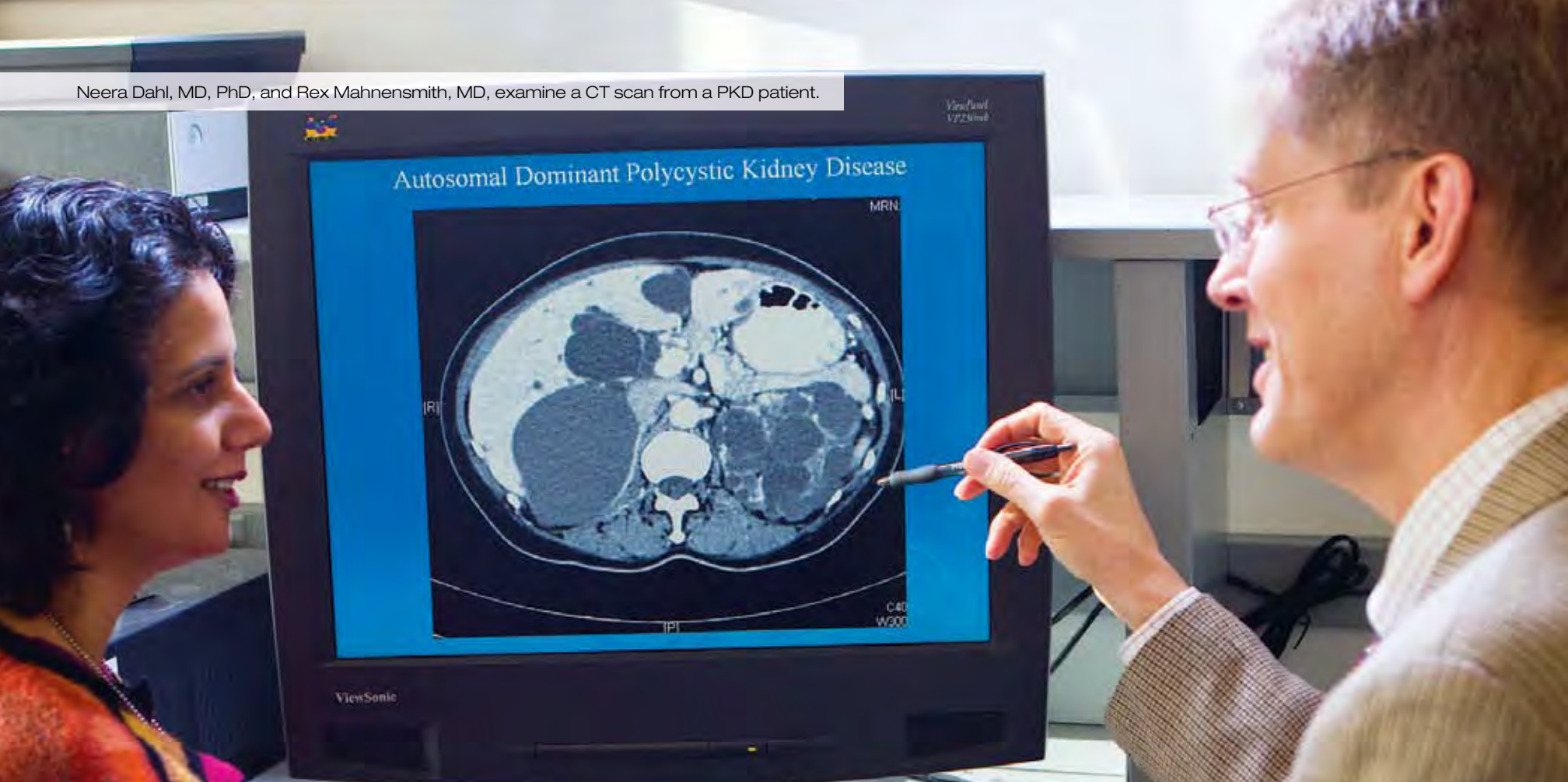

Neera Dahl, MD, PhD, and Rex Mahnensmith, MD, examine a CT scan from a PKD patient.

The genetics behind kidney disease are intricate and multifaceted. Only a few medical institutions in the country have the commitment to understanding and treating inherited kidney diseases and the resources to house the prestigious George M. O'Brien Kidney Research Center and a Polycystic Kidney Disease (PKD) Research Center, all supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). We are one of those centers.

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Continuous Renal Replacement Therapy: Modality of Choice in the Intensive Care Unit?

By Ashita Tolwani

Acute kidney injury (AKI) is a frequent complication in critically ill patients and is associated with a high mortality rate. Continuous renal replacement therapy (CRRT) represents a spectrum of dialysis modalities developed in the 1980s specifically for the management of critically ill patients with AKI who could not tolerate traditional intermittent renal replacement therapy (IRRT). Over the years, CRRT has found widespread use and acceptance due to its ability to provide effective volume and metabolic control in hemodynamically unstable patients.

Despite its physiologic benefits, randomized controlled trials (RCTs) have not shown a mortality benefit of CRRT over IRRT. Vinsonneau et al. performed the largest RCT comparing the effect of IRRT and CRRT on patient survival in 360 patients at several French institutions (1). Although the investigators found no significant difference in patient survival, several aspects of the study limit the applicability of the results to general clinical practice. First, patients with pre-existing chronic kidney disease (CKD) were excluded. Second, for unclear reasons, survival progressively increased in the IRRT group while it remained constant in the CRRT group, suggesting systematic changes occurred in the delivery of IRRT. Third, maintaining hemodynamic stability in the IRRT group required longer sessions with a mean IRRT treatment duration of 5.2 h per session.

As such, the applicability of the IRRT results to the "real world," where IRRT treatment times are significantly less than this on a routine basis, is questionable. Another concern is that the study only required achieving a mean urea concentration of 84 mg/dL or less, which is a low target according to current standards. This resulted in metabolic control not being achieved any better with CRRT than with IRRT. Finally, patients crossed over from CRRT to IRRT due to inadequate metabolic control from technical issues such as inability to keep the circuit patent and complications of anticoagulation.

Multiple published meta-analyses of RCTs comparing CRRT with IRRT in ICU patients with AKI also have not demonstrated a survival benefit with CRRT. However, the validity of the data from the studies is dubious because of issues related to study design, such as exclusion of patients with hemodynamic instability, improper randomization, differences in baseline characteristics between arms, and high crossover rates between modalities. Finally, no trial standardized the dose delivered or the timing of initiation. Notably, even though the meta-analysis by Bagshaw et al. (2) found no statistical difference in survival between the two modalities, there was a higher occurrence of hemodynamic instability and greater cumulative fluid balance in the IRRT groups.

If current studies cannot demonstrate a survival benefit of CRRT compared to IRRT, are there other outcome benefits for CRRT?

Hemodynamic stability

Hypotension is one of the most common complications associated with IRRT, occurring in approximately 20 percent to 30 percent of all treatments. This complication can lead to further organ ischemia and injury. Several observational studies and randomized studies have demonstrated better hemodynamic stability associated with CRRT. In a small RCT, Augustine et al. (3) reported a significant reduction in mean arterial pressure (MAP) during IRRT, which was not observed during CRRT. On the other hand, others have not reported any difference in hemodynamics between the two modalities. Uehlinger et al. (4) reported a similar frequency of hypotension between IRRT and CRRT.

The VA/NIH Acute Renal Failure Trial Network (ATN) study by Palevsky et al. (5) aimed to determine the optimal intensity of renal replacement therapy (RRT) in critically ill patients with AKI and at least one other failing organ or sepsis. The study compared two strategies for the management of RRT in critically ill patients with AKI. Both treatment strategies employed both conventional IRRT in patients whose blood pressure was stable and either sustained low-efficiency dialysis (SLED) or CRRT in patients who were hemodynamically unstable.

In one strategy, IRRT and SLED were provided three times per week, and CRRT was dosed to provide a clearance of approximately 20 mL/kg/h. In the other treatment arm, IRRT and SLED were provided six times per week and CRRT was dosed to provide a clearance of approximately 35 mL/kg/h. Overall, there was no significant improvement in patient outcomes with the more intensive treatments. Notably, only 4.6 percent of treatments performed in hemodynamically unstable patients were SLED. This low utilization of SLED in hemodynamically unstable patients occurred despite physicians' ability to prescribe either SLED or CRRT in the study. Moreover, hypotension was a more serious complication among patients treated with IRRT. Approximately 1.7 percent of all IRRT treatments required discontinuation of therapy due to hypotension compared to only 0.7 percent of CRRT/SLED treatments. These differences were observed despite the fact that the IRRT patients were considered hemodynamically stable.

The rate of renal recovery at hospital discharge was substantially lower in the ATN study than what has been reported previously, even with the exclusion of patients with moderate to severe CKD. A possible explanation is that the high rate of severe hypotension in the IRRT patients may have contributed to the relatively low rate of renal recovery. Finally, fluid removal was much less aggressive in the IRRT patients (approximately 6–9 L/week) compared to that in the CRRT patients (greater than 20 L/week). These findings support CRRT as the standard of care for hemodynamically unstable patients with AKI.

Renal recovery

Renal recovery is another important outcome for patients with AKI and may be affected differently by RRT modality. Failure to recover renal function after AKI has both short- and long-term implications with respect to morbidity and health care costs. Multiple observational studies and one randomized study support greater rates of renal recovery in patients with AKI requiring CRRT compared to IRRT. Mehta et al. randomized 166 patients in four centers to receive CRRT or IRRT and demonstrated no difference for hospital mortality using multivariate logistic regression analysis (6). However, CRRT was associated with a significantly higher rate of complete renal recovery in surviving patients who received an adequate trial of therapy with no crossover (92.3 percent versus 59.4 percent; $p < 0.01$).

Two recent large epidemiologic studies have also reported increased rates of renal recovery in patients on CRRT. In the Beginning and Ending Supportive Therapy (BEST) kidney trial (7), a multinational, prospective, epidemiologic study of AKI in the ICU including over 30,000 patients in 23 countries, 1218 patients received RRT. Although no mortality difference was detected between patients treated with CRRT compared to IRRT, dialysis independence at hospital discharge was higher after CRRT (85.5 percent versus 66.2 percent; $p < 0.0001$).

Bell et al. (8) retrospectively studied 2202 patients treated with RRT for AKI from 32 ICUs in Sweden. CRRT was used for 1911 patients and IRRT for 291. Ninety-day mortality was not significantly different between the two groups. Among survivors, 8.3 percent treated with CRRT became dialysis dependent compared to 16.5 percent treated with IRRT. Multivariate analysis showed that the adjusted odds ratio (OR) of dialysis dependence in IRRT was 2.60 compared with CRRT. Moreover, in patients who did develop chronic dialysis dependence, the subsequent survival rate was significantly lower in patients treated with HD compared to CRRT-treated patients.

In the ATN trial by Palevsky et al. (5), over 70 percent of patients in both treatment strategy arms (intensive and less intensive) had no recovery of kidney function by 28 days and were dialysis dependent. This is quite high compared to other trials, given that patients with CKD were excluded. It is important to realize that the two arms consisted of a mix of patients on CRRT, SLED, and IRRT. In the RENAL Replacement Therapy Study of dose intensity (9), patients were randomized to CVVHDF at 25 mL/kg/h versus CVVHDF at 40 mL/kg/h.

In contrast to the ATN trial, the RENAL investigators reported 14 percent of patients were dialysis dependent in both treatment arms by 28 days. Unlike the ATN trial, the two intensity arms only included patients on CRRT, and not on other modalities. Moreover, unlike the ATN trial, the RENAL study included patients with CKD. This finding supports the notion that CRRT leads to higher rates of renal recovery.

Fluid management

In critically ill patients, nutritional requirements and the use of intravenous medications necessitate the administration of large amounts of fluid, resulting in excessive volume overload. Excessive fluid administration can cause pulmonary edema, hypoxia, and the need for mechanical ventilation. In addition, excessive fluid accumulation can impair cardiac function and renal perfusion.

Several observational studies have shown a direct relationship between fluid accumulation and mortality in critically ill patients. The Acute Respiratory Distress Syndrome (ARDS) clinical trial network (10) demonstrated that a more liberal fluid

administration regimen (to CVP of about 12 cm H_2O) resulted in greater lung function impairment than a more conservative approach (target CVP of about 8 cm H_2O). Although survival at 60 days was not significantly different between the two groups, ventilator-free days and ICU-free days were both significantly lower in the conservative group. Moreover, the percentage of patients requiring dialysis in the conservative group (10 percent) was lower than in the liberal group (14 percent).

In the Program to Improve Care in Acute Renal Disease (PICARD) database (11) of critically ill patients with AKI in whom nephrology consultation was sought, volume overload in patients with AKI was independently associated with increased mortality. Fluid overload was defined as a percentage of fluid accumulation >10 percent over baseline weight at hospital admission. In 542 patients in whom fluid data were available, those with a >10 percent accumulation had a significantly higher risk of death at 30 and 60 days of enrollment.

Within the group requiring RRT, those with greater fluid accumulation at dialysis initiation had worse outcomes with an OR for death (adjusted for severity of illness and dialysis modality) of 2.07 (95 percent CI 1.27–3.37). Patients who remained fluid overloaded had a higher mortality rate that was proportional to the degree of fluid accumulation. Volume control was significantly better in those treated with CRRT versus IRRT. Importantly, the correction of volume accumulation had a positive effect on survival, making this an important therapeutic target in critically ill patients with AKI. Prospective randomized studies with different regimens of fluid administration are necessary to know their effects on mortality and the outcome of AKI in critically ill patients.

Augustine et al. (3) compared net fluid balance provided by IRRT and CRRT in an RCT. Even over a relatively short three-day period, significant differences were observed. In the CRRT group, a net loss of 4005 mL (approximately 4 kg) occurred, while the IRRT group sustained a net gain of 1539 mL (approximately 1.5 kg) on an average basis. Although RCTs have not been consistent in this area, these data are corroborated by other studies and general clinical practice and represent one of the benefits of CRRT over conventional IRRT. The capacity to adjust fluid balance on an hourly basis, even in hemodynamically unstable patients, is largely responsible for the growing popularity of CRRT.

In a survey by the National Kidney Foundation 10 years ago, IRRT was determined to be the preferred modality for renal support for AKI, used in more than 75 percent of cases by most nephrologists (12). More recently, a survey of intensivists and nephrologists who participated in the multicenter ATN study revealed that CRRT accounted for 36 percent of prescribed RRT treatments (13). In the multicenter PICARD study (14), 60 percent of dialyzed patients had received CRRT for some or all of their renal support.

Internationally, the multinational epidemiologic BEST Kidney Study (7) reported that CRRT was the initial modality used in 80 percent of AKI treatments in the ICU, followed by IRRT (17 percent). Finally, a recent survey of an international multidisciplinary cohort of renal practitioners showed that CRRT had become the standard for AKI support outside of the United States (15).

In summary, although there is a call for more outcomes-based RCTs, mounting evidence published in the last decade has propelled CRRT to become the preferred modality of choice in the ICU patient with AKI. This is due to the recognition by its users of the advantages of CRRT in volume management and hemodynamic stability in the critically ill patient.

Ashita Tolwani, MD, is associate professor of medicine in the division of nephrology at the University of Alabama at Birmingham.

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Biomarkers of Acute Kidney Injury: Dawning of a New Era

By Joseph Bonventre

The kidney community has devoted a great deal of effort to building consensus regarding the definition of acute kidney injury (AKI). This has resulted in RIFLE classification and AKI network (AKIN) criteria focused on changes in serum creatinine (SCr) and rate of urine production. These changes in SCr are important and have been shown to be predictive of outcome in a number of studies. SCr changes, however, can be affected by a large number of things unrelated to kidney injury, including drug interference with secretion of creatinine into the tubule, muscle mass, gender, age, and renal reserve, a measure of how much the kidney can compensate for injury.

Kidney injury, which leads to a reduction in GFR, is not immediately followed by an increase in SCr. This lag time greatly impedes the early diagnosis of AKI, delays therapy, and impairs our ability to test new therapies early in the course of the disease when AKI is much more likely to be amenable to interventions that might alter its natural history. SCr concentration can also increase due to functional decreases in GFR that are not associated with tubular injury. This is the case in prerenal azotemia. It has thus been recognized for a number of years that new biomarkers of injury would be very desirable. A "kidney troponin," for example, would allow for the identification of true injury to the kidney as troponin does for the myocardium.

A biomarker is defined as a characteristic that can be objectively measured and evaluated as an indicator of normal biologic or pathogenic processes of pharmacological responses to a therapeutic intervention (1). Examples of biomarkers are proteins; lipids; genomic, metabolomic, or proteomic patterns; imaging determinations; electrical signals; and cells present on a urinalysis. Having a biomarker that directly reflects injury and is easily measured from fluid that is easily obtained, such as blood or urine, would introduce a new paradigm in which we would be directly monitoring injury rather than a secondary consequence of injury—a reduction in GFR, as manifest by an increase in SCr.

In commenting on a major initiative of the FDA that focuses on biomarkers, Janet Woodcock, MD, deputy commissioner for operations and head of FDA's Critical Path Initiative, said: "Most researchers agree that a new generation of predictive biomarkers would dramatically improve the efficiency of product development, help identify safety problems before a product is on the market (and even before it is tested in humans), and facilitate the development of new types of clinical trials that will produce better data faster" (2). The FDA has provided guidance that a biomarker can be considered "valid" if (i) it is measured in an analytical test system with well established performance characteristics and (ii) there is an established scientific framework or body of evidence that elucidates the physiologic, pharmacologic, toxicologic, or clinical significance of the test result (3).

We need better biomarkers to diagnose AKI earlier, to predict outcome in a patient with AKI with standard therapy, and to identify who will respond to an intervention and whether the intervention is working. In addition, better biomarkers will permit better stratification of patients for clinical trials and potentially lead to definition of new therapeutic targets for AKI. A good predictive biomarker will have a significant effect on evaluation of potential therapies because it will enable the identification of subgroups of patients who will have a high incidence of kidney injury and hence reduce the number of patients needed to study in order to test potential therapeutic strategies.

A clinically useful new kidney biomarker will improve the sensitivity and specificity for the detection of renal injury and discriminate renal injury, which may have long-term consequences, from adaptive responses that may be reflected by transient BUN/creatinine increases that return to pre-elevated levels over time, even with continued exposure to the agent in question. It is also likely that some of these biomarkers will be useful not only for AKI, but also to monitor severity and progression of glomerular or tubular-interstitial disease in patients with chronic kidney disease.

Over the years, a large number of biomarkers of kidney injury have been suggested, yet for various reasons, none have been routinely accepted in animal or clinical studies. In some cases, the biomarker was felt to be too sensitive, not sensitive enough, or too nonspecific. In other cases, the biomarker was unstable with storage. More recently, however, there have been a number of advances in the application of biomarkers to AKI.

Promising biomarkers

A limited number of biomarkers are currently being evaluated by a number of groups, and clinically useful reagents have been developed. Some of the most promising urinary biomarkers for AKI include: microalbuminuria, kidney injury molecule-1 (KIM-1), N-acetyl ß-D glucosaminidase (NAG), neutrophil gelatinase associated lipocalin (NGAL), cystatin C, L-fatty acid binding protein (L-FABP), and interleukin-18 (4).

Translational biomarkers that can be measured in blood or urine in both experimental animals and humans are of particular interest. It may be possible to draw on the experimental information obtained for such biomarkers in animals to help guide the use and interpretation of biomarker studies in humans. Biomarkers that have been well studied and characterized as very sensitive biomarkers of injury in animals, if they function similarly in man, may make it possible to monitor safety and efficacy in clinical trials when the ability to obtain kidney tissue is severely constrained and when the severity of the injury early on is insufficient to result in an increase in SCr.

Blood and urine are two convenient fluids in which to measure a particular biomarker of kidney injury. Urine has the advantage of being readily available noninvasively and amenable to straightforward testing by both health care professionals and patients themselves. Given its normally low protein content, there is also less interaction in the biomarker assay with proteins. On the other hand, large variations in physical chemical properties of urine may affect reliability of the test for the biomarker and/or stability of the analyte.

Given the importance to the clinical, pharmaceutical, and regulatory communities motivated by early intervention and safer therapies, there has been a great deal of activity devoted to examining the role of various potential biomarkers of kidney injury in both animals and humans. Biomarkers have been proposed to reflect injury to various parts of the nephron or to reflect interstitial disease (5), although in many cases the specificity for particular nephron sites has not been sufficiently studied.

Ischemia/reperfusion injury and most tubular toxins have as their primary site of injury the proximal tubule. If in some cases the primary site of injury is more distal along the nephron, the proximal tubule is often also secondarily involved. Although there are some important exceptions to this generalization, such as lithium, whose toxicity is predominantly distal nephron-related, in general a biomarker sensitive for proximal injury will be useful for many clinical scenarios as well as very useful in safety monitoring and assessment.

Kidney biomarkers in drug approval

The importance of the identification of kidney injury biomarkers for patient safety was manifest quite clearly in July 2008 when the FDA and the European Medicines Agency (EMEA) agreed to accept data for seven kidney toxicity biomarkers as part of the drug approval process. This was the first time that a single application was submitted to both regulatory agencies.

These important additions to the drug approval process resulted from a historic collaboration among pharmaceutical companies, academia, and regulatory agencies, comprising the Predictive Safety Testing Consortium (PSTC). The seven biomarkers found in urine—KIM-1, albumin, total protein, ß2-microglobulin, cystatin C, clusterin, and trefoil factor-3—were deemed indicative of drug-induced damage to kidney cells and hence "qualified" for used in rat studies. The PSTC is currently working to obtain sufficient evidence for the FDA and EMEA to qualify some or all of these markers for human studies.

Much of the development of biomarkers has grown out of kidney safety and drug toxicity studies. The information obtained from these studies will go far to inform the use of these biomarkers—and potentially others—for patients with sepsis, ischemia, and other drug and nondrug-related forms of injury. Understanding the performance of kidney injury biomarkers, however, is much more straightforward in animals than it is in humans. In animals there is a very good "gold standard": renal pathology. In humans, pathology is infrequently available.

Novel approaches must be developed because comparisons to SCr are not satisfactory for the reasons already mentioned. A change in SCr, especially if it is transient and reasonably modest, does not necessarily imply kidney injury. A biomarker may be increased without a change in SCr but that does not impugn the biomarker necessarily since there may be significant injury that is not sufficient to produce an increase in SCr. On the other hand, SCr may be increased and a biomarker not increased when there is no injury but rather a hemodynamic change that results in an elevation in SCr.

There is a strong tendency in the growing literature on this topic to compare biomarkers to SCr as a gold standard. Under certain circumstances SCr is a very reasonable metric since it provides insight into GFR; however, the inadequacies of SCr as a gold standard represent barriers to understanding of the true performance of the biomarker to diagnose injury. Patient outcome is a "hard endpoint." Patients are quite complicated, however, with many things contributing to long-term outcome. It has been suggested that multiple biomarkers will be more useful than one and this, I believe, may be true if we really understand what each biomarker is telling us. Point-of-care technologies, including dipsticks, will be very useful in making the biomarkers more available for routine clinical use (6).

The recognition of the inadequacy of kidney injury biomarkers that have been used for 50–100 years (BUN and creatinine) has led to intense interest in finding and validating new biomarkers. New biomarkers will enable us to diagnose kidney injury earlier and provide better information about the status of ongoing injury in patients with chronic kidney disease. This will add to the armamentarium of personalized medicine by better informing interventional, diagnostic, and therapeutic decision-making to minimize kidney injury and optimize interventional strategies. I am convinced that better kidney injury biomarkers will provide us with better tools that will result in better outcomes for our patients.

Joseph Bonventre MD, PhD, is with the Renal Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Harvard Institutes of Medicine, in Boston. Bonventre declares that he is co-inventor on KIM-1 patents that are licensed by Partners Healthcare to Johnson and Johnson, Inc., and Genzyme Corp.

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Pharmacological Treatment of Acute Kidney Injury:

Where Are We and Where Are We Going?

By Mark Okusa

Over the past few years, and for appropriate reasons, the field of acute kidney injury (AKI) has evolved at a rapid pace. Even the name acute renal failure (ARF) was changed to AKI, and ICD-9 codes adopted AKI in October 2008. The primary reason for the change in nomenclature was the repeated observation that pharmacological therapy of AKI has been unsuccessful despite proven benefits seen in preclinical studies. Prevention and treatment of AKI are indeed important clinical issues, as the incidence and mortality in patients with AKI, especially in critically ill patients, remains alarmingly high despite substantial advances in techniques of resuscitation and renal replacement therapy.

Recognizing the importance of AKI and mortality, investigators over the past few decades have identified many compounds and drugs that have benefited animals, but none so far that have been useful in humans. So why have we failed to identify a "silver bullet," or even a bronze one, in the prevention and treatment of AKI? The answer may be simply that these therapeutic agents may be effective, but a number of barriers exist that preclude favorable outcomes. Thus a large number of investigators began a more coordinated effort at reappraising the barriers to progress in human AKI.

A reappraisal of the field of acute kidney injury

Recently, concerted effort has been made to determine and understand gaps in our knowledge. With better understanding of these deficiencies, progress might be made in reducing the morbidity and mortality of AKI. There have been a number of consensus conferences from different groups, including the Acute Dialysis Quality Initiative (ADQI), the Acute Kidney Injury Network (AKIN), the Acute Kidney Injury Advisory groups to the American Society of Nephrology, and the International Society of Nephrology, as well as the National Kidney Foundation and Kidney Disease: Improving Global Outcomes (KDIGO) groups.

Two important barriers to advancement are: i) lack of a definition of AKI and ii) lack of an accurate way to detect AKI early in its course. This recognition has inspired leaders in the field of AKI. As a result, major advances have been made in classification of AKI, biomarkers, epidemiology, pathophysiology, and drug development. These new drugs on the horizon have led to a tremendous effort in the translational research arena in AKI.

Why we need a definition of AKI

The AKIN group sought to change the name from ARF to AKI given the fact that ARF includes a spectrum of clinical conditions from subclinical injury and prerenal azotemia to acute tubular necrosis. This all-inclusive terminology of AKI has been adapted and has been used with increasing acceptance worldwide.

The literature indicates that for a single procedure, such as cardiac surgery, there are over 30 definitions for AKI leading to highly variable incidence of AKI of 1–31 percent. With such high variability one cannot compare studies to determine whether drugs are efficacious or not. Severity of injury may be highly variable between studies.

Recently, two classification schemes have been described: RIFLE (Risk, Injury and Failure) and Acute Kidney Injury Network (AKIN) Staging (I, II, III) based upon graded levels of rise in serum creatinine and/or decrease in urine output (4,10). In 2000, the ADQI was established to develop an evidence-based assessment and consensus guidelines to standardize care and direct further research (11). The ADQI group classified ARF based upon creatinine and urine output. A growing number of studies have validated this classification scheme of AKI (12,13).

In light of recent studies indicating that even a small rise in creatinine was associated with an increase in mortality, the AKIN group proposed the AKIN staging (I, II, III). These studies highlight the important effects of a small decline in GFR on the overall outcome of critically ill patients. Even the least severe category of RIFLE, "R," or AKIN stage I, was associated with a mortality rate of 30.9 percent or 30.7 percent, respectively (14). Recent studies indicate that both classification systems perform well. Thus, these new classification systems will allow future studies to be done using a single definition of AKI.

Chronic kidney disease increases risk of AKI

Most recently, in population-based studies, there is evidence that strongly suggests an important and growing role of AKI in the global epidemiology of chronic kidney disease (CKD) and end stage renal disease (ESRD). A recent study highlights the important association between baseline kidney function and the risk of hospital-acquired AKI (15). In this study they found that in cases of dialysis-requiring AKI, 74 percent occurred among patients with an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2. There was a graded association between baseline eGFR and the risk of AKI, ranging from a twofold increase among patients with eGFR 45–59 mL/min/1.73 m^2 to a 40-fold increase among patients with eGFR <15 mL/min/1.73 m^2.

Although no drug has been shown to be beneficial in the prevention of AKI, understanding that CKD increases the risk of AKI should lead physicians to use caution in this high risk group. Avoidance of nonsteroidal anti-inflammatory drugs, avoidance of contrast imaging studies, and using isosmolar contrast agents or avoiding invasive procedures are critical measures in the prevention of AKI.

Acute kidney injury increases risk of chronic kidney disease and ESRD

Although the high mortality associated with AKI has long been recognized, only recently have the long-term effects of AKI on renal outcomes been demonstrated. Ishani et al. demonstrated for the first time that patients with AKI and preexisting CKD had an increased risk for progression to ESRD, an observation suspected but not previously demonstrated (16). In this study, a 5 percent random sample of Medicare beneficiary claims data from the Centers for Medicare and Medicaid Services (CMS) and the ESRD incidence database from the United States Renal Data System (USRDS) was used. The risk for developing ESRD was greatest in patients with AKI and CKD with a hazard ratio of 41.2 [95% confidence interval (CI) 34.6 to 49.1] compared to AKI without CKD, 13.0 (95% CI 10.6 to 16.0) and with CKD without AKI, 8.4 (95% CI 7.4 to 9.6). Therefore, AKI in older patients with CKD poses a significantly increased risk for ESRD, and AKI may accelerate a progressive decline in renal function.

Distant organ effects of AKI

Recent studies have focused on the observation that a small increase in creatinine is an independent predictor of increased mortality. What is becoming increasingly evident is that AKI is a complex and multisystemic condition, which is thought to lead to a distant organ dysfunction syndrome contributing to fatality in such patients. Experimental studies provide some insight into the mechanism by which isolated events leading to the loss of GFR can lead to distant organ effects, including circulating factors such as cytokines and chemokines, activated leukocytes, and adhesion molecules leading to immune cell infiltration.

Oxidative injury, apoptosis, and cellular necrosis contribute to the final pathway of organ dysfunction (17). Thus the ability of kidney dysfunction to affect other organs likely contributes to the high mortality associated with AKI. This concept implies that future drugs for the treatment of AKI should have broad effects that may ameliorate damage to multiple organs.

Biomarkers of AKI

Serum creatinine is a poor biomarker of AKI. Although both the RIFLE and AKIN criteria use serum creatinine in their staging, it is hoped that sensitive biomarkers will be employed in the future. There is a considerable amount of injury that may occur without a change in GFR. At the same time there may be changes in GFR without a change in tubular injury (prerenal). Furthermore, there is a delay in the rise in serum creatinine so that by the time a change is observed, intervention may be too late. Lastly, a number of factors affect serum creatinine independent of a change in GFR, including but not limited to nutrition, muscle mass, infection, edema (which affects the volume of distribution), and drugs such as n-acetyl cysteine, which may alter the metabolism of creatinine.

Over the past several years, a concerted effort has been made to identify the "kidney troponin." Biomarkers may be used to identify, early in the course of AKI, different forms of AKI, and they may predict the severity and prognosis of patients with AKI. A number of biomarkers have been identified, and prominent among these are kidney injury molecule 1 (KIM-1), neutrophil gelatinase associated lipocalin (NGAL), interleukin-18 (IL-18), and liver fatty acid binding protein (LFABP) to name a few.

The value of biomarkers as diagnostic tools and predictors of clinical course will depend on their individual performance. Given the heterogeneity of causes of AKI, background conditions, and age, it is likely that a panel of biomarkers will be most effective. A highly sensitive, high-throughput method that can be performed within 3-4 h has been developed by Bonventre's group and uses a multiplex microbead technology capable of simultaneously measuring multiple biomarkers within a single well (18). Another high-throughput, easy to use immunochromatographic assay developed for KIM-1 is sensitive and specific and will permit rapid (within minutes) point-of-care detection of urinary biomarkers in humans with AKI (19). We are hopeful that a rapid "dipstick" method or multiplex technology will lead to early diagnosis of AKI where therapies may be instituted early in the course of disease to minimize the extent of injury.

In the end, one must ask, why do we not have drugs to treat AKI? Clearly the disease is complex, but over the past five years there has been a reappraisal of the field of AKI that has led to intense investigation. Significant progress has been made to: i) understand the epidemiology of the disease, ii) understand the pathophysiology and multisystemic nature of AKI, iii) standardize the definition of AKI, iv) identify new biomarkers to diagnose patients

with AKI early in the course of the disease, and v) develop novel compounds through advanced drug discovery programs and innovative translational sciences.

Further initiatives are underway to rapidly synthesize new knowledge in the field of AKI. In sequential and complementary fashion, the AKIN group is planning a summit focused on defining appropriate clinical endpoints for outcomes in AKI research in San Diego February 27–28, 2010, and the National Institute of Diabetes and Digestive and Kidney Diseases/ National Institutes of Health is planning a conference focused on current opportunities of clinical trials in AKI, October 2010, in Bethesda, Md. Leading investigators in the field of AKI from around the world will gather and finalize important guidelines and therapeutic opportunities in AKI.

We are now ready to implement newly acquired knowledge and develop well-designed clinical trials of promising new drugs as well as re-evaluation of older drugs that have failed in past studies. We anxiously await clinical trials in AKI in the next five years as the results of these trials should finally lead to new treatments for a devastating disease. The fruits of these studies should justify the time spent in re-appraising the field of AKI.

Mark Okusa, MD, is the John C. Buchanan Distinguished Professor of Medicine, Division of Nephrology and Center for Immunity, Inflammation and Regenerative Medicine at the University of Virginia Health System in Charlottesville, Va.

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ASN Prepares for World Kidney Day 2010

To increase public awareness about kidney disease, the American Society of Nephrology (ASN) is participating in the fifth annual World Kidney Day on Thursday, March 11, 2010. The International Society of Nephrology and the International Federation of Kidney Foundations established World Kidney Day in 2006 to raise awareness of kidney disease, highlight risk factors, and encourage behaviors that reduce the incidence of kidney disease. The theme for this year's World Kidney Day is "Protect Your Kidneys: Control Diabetes."

According to the National Institute of Diabetes and Digestive and Kidney Diseases, diabetes is the most common cause of kidney failure, accounting for nearly 44 percent of new cases. As a result, approximately 180,000 people in the United States "are living with kidney failure as a result of diabetes."

Building on traditions established during previous World Kidney Day events, ASN will hold a reception on Capitol Hill with other organizations (such as the National Kidney Foundation), and ASN leaders will visit nearly 100 congressional offices to inform lawmakers about the most pressing issues facing patients with kidney disease and those who care for them. In addition, ASN will coordinate a media campaign to help inform the public about kidney disease.

The ongoing debate about health reform and the proposed rule for implementing the end stage renal disease provisions of the Medicare Improvements for Patients and Providers Act highlight the critical need to improve care for patients with kidney disease. To learn more about World Kidney Day, please visit www.asn-online.org

ASN Responds to Disaster in Haiti

By Rachel Shaffer

The massive earthquake of 7.0 magnitude that hit Haiti Tuesday, January 12, resulted in an estimated 75,000 dead, 200,000 injured, and 1 million displaced people.

To help respond to this crisis, the American Society of Nephrology (ASN) immediately contacted other kidney-related organizations, including the International Society of Nephrology, the Kidney Care Emergency Response (KCER) Coalition and the Florida ESRD Network, the National Kidney Foundation, the Sociedad Latino-Americana de Nefrologia e Hipertension (SLANH), and the Society of Nephrology of the Dominican Republic (SNDR) as well as dialysis providers and industry organizations. ASN also worked with the U.S. government, Doctors Without Borders, the USNS Comfort, and Partners in Health.

Led by its Disaster Relief Task Force, ASN helped:

- develop a protocol for crush injury currently employed in Haiti to reduce the incidence of AKI from rhabdomyolysis.
- identify over 60 members who volunteered to travel to the region and provide care.
- coordinate supplies generously donated by dialysis providers and industry to ensure medical providers had the items they needed to treat patients in crisis including dialyzers, dialysis machines, dialysis fluids, sodium polysytrene sulfonate for treatment of hyperkalemia, handheld portable systems for measurement of renal function, and serum electrolytes and dialysis catheters.
- create a supply chain to rapidly deliver the items of greatest need.
- support the health care infrastructure in the region.
- establish daily conference calls for the nephrology community to coordinate relief efforts.

"Nearly 30 members of the nephrology community met daily by conference call during the crisis," said Didier Portilla, MD, chair of the ASN Disaster Relief Task Force. "KCER organized these calls, which provided updates from nephrologists in Haiti and the Dominican Republic, assessed the health care infrastructure in these countries, and identified needs for physicians and nurses."

"Dialysis providers and other organizations worked to target supplies to reach the areas where they were most needed," said Mark Okusa, MD, FASN, chair of the ASN Acute Kidney Injury Advisory Group. "Due to logistical problems in transport to Port au Prince, Haiti, we focused on three cities in the Dominican Republic to rapidly transport supplies into Haiti."

According to Portilla, "SLANH President Ricardo Correa-Rotter, MD, and SNDR President Sandra Rodriguez, MD, deserve tremendous credit for establishing this connection and saving lives, as do Dr. Okusa and Rajnish Mehrotra, MD, FASN." Mehrotra chairs the ASN Dialysis Advisory Group.

ASN encourages its members and the rest of the community to contribute directly to entities specifically dedicated to providing disaster relief to Haiti, such as the American Red Cross or the William J. Clinton Foundation. A list of organizations collecting funds for the disaster is provided by InterAction through its website at http://www.interaction.org/crisis-list/earthquake-haiti.

Industry Spotlight

FDA to Review ESAs

In the latest word on the safety of erythropoiesis-stimulating agents (ESAs), the FDA plans a public meeting this year to reevaluate the use of the agents in the treatment of anemia in patients with chronic kidney disease. The recent findings of the TREAT trial (Trial to Reduce Cardiovascular Events with Aranesp Therapy) of the Amgen ESA Aranesp, in combination with earlier findings about ESAs, has prompted the reevaluation. The news appeared in a Jan. 7 *New England Journal of Medicine (NEJM)* article written by four physician-authors from the FDA's Center for Drug Evaluation and Research.

The TREAT trial found a significant, substantial increase in the incidence of fatal or nonfatal stroke in the ESA group compared with a placebo group (5 percent of patients vs. 2.6 percent) and also a significantly higher rate of thromboembolic events among patients taking ESAs.

The *NEJM* authors noted that three trials showed that hemoglobin concentration targets of 14.0, 13.5, and 13.0 g/dL—and the ESA regimens used to achieve them—are harmful. According to their commentary, a future, controlled trial needs to show that assignment to any higher hemoglobin target, compared with any lower target, or to ESA dosing regimens necessary to attain these targets, prevents cardiovascular events or does not increase their likelihood.

Is Salt the New Trans Fat?

Salt in food, like sugar and fat before it, appears to be the latest target of ingredient awareness.

In January, New York City Mayor Mike Bloomberg announced a health initiative that encourages food manufacturers and restaurant chains across the country to reduce the amount of salt in their products by 25 percent over the next five years. In December 2009, Sara Lee announced its commitment to reducing salt an average of 20 percent over that time period. Sara Lee announced it would concentrate its efforts to reduce salt in fresh bread, hot dogs, lunchmeat, breakfast foods, and cooked sausage. Earlier, the company launched a line of lower-sodium lunchmeats and sodium-reduced breads.

Salt has long been on the health consciousness radar screen for its role in high blood pressure and links to cardiovascular disease. Now salt's role in kidney health is coming into consciousness too.

World Action on Salt and Health (WASH) is a global group seeking to improve the health of populations throughout the world by achieving a gradual reduction in salt intake. Of the 80 nations—including the United States—that make up WASH members, Australia is working very hard to impress citizens about kidney danger. The Australian arm of WASH, AWASH, notes that 14 percent of Australians have some form of kidney damage. The AWASH website notes that high blood pressure, caused by salt, contributes to kidney damage because of the harm it does to blood vessels. For the same reason, once kidney damage has occurred, high blood pressure accelerates the progression toward kidney failure.

ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

ASN Membership

Member Benefits

Education

ASN provides member discounts for a variety of exceptional educational activities:

- **Renal WeekEnds 2010** summarize, critique, and integrate key Renal Week 2009 presentations in powerful two-day courses (presented in six locations across the United States).
- **15th Annual Board Review Course and Update** prepares nephrologists for the ABIM initial certification and maintenance of certification examinations and provides a comprehensive update for the practicing nephrologist.
- **ASN Renal Week 2010** remains the world's premier gathering of kidney professionals presenting advances in treatment, research, and education.

Abstract Submission allows members to submit and sponsor abstracts for oral and poster presentation at ASN Renal Week.

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Member Categories

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- Completion of research or clinical training in nephrology.
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- Publication of at least one peer-reviewed paper in nephrology.
- Experience as a specialist in kidney disease and related conditions.

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Only **Active, Corresponding,** and **Affiliate** members may use the online membership system. To enroll in the Retired and Fellow-in-Training categories, please download and print the membership form from the ASN website or contact ASN Membership Director Pamela Beard at 202/416-0657 or pbeard@asn-online.org.

Join or Renew ASN membership online at

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Fellows Corner

What I Wish I'd Known Before I Started Fellowship

We have all experienced those moments when we wonder what we have gotten ourselves into. Nephrology fellowship is one of these life-altering events, so we asked a sampling of current fellows the one thing they wish they had known before starting training.

Some answers focused on the practical. Deepti Torri, of North Shore Long Island Jewish Medical Center in New Hyde Park, N.Y., said better understanding of renal physiology would have helped. "Taking *Texbook of Medical Physiology* by Arthur Guyton out of the dusty bookshelf and reading the renal physiology chapters from beginning to end would have been time well spent," Torri said.

Ruba Nijmeh, fellow at Ohio State University Medical Center in Columbus, remembers the first overwhelming days of fellowship when the pager went off for the acute dialysis room. "You answer your page, and the nurse on the other end of the phone is asking you for orders: what type of bath you want, how many hours, what anticoagulation, etc.," Nijmeh said. "Of course, as you don't happen to know the right answer, you go with what the nurse says. Most of the time, the nurse is experienced and helps you make the right decision." Any of the basic building blocks of inpatient nephrology would have been helpful, she added.

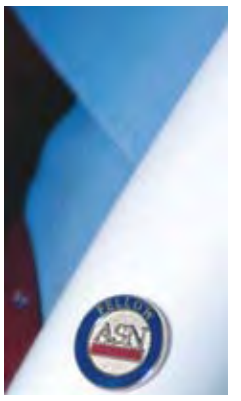
Rajiv Vij of the North Shore University Hospital did not realize how many choices there were within nephrology. These include private practice, clinical investigation, and basic science research. "For candidates who are uncertain, I support application to either clinical fellowship programs with an option to do a third year of research, or to programs that have an open-mindedness with respect to the new niches in nephrology," he said.

One interesting answer focused on the transition from resident to specialty fellow. As a resident, "your goal was more of a facilitator and making sure all of your patients' bases were covered," according to Josh Bitter of the Ohio State University Medical Center. Transitioning from the big-picture, coordination of care view to an organ system view presented challenges. "Once I realized my role as a consultant was to provide the best, most focused input in my area of expertise, primary services were much more appreciative."

Finally, Nathan Hellman of Massachusetts General Hospital focused on more personal aspects. Hellman is a new member of the *ASN Kidney News* editorial board.

"Try and think beyond the two to three years of fellowship to what you will be doing in your post-educational life." Changes in personal status, like marriage and children, alter one's perspective. "I find myself having to incorporate into my professional desires a whole new series of variables: affordability of day care options, employability options for my wife, and proximity to relatives are just a few examples," Hellman said. "I am not suggesting that the academic aspects of a nephrology program be overlooked—they are still probably the most important factor to consider—but rather that the decision-making process becomes more complex with increasing life responsibilities.

"Even though things have generally worked out for me despite my ignorance of these family-related variables at the time of my fellowship interviews, it now seems silly to have not taken these factors into account at the time of my decision," Hellman said. "I do not think that my situation is that unique, as the fellowship period is very often a time of rapid change: new relationships, marriage, children; even the transition from everyday clinical work to the different pace of a research project can be profound. It may be impossible to predict exactly how things will change, but keep in mind that they certainly will."



Change is almost universal, but one thing will remain constant: new fellows will always find something they wish they had known before their journey to become nephrologists.

ASN Provides Key Information to U.S. Senate Finance Committee

In December 2009, Sen. Charles E. Grassley (R-IA), ranking minority member of the U.S. Senate Finance Committee, wrote 33 nonprofit medical groups—among them the American Society of Nephrology (ASN), the American Medical Association, and the American College of Physicians—to request information on industry funding awarded to those societies. As part of his ongoing review of medical education programs in the United States, Sen. Grassley asked each organization to supply details about commercial support received in the years 2006 through 2009, as well as information about internal policies on managing and disclosing potential conflicts of interest.

ASN leaders were pleased to be able to send to Sen. Grassley the information requested and share with the Senate Finance Committee the society's long-standing commitment to educational and scientific objectivity. ASN maintains a strong foundation of institutional integrity, integrity in its interactions with other organizations, and serves as a model for self-governance and transparency.

Because ASN is an accredited provider of continuing medical education, the society adheres to the six "Standards for Commercial Support" recommended by the Accreditation Council for Continuing Medical Education (ACCME). These standards (www.accme.org) ensure independence and objectivity of the programs presented to physicians and other learners. Commercial interests do not plan, deliver, or evaluate educational content provided by ASN, and ASN has established numerous means of separation between fundraising and planning, executing, and evaluating educational programs.

Any professional society should actively and regularly assess potential conflicts of interest related to executing its mission, goals, and agendas. Thus, in addition to supporting ACCME guidelines, ASN regularly examines and updates its own policies on managing potential conflicts. Most recently, ASN in 2008 convened the Committee on Corporate Relations, and this group conducted a comprehensive assessment of the society's mechanisms for addressing and managing potential conflicts. The ASN Committee on Corporate Relations presented its final report to the ASN Council in early 2009, and the committee's recommendations were endorsed unanimously.

This effort resulted in a number of advances such as developing a new section on the ASN website: the ASN Conflict of Interest Initiative: Transparency in Relationships with Commercial Interests (http://www.asn-online.org/coi/). This section, open to the public, provides a wealth of information about ASN as well as general resources on managing potential conflicts. In a further effort to provide vital information and resources to ASN members and others in the kidney community, ASN published the committee's final report and an editorial outlining ASN policies and plans for implementing the recommendations (*J Am Soc Nephrol* 2009; 20:1853–59 and 1860–62).

ASN also provided Sen. Grassley information on advertising in ASN journals and *ASN Kidney News*, meeting exhibits at ASN Renal Week and other ASN venues, as well as unrestricted educational grants for ASN Renal Week, Renal WeekEnds, and the Annual Board Review Course and Update. Speakers at ASN meetings follow all ACCME standards regarding disclosure, and the society makes every effort to see that presenters disclose all potential conflicts of interest, and that sessions are moderated to meet these standards of disclosure.

Having successfully partnered in the past to advance patient care, clinical research, and medical education, societies and commercial interests can continue to do so in the future provided they follow strict standards of disclosure, evaluation, and documentation. ASN recognizes the value of inquiries such as those conducted by Sen. Grassley and supports all efforts that promote effective policies such as those outlined by the society at http://www.asn-online.org/coi/.ASN members, other kidney professionals, and patients benefit from the society's ongoing review of its policies to ensure they appropriately support ASN's mission of promoting the highest quality care for patients, supporting cutting-edge research, and educating the next generation of kidney professionals.

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Policy Update

Medicare Moves Forward with Elimination of Consultation Codes

As of Jan. 1, the Centers for Medicare and Medicaid Services (CMS) changed physician coding to eliminate inpatient and outpatient consultation codes. CMS published a "Medicare Matters" article guiding physicians on coding under the new policy. Readers may review the changes on ASN's Policy and Public Affairs—Patient Care website at http://asn-online.org/policy_and_public_affairs/patient-care.aspx.

Sen. Arlen Specter (D-PA) contemplated offering an amendment that would delay the elimination of consultation codes for one year in the Senate version of the health reform bill, but it was not ultimately included. Such an amendment may be introduced as the bills are merged, though none had been at presstime. ASN will alert members of any changes regarding the use of consultation codes.

ASN Leaders Advance Partnership with National Institutes of Health

Also this January, ASN representatives including Sharon Anderson, MD; Thomas Coffman, MD; Jonathan Himmelfarb, MD; Thomas Hostetter, MD; and John Sedor, MD; met with the National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK) Division of Kidney, Urologic, and Hematologic Diseases Director Robert A. Star, MD, and other NIDDK leadership. The group discussed issues including areas where ASN could strengthen their relationship with NIDDK, community involvement with the institute, research infrastructure concerns, and interdisciplinary research.

To help publicize kidney disease as a public health issue and advocate for a kidney disease research agenda, ASN plans to meet with other NIH institutes and government agencies including, but not limited to, the National Heart, Lung, and Blood Institute, the National Institute on Aging, the National Institute of Environmental Health Sciences, the National Center on Minority Health and Health Disparities, the Center for Scientific Review, the Agency for Healthcare Research and Quality, the Department of Veteran Affairs (VA), the Centers for Disease Control and Prevention, and CMS.

Health Reform Legislation

ASN Meets with Key Legislators

Lawmakers began reconciling the House and Senate versions of health reform legislation (H.R. 3692 and H.R. 3590, respectively) in closed-door negotiations on their return to Capitol Hill in early January. Were a single version developed through this process, the bill would go back to each body for a final vote before being sent to the President for his signature.

Yet after the Jan. 19 Republican victory in the Massachusetts special Senate election eliminated Democrats' 60-seat Senate majority, lawmakers halted negotiations and signaled they would suspend health reform progress until the new Massachusetts Senator takes his seat.

Earlier in January, an ASN delegation including President Sharon Anderson, MD, FASN, met with Sen. Richard Durbin's (D-IL) staff on Capitol Hill to discuss and advocate for inclusion of lifetime immunosuppressive drug coverage in the final health reform bill. ASN representatives reiterated the society's support of lifting the current 36-month Medicare limit on immunosuppressive coverage and collaborated on strategies to shepherd the measure into final health reform legislation. In addition, ASN staff promoted the immunosuppressive issue to other key members of Congress independently and in partnership with organizations such as the American Society of Transplantation and the Renal Physicians Association (RPA)—including publishing an open letter to members of Congress in the Washington, DC, newspaper *Roll Call*.

Although at press time it remained unclear exactly what path the health reform bills would take, ASN will continue to closely monitor the legislation and advocate for appropriate policies over the coming month. Key provisions of each bill relevant to the nephrology community are included in the chart.

H.R. 3962 (House version)

- Sec. 1232: Provides extended lifetime coverage of immunosuppressive drugs for kidney transplant patients. Includes all oral drugs in the bundled prospective payment system including oral drugs that are not the oral equivalent of an intravenous drug (such as oral phosphate binders and calcimimetics)
- Sec. 2575-2577: Establishes a pathway for the licensure of biosimilar biological products, and for other purposes. This would provide up to 12 years of data exclusivity to manufacturers of a new biologic product, and provides an additional 6-month exclusivity extension for pediatric applications.
- Sec. 1401: Establishes within the Agency for Healthcare Research and Quality (AHRQ) a Center for Comparative Effectiveness Research to conduct, support, and synthesize research relevant to the comparative effectiveness of the full spectrum of health care items, services and systems, including pharmaceuticals, medical devices, medical and surgical procedures, and other medical interventions.
- Sec. 1730A: Establishes an Accountable Care Organization (ACO) pilot program.
- Sec. 1191: Adds renal dialysis facilities as an additional telehealth-eligible site.

H.R. 3590 (Senate version)

- Sec. 10336: Requires GAO to conduct a study on the impact on Medicare beneficiary access to dialysis services, including oral drugs, that are furnished under the bundled prospective payment system.
- Sec. 7002: Establishes a pathway for the licensure of biosimilar biological products, and for other purposes. This would provide up to 12 years of data exclusivity to manufacturers of a new biologic product, and provides an additional 6-month exclusivity extension for pediatric applications.
- Sec. 6301: Establishes a Patient-Centered Outcomes Research Institute aimed at assisting "patients, clinicians, purchasers, and policy-makers in making informed health decisions by advancing the quality and relevance of evidence concerning the manner in which diseases, disorders, and other health conditions can effectively and appropriately be prevented, diagnosed, treated, monitored, and managed through research and evidence synthesis."
- Sec. 3022: Establishes a "Medicare Shared Savings Program" under which physicians may work together to manage and coordinate care for Medicare fee-for-service beneficiaries through an accountable care organization" (ACO).

Journal View

Medicare Data Show Rising Rate of Atherosclerotic Renovascular Disease

The diagnosis of atherosclerotic renovascular disease (ARVD) among older Americans has tripled in recent years, while the percentage of patients undergoing revascularization appears to be decreasing, reports a study in *Kidney International*.

Based on U.S. Medicare 5% Denominator Files from 1992 to 2004, the study included more than 16 million patients 66 years or older. Trends in the diagnosis, rates, associated factors, treatment, and outcomes of ARVD were analyzed.

The overall incidence of ARVD diagnosis during the 13-year study period was 3.09 per 1000 patient years. The rate of ARVD increased progressively over the years, increasing more than threefold between 1992 and 2004.

Revascularization was performed within six months of diagnosis in 13.4 percent of patients. The rate of revascularization increased progressively from 1992 to 1999, but then declined from 1999 to 2004. There was a trend away from direct surgical revascularization and toward endovascular revascularization—by 2004, 98.5 percent of patients were treated by endovascular intervention.

Atherosclerotic renovascular disease was associated with excess mortality in each year studied, although the estimated hazard ratios were lower in more recent years. Overall, 15.51 percent of patients died, with a mortality rate of 57.87 per 1000 patient years.

Atherosclerotic renovascular disease is increasingly being diagnosed, mainly in elderly patients. Studies have shown a rising prevalence of ARVD among patients starting renal replacement therapy, but there are few data on the burden of ARVD in the general population.

The new analysis shows that the rate of ARVD among U.S. older adults has increased substantially since the early 1990s. The use of revascularization likewise increased during the 1990s, but appears to be decreasing in more recent years. The trend toward decreased mortality suggests that earlier recognition may permit more timely and effective management of renovascular disease [Kalra PA, et al. Atherosclerotic renovascular disease in the United States. *Kidney Int* 2010; 77:37–43].

Increased Physical Activity May Protect Against Rapid Drops in Kidney Function

Older adults with higher levels of habitual physical activity are less likely to experience rapid declines in kidney function, reports a study in the *Archives of Internal Medicine*.

The study included 4011 ambulatory older adults (mean age 72 years) from the Cardiovascular Health Study. All underwent kidney function measurement at least twice over a seven-year follow-up period. Information on weekly energy expenditure and walking speed was used to calculate a physical activity score (with a possible score of 2 to 8). Rapid decline in kidney function was defined as a reduction of greater than 3.0 mL/min/1.73 m^2 per year in estimated glomerular filtration rate, based on cystatin C measurements.

Rapid decline in kidney function occurred in 23.9 percent of study participants, with a rate of 4.1 events per 100 person-years. Such a rapid drop in kidney function occurred in 16 percent of participants in the most active group (physical activity score of 8), compared to 20 percent in the least active group (physical activity score of 2). On multivariate analysis, the risk of rapid decline in kidney function was 28 percent lower for participants with a physical activity score of 7 or 8, compared to those with a score of 2 or 3. Leisure-time energy expenditure and walking pace were both associated with reduced risk of decreased kidney function.

Information on identifiable risk factors affecting the age-related decline in renal function could have important implications for public health. Increased physical activity is associated with a decreased risk of cardiovascular disease and mortality. The metabolic benefits of exercise might also influence the long-term risks of glomerulosclerosis and progressive kidney dysfunction.

Older adults with higher levels of physical activity appear to be at lower risk of rapid declines in kidney function. The protective effect increases along with the intensity and amount of physical activity, and remains significant after adjustment for other disease risk factors. Further studies are needed to determine whether exercise can protect against age-related declines in kidney function [Robinson-Cohen C, et al. Physical activity and rapid decline in kidney function among older adults. *Arch Intern Med* 2009; 169:2116–2123].

Network of Minority Research Investigators to Meet in April

The Network of Minority Research Investigators (NMRI) will hold its 8th Annual Workshop April 22–23, 2010, at the Bethesda Marriot Hotel in Bethesda, Md. NMRI, a collaboration of current and potential biomedical research investigators and technical personnel from traditionally underserved communities, was established by the Office of Minority Health Research Coordination within the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), to facilitate participation in medical research in fields relevant to NIDDK.

Chronic kidney disease (CKD) has increased 30 percent during the past decade. Today, approximately 26 million Americans suffer from the disease. Characterized by substantial differences in incidence, progression, treatment, and outcomes across racial and socioeconomic lines, CKD is a global public health problem that cannot be overlooked. The NMRI Workshop will draw attention to these issues and highlight possible avenues for future research.

Designed for NMRI members as well as minority investigators from the training level to senior faculty, the workshop aims to provide mentorship, poster presentations, and scholarly exchange among leaders in the field.

Participation in the workshop is by invitation only, and invited attendees are reimbursed for travel expenses. Participants are strongly encouraged to submit an abstract for poster presentation. To determine your eligibility to participate, or for more information on the workshop, please contact Winnie Martinez at martinezw@mail.nih.gov.

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A. C. Craig Tisher, MD; John Stokes, MD, FASN; and Robert Alpern, MD

B. Heini Murer, PhD, and Gerhard Giebisch, MD

C. Founding Fathers of the US with Richard Glassock, MD, in Philly

D. Patricia Preisig, PhD, FASN

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