ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

KidneyNews

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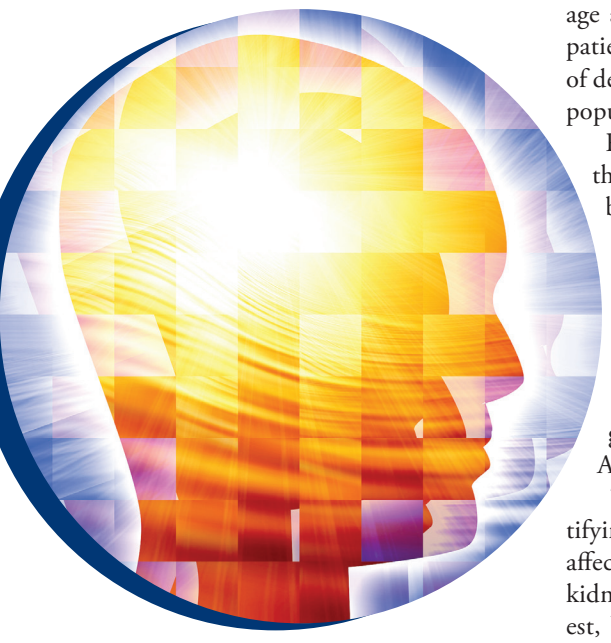
Kidney Impairment Limits Cerebral Blood Flow, May Increase Risk of Stroke and Dementia

By Tracy Hampton



The incidence of stroke is estimated to be 2- to 7-times higher in patients with chronic kidney disease (CKD) than in individuals with normal kidney function, depending on age and the population studied. Also, patients with CKD have a higher risk of developing dementia than the general population.

Results from a new study indicate that decreased blood flow to the brain may play a role. The study, which is published in the *Journal of the American Society of Nephrology*, found a link between impaired kidney function, even in patients not diagnosed with CKD, with lower cerebral blood flow (Sedaghat S et al. *J Am Soc Nephrol* 2015 Aug 6. pii: ASN.2014111118.)

There is increased interest in identifying conditions and risk factors that affect the brain. In recent years, the kidney has received considerable interest, because both the brain and kidney share many characteristics. For example, both are so-called low resistance organs with hemodynamic auto-regulation, meaning that they are capable of regulating the amount of blood that flows through them. Both are also susceptible to damage to the small arteries penetrating them, which can lead to arteriosclerotic small vessel disease. The brain and kidney also share common traditional cardiovascular risk factors, such as hypertension and diabetes. Despite these apparent similarities, the link between kidney disease and brain disease has remained unclear.

A team led by M. Arfan Ikram, MD, PhD, and Sanaz Sedaghat, MSc, of the Erasmus University Medical Center, in the Netherlands, decided to focus on the knowledge that proper kidney function is crucial for regulating blood volume and vascular tone. To study the impact of kidney health on cerebral blood flow, the investigators examined information on 2645 participants in the population–based Rotterdam Study, looking at individuals' kidney function and blood flow to the brain. The researchers used estimated glomerular filtration rates (eGFR) and albumin-to-creatinine ratios to assess kidney function and

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World Study Finds Differences in Acute Kidney Injury Characteristics, Outcomes

As '0by25' Gets Moving, New Data on Global Burden of AKI

By Timothy O'Brien

Acute kidney injury (AKI) is a global problem affecting patients all over the world—but it's not the same everywhere. A prospective, worldwide comparison of AKI patients revealed significant differences in patient characteristics, treatment, and outcomes between developed and emerging countries, according to a study in the *Clinical Journal of the American Society of Nephrology*.

Led by Ravindra Mehta, MD, of the University of California, San Diego, and Josée Bouchard, MD, of the University of Montreal, the researchers analyzed data on the characteristics, treatment patterns, and

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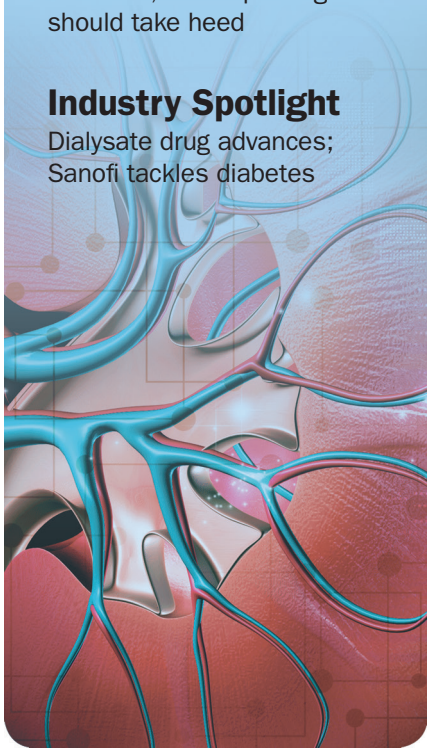

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Gout preys on more than just bones and joints— monosodium urate (MSU) crystals can deposit in the kidneys, spine, and soft tissues, including ligaments or tendons.[1,2] Even when patients are not flaring, these crystals can be associated with chronic inflammation, bone erosion, organ damage, and other systemic diseases.[2-6]

Keeping uric acid levels consistently <6 mg/dL—below the MSU saturation point—can dissolve existing crystals and prevent new crystal formation.[7-10]

Take a deeper look at TheRealGout.com

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World Study

Continued from page 1

clinical outcomes in a worldwide sample of intensive care unit (ICU) patients with AKI. Patients were treated at nine ICUs in developed countries: the United States, Canada, Ireland, and Greece; and five ICUs in emerging countries: China, Brazil, and India. "This is very helpful in terms of giving at least a glimpse of what the broader issues are in terms of this highly prevalent disease," Mehta said.

The results appear as the world nephrology community gears up for the "0by25" Initiative—a global project with the ambitious goal of eliminating preventable deaths from AKI within the next decade. Mehta is program director of the initiative.

"This immense and vanguard effort, led by Dr. Mehta, and many collaborators worldwide, will focus on establishing that AKI is a contributor to the global burden of disease, increasing awareness in the world, and developing an infrastructure for education, training and care delivery, said Mark D. Okusa, MD, FASN, of the University of Virginia School of Medicine. "Through the collaborative efforts of the global community, AKI outcomes will be markedly improved and the outlook will be much brighter.

World differences in AKI—emerging versus developed countries

Data for the *CJASN* study were drawn from an ongoing web-based database created by the UAB-UCSD O'Brien Core Center for Acute Kidney Injury (www.obrienaki.org). Supported by The National Institute of Diabetes and Digestive and Kidney Diseases, the O'Brien Center is one of eight interdisciplinary centers of excellence in AKI-related research.

From 2008 to 2012, a total of 6647 patients were screened for inclusion. Acute kidney injury was defined by the modified AKIN creatinine criterion of 0.3 mg/dL or less within 48 hours. Of these, 1275 developed AKI within seven days after ICU admission—a rate of 19.2 percent. The incidence was similar for patients in developed and emerging countries: 19.1 versus 19.9 percent, respectively. About 62 percent of cases in developed countries were de novo AKI (without known chronic kidney disease), compared to 46 percent in emerging countries.

Complete data were available for 745 consenting patients. Bouchard and colleagues compared differences in the causes, risk factors, and course of AKI for patients from emerging versus developed countries.

The results showed some noteworthy differences in the causes of AKI: patients in emerging countries were more likely to have glomerulonephritis and acute interstitial nephritis, while those in developed countries had higher reported rates of prerenal AKI, sepsis, and acute tubular necrosis.

While the data on causes have some important limitations, the findings are consistent with differences in the exposures leading to AKI, according to Mehta. For example, patients in developing countries may be more likely to have envenomation from snake bites, or toxicity related to indigenous drugs or misuse of medications.

But the variation may also reflect differences in medical care and resources—for example, patient monitoring after septic exposures or use of contrast agents. Limited access to diagnostic testing might also be a significant contributor. "Most people in the developing world have to pay for every lab test," Mehta said. "And if they don't have the resources, then the lab tests may not be done or frequency of the lab tests goes down."

He also noted that the information on causes came from case report forms asking what was documented as the potential reason for AKI. "We don't have a clear explanation as to why there are differences or what they represent in the general population—other than simply saying that they exist and are likely conditioned by the different settings."

Differences in AKI severity, treatment, and outcomes

Patients in developed countries tended to have less severe AKI. However, this difference became nonsignificant after exclusion of patients with chronic kidney disease.

Patients in developed countries actually received dialysis less often: about 16 percent, compared to 30 percent in emerging countries. Dialysis was also started later in developed countries, 2 versus 0 days. The duration of dialysis was similar between the two groups.

Crude hospital mortality was 22 percent overall, but substantially higher in developed countries: 28 percent, compared to 18 percent in emerging countries.

On logistic regression analysis accounting for a wide range of patient and clinical characteristics, however, residence in an emerging country was associated with more than a twofold increase in hospital mortality: odds ratio 2.32. "Unfortunately, we do not know the exact reason(s) underlying this finding," said Bouchard. "Some of the risk factors for mortality, like a higher cumulative fluid balance, were significant in developed countries only, while the use of vasopressors was significant in emerging countries only.

"Are these related to differences in the timing, type, and amount of fluids or vasopressors used? There may also be differences in access to general and specialized care and possible confounding factors which may explain this result." Other independent risk factors for death were older age, use of mechanical ventilation, higher APACHE score, and stage 3 AKI with renal replacement therapy.

Seventy-two percent of survivors in developed countries recovered renal function, while only 52 percent of survivors in emerging countries did so. Six percent of survivors in developed countries were dialysis dependent at hospital discharge, compared to nearly 19 percent in emerging countries.

Residence in an emerging country was also associated with nearly a threefold increase in the risk of discharge without renal recovery: odds ratio 2.91. Stage 3 AKI with renal replacement therapy was also an independent risk factor for lack of renal recovery.

The findings provide "a novel assessment of commonalities and difference in the natural history and management of mild to severe AKI"—but interpretation of those differences is far from clear-cut. For example, while the increases in AKI severity and higher use of renal replacement therapy in emerging countries may partly reflect lower baseline kidney function, there are also substantial differences in treatment patterns, including lower use of vasopressors and mechanical ventilation in emerging countries.

For patients with more severe AKI, access to high-tech care is almost certainly a contributor to the higher survival rate in developed countries. Bouchard, Mehta, and colleagues noted that in their cohort, some AKI patients in India and China had to pay for their dialysis therapy. Other patients in countries with limited resources may not have had access to optimal treatment, owing to poor prognosis or lack of resources. In these countries, the convenience sample was limited to patients from large urban centers—many more patients in outlying areas likely receive no specialized care.

Although the study focused on the ICU population, it provides new insights into the entire spectrum of the disease—including milder cases of AKI tracked forward over time. "You can see that there are obvious differences in outcomes from AKI, and what are the factors that influence how these patients are managed," said Mehta. "And to some extent, that represents not only the inherent population differences in emerging and developed countries—but also the fact that the resources available in each setting influence how AKI patients are managed and what ultimately happens to them."

The new research begins to address major gaps in knowledge of the worldwide burden of AKI and regional variations in its causes and treatment, Okusa said. "This paper by Bouchard et al. is highly informative, timely, focuses on the global nature of AKI and is a harbinger of a wealth of information to follow. [It] provides a glimpse into the disparities and variations in global AKI.

"However, since these studies were done in academic centers worldwide, these data likely represent an underestimate of the magnitude of variations, given that access to care may be a much greater problem in emerging countries," Okusa said. "In emerging countries there is likely a greater degree of avoidable causes of death due to access of care, lack of resources to diagnose and treat AKI and need for greater education. By addressing these issues AKI can be largely prevented or mostly treated."

Growing body of evidence on global burden of AKI

The results help to set the stage for the International Society of Nephrology's 0by25 initiative, with its ambitious goal of "Zero preventable deaths from AKI by 2025"—focusing on understanding AKI and intervening to prevent adverse outcomes in low- to middle-income countries.

The study by Bouchard et al. is not a part of the 0by25 initiative—data collection began several years earlier. "But in the context of 0by25, the whole idea is that many of these cases—in poor and rich countries alike—are potentially survivable, if appropriately targeted and treated," Mehta said. He targeted three areas that must be assessed and understood in developing effective interventions to prevent AKI deaths:

- *Environmental exposures and risks*. A major goal will be to identify the environmental factors and risks that contribute to preventable mortality from AKI in low- to middle-income countries. "So for example if you don't have access to water, sanitation, or hygiene, to what extent does that contribute to diarrheal illnesses, which in turn contribute to downstream events?" asked Mehta. "Or endemic malaria or leptospirosis—how do those things contribute?"
- *Failed recognition or inadequate resources*. Failed or delayed recognition of sudden declines in kidney function is a critical contributor: "It occurs daily even in our hospitals here in the developed countries," said Mehta, giving the example of a small rise in creatinine that is not recognized and doesn't translate into action.
- *Lack of resources*. Lack of necessary health care resources is of course a critical factor affecting the risk of death from more severe AKI. Many poor countries simply do not have dialysis facilities. In others, access is limited by cost or distance.

Addressing these factors will require understanding how they contribute to the burden of AKI on the regional as well as global level. A major 0by25 initiative is the Global AKI Snapshot—a prospective, cross-sectional study assessing the incidence of AKI in a wide range of settings worldwide. Over a 10-week period between September and December last year, "contributing nephrologists and other physicians were asked to pick one day on which they were asked to record information on any person they saw who met criteria for AKI," Mehta said. "Then we also asked them to tell us seven days later what happened to those patients."

Data on more than 4000 adults and children with AKI were contributed by over 320 participating centers in more than 72 countries. Data analysis is ongoing, with a final report expected to be published later this year. Some preliminary findings were presented at the ISN World Congress of Nephrology in March.

The data are "pretty striking" in demonstrating the etiologic factors contributing to AKI, according to Mehta. "Dehydration and hypotension and shock emerge as major factors across all settings, but there are differences across countries. So we have a rich data set that we are exploring further."

Building on those findings, 0by25 investigators are now in the planning phases to implement a prospective pilot study aimed at further understanding and acting to reduce the burden of AKI in low- to middle-income countries. Teams will travel to three target regions—Africa, Asia, and Latin America—in a demonstration project to track patients with AKI, starting at the community health level. The pilot study will also include initial interventions to identify high risk patients and carry out specific interventions to improve AKI management and outcomes. Project implementation is planned for late 2015 or early 2016.

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Kidney Impairment

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performed phase–contrast magnetic resonance imaging of basilar and carotid arteries to measure cerebral blood flow.

Poor kidney function was strongly related to decreased blood flow to the brain, or hypoperfusion, and there was a linear trend between different categories of kidney function and cerebral blood flow. Each 1 standard deviation lower eGFR was associated with 0.42 mL/min per 100 mL lower cerebral blood flow. Also, poor kidney function was linked to stroke and dementia most strongly in participants with hypoperfusion. These results were independent from known cardiovascular risk factors. The association between higher albumin-to-creatinine ratio and lower cerebral blood flow was not independent of cardiovascular factors, however.

"Our findings provide a possible explanation linking kidney disease to brain disease," Ikram said. "Also, given that kidney disease and hypoperfusion of the brain are both possibly reversible, there might be an opportunity to explore how improving these conditions can ultimately reduce one's risk of developing brain disease."

The study also revealed that the kidney-brain link is not confined to patients with CKD, but extends to individuals without overt disease.

Continued research in this area will likely provide important insights on how reduced kidney function may adversely affect the brain. Another recent study by Ikram's group found that kidney function may have a significant impact on the microstructural integrity of brain white matter, which is composed of nerve fibers and myelin (*Sedaghat S* et al. *Neurology* 2015; 85:154–61).

Study co-authors include Meike Vernooij, MD, PhD, Elizabeth Loehrer, MSc, Francesco Mattace-Raso, MD, PhD, Albert Hofman, MD, PhD, Aad van der Lugt, MD, PhD, Oscar Franco, MD, PhD, and Abbas Dehghan, MD, PhD.

Disclosures: The authors reported no financial disclosures.

The article, entitled "Kidney Function and Cerebral Blood Flow: The Rotterdam Study," is available at http://jasn.asnjournals.org/content/early/2015/08/05/ASN.2014111118.long.

Employed Physicians: Negotiating Successful Contracts

By Adrienne Lea

The number of physicians employed by hospitals or medical groups continues to increase, reflecting changing trends in physician reimbursement and pay-for-performance models as well as the increased infrastructure to support ongoing changes. According to a 2014 survey of more than 20,000 physicians conducted by the Physicians Foundation, 53% of US physicians describe themselves as hospital or medical group employees, an increase from 44% in 2012 and 38% in 2008.

Negotiation

You may not have ever negotiated an employment contract, and you may face a significant debt burden. These factors can shift your focus to the base salary number in a proposed contract; while that's important, you need to assess all aspects of the agreement to ensure your professional and personal satisfaction.

First things first:

- Make sure you know the difference between the offer letter and the signed agreement, and that you understand what you are committing to when you sign an offer letter. This varies from state to state, and most experts recommend you seek an attorney's advice before signing an offer letter.

Negotiation is an art:

- Educate yourself by understanding the interests of your employer and determining your own interests.
- Hire an attorney who understands physician employment contracts; this is probably not your real estate attorney. Ask people who have been through the process to recommend attorneys you should—or should not—use. Make sure your attorney understands the specifics of nephrology practice.
- Don't assume your attorney knows everything. Take the time to educate yourself (Table 1).
- Work with your attorney to set priorities, and convey the items you consider immutable, and those about which you are more flexible. Your attorney should protect your interests, and should fully understand your priorities in order not to sour the future employer/employee relationship.
- De-personalize the process. Pretend you are reviewing the agreement for a brother, a sister, or a friend. What advice would you give that person regarding relative importance of the items in the agreement?

Hidden costs and benefits

The salary number provided on the proposed contract should be a fair reflection of the market value for nephrologists with your experience, training, and in that geographic area. That is only part of the story: the total compensation package may contain hidden costs and benefits.

A few items you should review:

- Health benefits and out-of-pocket health insurance costs for you and your family.
- The nature of the retirement benefits, including when you become fully vested.
- Vacation time, how often you are paid, timing of salary review, nature and timing of bonus payments.
- Performance-based metrics:
  - Understand how your employer integrates production (relative value units) or quality-focused incentives into your compensation plan. Before you finalize an agreement, learn how these metrics may affect the hours you work and the money you take home, and possible incentive payments.
- How you care for patients:
  - Are there limitations on where you can practice, what patients you see, treatments you can prescribe, or other restrictions on how you will administer care to your patients?
- Telehealth requirements and/or restrictions?
- Requirements and/or restrictions regarding exchanges with patients via email? If you are required to respond to patients via email, does the contract include reimbursement for this time?
- Are there restrictions on your personal use of social media? Or are you required to maintain a professional social media presence, and if so, how much of your time will be required to maintain this presence?
- If you are just entering the workforce, educate yourself regarding the personal financial costs and time requirements related to licensing, certification and recertification, and credentialing.
- Your contract may restrict outside compensation, so understand the details and limitations.

A few worst-case scenarios

- Discuss with your attorney hidden malpractice costs, most notably "tail coverage"—coverage that extends after you leave the organization. If tail coverage is not part of your agreement, providing it yourself can be expensive.
- Restrictive covenants. If your employment ends, does the contract place restrictions on your ability to practice in that geographic area? How is the geographic area defined? How long do the restrictive covenants remain in place?
- What will happen if your employer merges with another organization, or if your employer is purchased by another organization? Work with your attorney to anticipate the worst-case scenarios and make sure they are addressed in the contract, including whether certain restrictive covenants otherwise in place might be lifted in the event of a merger or acquisition.
- If you are participating in a loan forgiveness/loan repayment program, find out how your new salary might impact your eligibility. If you will no longer be eligible for loan forgiveness/repayment, this should be figured into your assessment of your total compensation.

Bottom line: you may be negotiating an employment contract during one of the busiest times in your life—wrapping up a fellowship, selling a house (or finding a new place to live or both), and coordinating with your partner regarding his or her future employment. This employment contract will affect your future professional and personal life, so do not shortchange yourself, your ability to achieve professional satisfaction and provide optimal care to your patients.

Adrienne Lea is a healthcare consultant.

Table 1. Useful resources

Changing landscape

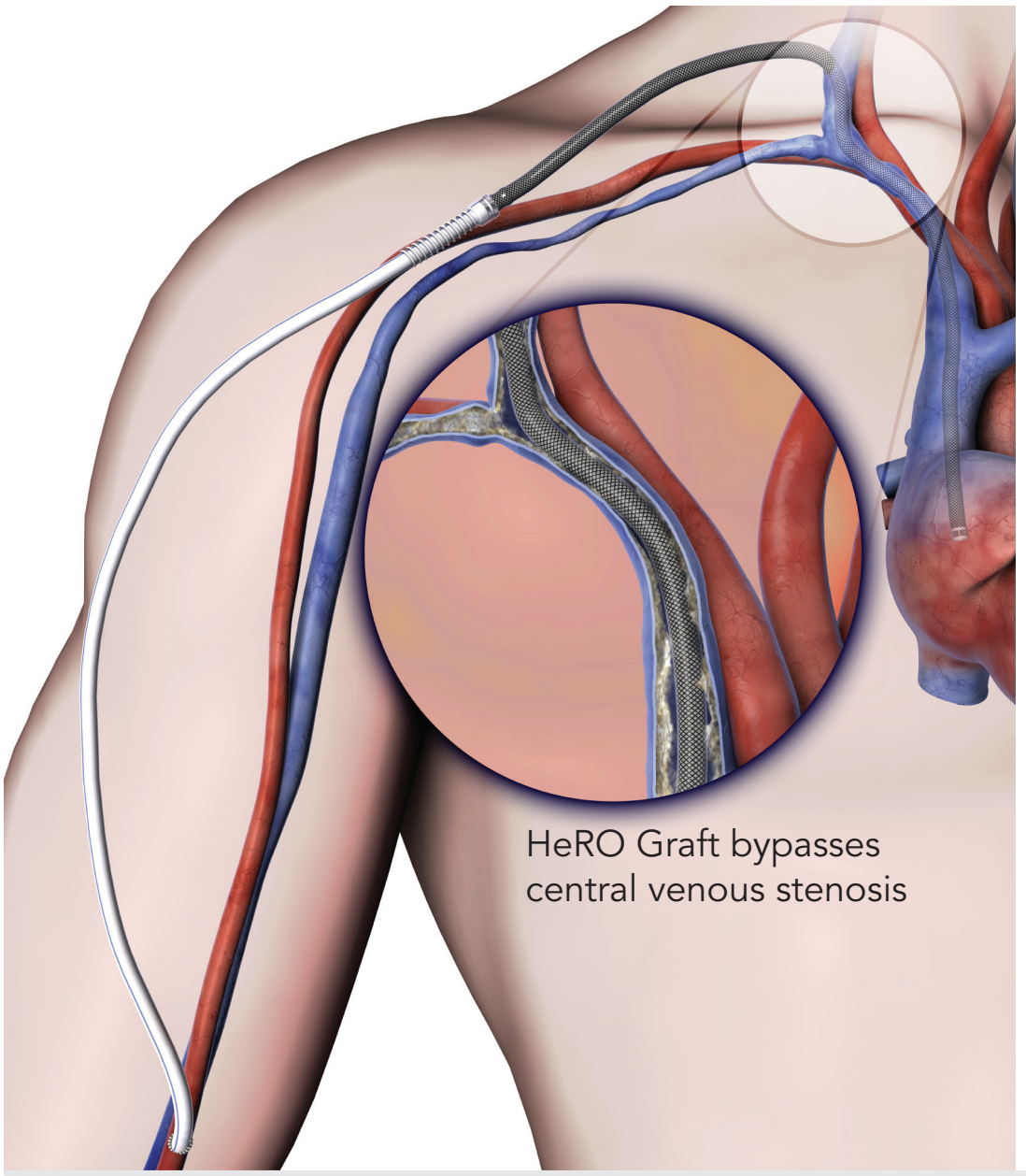
1. **Understanding the Physician Employment "Movement."** ***NEJM*** **Career Center.** http://www.nejmcareercenter.org/article/understanding-the-physician-employment-movement-/
2. **Physicians Foundation Biennial Physician Survey 2014.** http://www.physiciansfoundation.org/uploads/default/2014_Physicians_Foundation_Biennial_Physician_Survey_Report.pdf
3. **H-225.950 Principles for Physician Employment. American Medical Association.** https://ssl3.ama-assn.org/apps/ecomm/PolicyFinderForm.pl?site=www.ama-assn.org&uri=%2fresources%2fhtml%2fPolicyFinder%2fpolicyfiles%2fHnE%2fH-225.950.HTM
4. **7 Trends in Hospital Employed Physician Compensation** http://www.beckershospitalreview.com/compensation-issues/7-trends-in-hospital-employed-physician-compensation.html
5. **Integrating Value into Physician Employment Compensation Models**
6. http://www.beckershospitalreview.com/compensation-issues/integrating-value-into-physician-employment-compensation-models.html
7. **Physician Pay Increasingly Linked to Value-Based Metrics** http://healthleadersmedia.com/content/PHY-306244/Physician-Pay-Increasingly-Linked-to-Valuebased-Metrics

Contract Negotiation

1. **5 Mistakes to Avoid When Signing Employment Contracts** http://www.medicalpracticeinsider.com/best-practices/5-mistakes-avoid-when-signing-employment-contracts
2. **Negotiating Hospital Contracts: What Physicians Need to Know Before Signing** http://medicaleconomics.modernmedicine.com/medical-economics/content/tags/careers/negotiating-hospital-contracts-what-physicians-need-know-sign
3. **A Physician's Guide to Employment Contracts** http://www.practicelink.com/magazine/featured/a-physicians-guide-to-employment-contracts/
4. **Knowing How Hard to Negotiate in Physician Employment Contracts** https://www.physicianadvisorsllc.com/library/knowing-how-hard-to-negotiate-in-physician-employment-contracts/

State Medical Societies

Many state medical societies offer advice regarding physician employment contracts on their websites. Some offer initial consultation with an attorney to their members. In any case, checking the state society site may provide you key information specific to the state in which you will be practicing.



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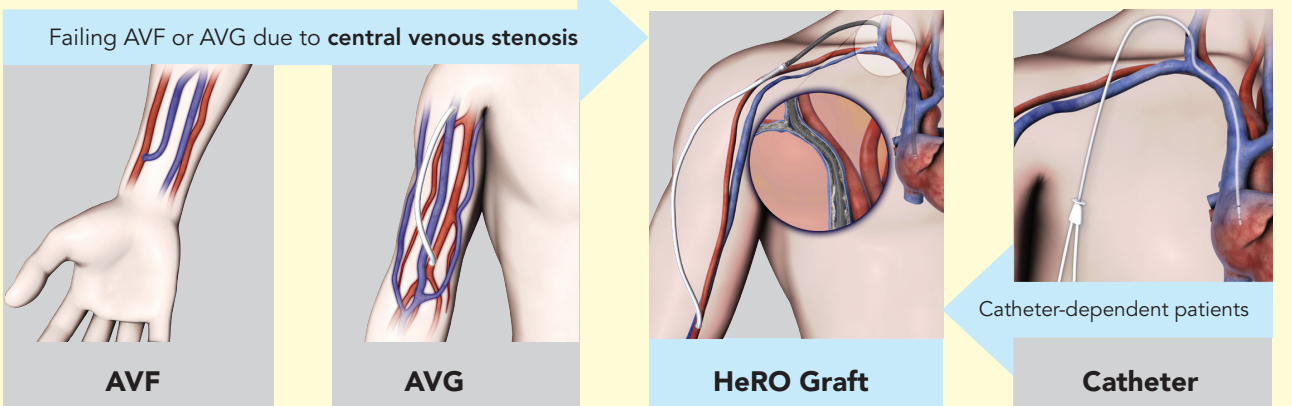

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References:
1) Katzman et al., J Vasc Surg 2009. 2) Gage et al., EJVES 2012. 3) Dageforde et al., JSR 2012.

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Updates in Dialysis

ASN Kidney News gratefully acknowledges the editor of this special section, *Kidney News* Editorial Board member Edgar V. Lerma, MD, FASN, for his contributions to this issue.

Nocturnal and Home Dialysis in the United States

By Michael A. Kraus

In December 2014 the US Food and Drug Administration (FDA) granted clearance for a dialysis device to be used for nocturnal home dialysis. This step should open the door for patients with ESRD to have access to a full array of dialysis modalities, including in-center therapies of self-care, thrice-weekly and nocturnal dialysis, and home therapies consisting of continuous cycling peritoneal dialysis, continuous ambulatory peritoneal dialysis, conventional home hemodialysis, portable low-flow hemodialysis, short daily dialysis, and nocturnal home dialysis 3.5 to 6 nights per week. Multiple devices are on the horizon, and flexibility of therapy should be an option for a majority of ESRD patients.

A properly educated family and patient can decide which therapy offers the greatest advantage to the patient. The patient and family can balance the issues of frequency, timing, quality of life, and mortality. It is appropriate to empower patients with the honest outcomes of dialysis and help them determine the best individualized course of action.

Although there has been an increase in home hemodialysis since 2004, many more patients could benefit from the improved quality of life and flexibility offered by increased-frequency home dialysis. It is interesting that when queried, health care providers in the dialysis industry would overwhelmingly choose a home therapy for themselves. The nephrology community is left trying to explain the disparity between our own desires and how patients are treated in the United States.

Since 2004 there has been a steady gain in the use of home dialysis in the United States associated with FDA clearance of the NxStage System One, a low-flow dialysate system for home use. This device has brought increased ease of use, lower utility costs, and portability. Home dialysis in the United States has become a predominantly short daily therapy with increased frequency but remains limited in its use. Data from the United States Renal Data System show an increase in use from 1831 prevalent ESRD patients in 2004 to 7923 in 2012, or an increase of just 0.5 percent to 1.8 percent of the prevalent ESRD patient population.

Thrice-weekly in-center dialysis has shown an improvement in premature mortality recently, but the mortality still is around 20% yearly. In-center patients experience postdialysis fatigue, increasing left ventricular hypertrophy (LVH), sleep apnea, restless legs, hypertension with multiple agents, high hospitalization rates, increasing rates of infection and death, and increases in hospitalization with the 48-hour intradialysis period.

Increased-frequency dialysis has been demonstrated to improve quality of life scores, decrease postdialysis recovery, improve sleep, improve BP with decreased medications, decrease LVH, and improve mortality when compared with in-center or peritoneal dialysis. Increased-frequency nocturnal dialysis also improves these factors. In addition, nocturnal dialysis improves sleep apnea and allows a normalized diet with the discontinuation of phosphate binders. Nocturnal dialysis moves the burden of therapy to bedtime, increasing freedom from therapy during daylight hours and decreasing the overall burden of therapy for patients and their partners. Both therapies can eliminate the 48-hour break from the dialysis schedule. Increasing use of increased-frequency home therapies will require better knowledge among nephrologists, improved education and communication with patients, and removal of barriers to use by patients and health care givers.

Nocturnal dialysis is not just more of the same. Prescriptions for nocturnal dialysis vary based on frequency and device. Nocturnal therapy can be delivered in the patient's home with the low-dialysate device (FDA cleared with NxStage System One) or a conventional hemodialysis device.

Conventional dialysis requires electrical and plumbing changes to the home. A dedicated 20-A circuit for dialysis must be hardwired, and water treatment with a softener, charcoal filter, and reverse osmosis or DI (deionization) treatment is required. The differences between nocturnal dialysis and thrice-weekly in-center dialysis are decreased blood flow, decreased dialysate flow, and a higher calcium bath with increased frequency.

Low-flow dialysis with the NxStage System One is a different prescription. It uses lower dialysate volumes of 20 to 60 L per treatment. The lower dialysate flow increases the saturation of dialysate composition and allows for lower volumes. No studies have determined the best dialysate volumes. At Indiana University, for short daily treatments, we prescribe a minimum of 20 L for all patients and roughly 20% of body weight for women and 25% for men. We increase this for 5 days versus 6 days. Generally, nocturnal dialysis at home is prescribed with increased frequency. If 5 days or more are prescribed, we prescribe 30 L for smaller patients and 45 to 60 L for larger patients. The dialysate volume can be increased if phosphorus is not controlled. Conversely, the dialysate volume can be decreased if phosphorus is low despite increasing dietary intake of phosphorus. For nocturnal dialysis, a heparin pump is generally used, and the dialysate bath is 2K and 40 to 45 lactate. Blood speed is 250 to 300 mL/min, and the dialysate flow is adjusted to allow for 6 to 8 hours of dialysis to meet the patient's needs. Water treatment occurs with online generation and storage of ultrapure dialysate. This requires much less water and electricity.

Despite the many advantages of increased-frequency home dialysis, there are significant concerns. Access infection and necessity for procedures are increased in some studies. Dislodgement of venous access is a potentially fatal complication and must be avoided, particularly in the sleeping patient. Infection can be addressed by proper education and reeducation on technique and the importance of proper technique. We have markedly decreased infection by addressing these factors in training and reeducation monthly in the clinic. Noninfectious complications are expensive and morbid. A thorough physical examination in the clinic and education of patients in the signs of decreased flow are mandatory.

With proper education, reeducation, and training at Indiana University Health Dialysis, our home program enjoys a very low rate of infectious and noninfectious complications. Over the past 18 months, the Indiana University Health home program has had a rate of 4 thromboses in 97 patient months (1 thrombosis every 24.25 months) for arteriovenous (AV) grafts and 5 thromboses in 841 patient months (1 thrombosis every 168.2 months) for AV fistulas. During the same period, the two in-center units have had a rate of 48 thromboses in 762 patient months (1 every 15.88 patient months) for AV grafts and 75 events in 2091 patient months (1 every 27.8 patient months) for AV fistula. Fistulas fared better than AV grafts, and increased-frequency home access fared better than in-center access with thrombosis.

The infection rate in the home dialysis unit is better than expected as well. Over the past 18 months, the home unit AV fistula infection rate is 1 episode every 210.2 months (4/841 months). The AV graft infection rate is 1 every 19.4 months (5/97 months),

and the central venous catheter infection rate is 1 every 34.3 months (6/206). Also, in the first 6 months of calendar year 2015 we have had no AVG infections.

The potentially fatal noninfectious complication of venous dislodgement must be avoided. It is life threatening in all forms of hemodialysis but is particularly worrisome in the sleeping patient at home. Traditionally, taping has been used to secure the needle sites. An incontinence alarm can be taped to the venous needle site; the alarm when activated by wetness will wake the patient. A fiberoptic device to sense a blood leak (Redsense, Redsense Medical AB, Chicago, IL) is also available. More recently, Fresenius Medical Care has added a wireless wetness device for use with the 2008K at home. If the device senses moisture it shuts down the blood pump and sets off an alarm. Finally, Medisystems has recently received FDA clearance for a dual-lumen single-needle for use with dialysis. Its use differs from traditional single-needle dialysis in that it is actually two separate needles in one. It is available for the rope-and ladder-technique or the buttonhole technique. If the needle dislodges, the dialysis machine will shut off and give an alarm. The characteristics of this needle limit blood flow to 250 to 300/min. We have found excellent patient acceptance and improved burden of therapy, with reduction in cannulation by half.

Nocturnal dialysis at home with increased frequency can now be added to the available therapies for patients in the United States. Work to decrease complications should continue. Proper education of the patient and dialysis team is essential while novel therapies are being adapted. Work is needed to improve patient education and assurance of appropriate care and assistance 24 hours a day. Physicians need to understand and communicate the options, benefits, and risks of all modalities.

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Peritoneal Dialysis: An Update for 2015

By John Burkart

In 2015, the overwhelming majority of patients with treated ESRD in the United States are treated with in-center hemodialysis (CHD), whereas peritoneal dialysis (PD) is the predominant modality used by home dialysis patients. Overall, this is not markedly different from the historical distribution of modality use: most patients use CHD. However, not only has the observed historical decline in percentages of patients using PD (1995–2009) stabilized, but the percentage of those using PD has actually been increasing since 2010 (1).

This trend is most likely a result of the new prospective payment system for Medicare patients, which has "bundled" the payment and treatment so that the overall payment amount per week of typical dialysis is the same for CHD and PD, effectively removing any unintended financial incentives that had favored the use of CHD. This trend may also be fueled by clinical observations over the past decade, such as those showing that in the United States, improvements in survival for patients using PD have outpaced those for patients using CHD, so that the differences in 5-year survival, if any, are probably not clinically meaningful (2–4). As a result, the PD population in the United States has almost doubled since 2008 (from about 23,000 in 2008 to about 46,000 in 2014 in the 10 largest providers) (1).

Some have been concerned that because of lack of infrastructure and of nurses' and physicians' experience, this new growth would be associated with a reported increase in mortality or a decrease in technique survival. To date there have been no published data to support that concern. One unexpected problem associated with this rapid growth in PD is the inability of the current manufacturers of peritoneal dialysate fluids to keep up with the demand for bags needed for cycler therapy. This is being addressed by industry, national societies, and the US Food and Drug Administration. Most patients now use cycler therapy (automated peritoneal dialysis [APD]), one of the submodalities of PD, because of issues related to their quality of life. Although there could be differences in selected patient outcomes between these two submodalities of PD, there are no consistently reported clinically relevant differences in clinical outcome between APD and manual exchanges (5). Transfer to hemodialysis for catheter-related problems and peritonitis continues to be a major concern, as is the realization that BP and volume may not be managed in PD as well as they potentially could be, given the daily nature of the therapy.

Peritoneal dialysis access–related issues

Catheter-related issues remain a reason for transfer to CHD. Most PD catheters are placed in the operating room by surgeons using open dissection. This requires general anesthesia, does not allow direct visualization of the peritoneal cavity and true pelvis, and may frequently result in primary catheter dysfunction because of the inability to identify anatomic arrangements that interfere with catheter function. In addition, because of difficulties in scheduling surgeons and operating rooms, delays in peritoneal catheter placement have often necessitated the initiation of dialysis with CHD by use of a temporary vascular access and delaying the start of PD.

The degree of success with the historical open dissection approach and other techniques (such as the percutaneous needle–guide wire approach, with or without imaging guidance, and the laparoscopic technique) is provider related and is associated with matching the appropriate placement technique with the appropriate patient. Ancillary procedures such as tacking of redundant omentum (omentopexy) and lysis of adhesions that can potentially be performed by the advanced laparoscopic approach cannot be done with open dissection. In one report, when the advanced laparoscopic technique was used for catheter implantation, only 3 percent of patients transferred to hemodialysis as a result of catheter failure, compared with 17 percent nationally (6), and one center reported that 99 percent of catheters were problem free at 24 months (7). These ancillary procedures, however, are needed in only about one third of all patients, so it may be reasonable to avoid costs and minimize the risk of general anesthesia by using other implantation techniques.

Coincident with the recent growth in PD use are data such as the estimates from the 2013 Medicare Physician/Supplier Procedure use summary, which suggests that the use of open dissection for PD catheter placement is decreasing (now 22 percent of catheters placed) whereas the use of other techniques such as surgical laparoscopy (26 percent in 2007; 52 percent in 2013) is increasing. In addition, to facilitate the need for short-term and urgent PD catheter placement and avoidance of scheduling conflicts, general anesthesia, and overall costs, percutaneous needle–guide wire techniques (with imaging guidance, generally by interventional radiologists [22 percent], or without imaging guidance, generally by interventional nephrologists [4 percent]) have become more commonly used for placing PD catheters.

The important issue when other techniques are used is how the subcutaneous portion of the PD catheter is placed, because the ability to salvage rather than replace a PD catheter when there is a complication or nonfunction is related to the correctness of the original placement. Therefore, to improve overall outcomes and minimize costs, we should foster the use of a multidisciplinary approach to PD catheter implantation. This multidisciplinary approach does not necessarily involve all physicians at once but does imply that different physician specialists must work together to promote the delivery of seamless medical care. PD catheters are currently placed by surgeons, interventional radiologists, and interventional nephrologists.

Most practicing interventional radiologists and interventional nephrologists did not learn how to place PD catheters during training and are learning on the job. Moreover, surgery, radiology, and nephrology residency and fellowship programs continue to be poorly prepared and largely inadequate with respect to teaching PD catheter access procedures. In a survey of surgical residency programs in the United States, it was found that fellows typically place only two to five catheters during their training, and when asked, 38 percent of fellowship directors stated they could not provide more training. Unfortunately, 77 percent of PD programs start fewer than 10 patients with PD each year (8). As a result, catheter dysfunction remains a problem for PD patients and one of the major causes for morbidity and transfer to hemodialysis. Educating the person who places the PD access is important, and efforts are being put in place by major national dialysis providers and the Interna-

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Peritoneal Dialysis

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tional Society for Peritoneal Dialysis to provide such training (9).

Infectious complications

Infectious complications of PD, specifically peritonitis, remain a major cause of patient morbidity, hospitalization, technique failure with transfer to CHD, and occasionally death worldwide (10). Therefore, prevention of infections is of significant importance, and a multifaceted, multidisciplinary approach is needed to optimize patient outcomes (11). Dialysis unit home therapy infrastructure, nursing expertise, and patient training are keys to success. Meticulous care of the catheter exit site is an important element of patient training. Part of the the unit's infection prevention protocol should include the use of daily topical prophylactic antibiotics such as mupirocin (12) or gentamicin cream (12) at the exit site. Mupirocin cream has been shown to result in a significant reduction in exit site infections compared with routine care in more than one study, and in another study gentamicin was found to be superior to mupirocin. Other antibiotics have been tried but have not been found to be superior to mupirocin or gentamicin and, in the case of Polysporin triple antibiotic use, may be associated with increased risk of fungal colonization (14).

Other prophylactic measures should include use of appropriate antibiotic prophylaxis during procedures such as dental care, gastrointestinal procedures, and gynecologic procedures and after trauma to the exit site. Units should develop policies and procedures for timely diagnosis and treatment of peritonitis. It is important to state that many factors other than bacterial peritonitis may cause cloudy fluid. They include, but are not limited to, fungal peritonitis, chemical peritonitis, eosinophilic peritonitis, malignancy, and a specimen that is taken from a "dry" abdomen.

It is important not only to get a total white blood cell (WBC) count but also to obtain a differential count. If more than 50 percent of the cells present are polymorphonuclear neutrophils (PMNs), it is likely that the patient has bacterial peritonitis no matter what the total cell count may be. With these approaches, generally one should expect an overall infection rate of less than one episode of peritonitis every 3 years. With the use of exit-site antibiotic prophylaxis, the relative proportion of gram-positive episodes of peritonitis has markedly decreased, so when the patient presents with peritonitis, broad-spectrum antibiotic therapy should be initiated until the specific culture results are known.

The International Society for Peritoneal Dialysis has published guidelines for the diagnosis and treatment of PD-related infections (15). Center-specific protocols that take into account local sensitivities should be developed. What has been increasingly recognized is the prognostic value of trends in effluent WBCs during the course of therapy. In one study, if the effluent WBC count exceeded 1000 cells/mm^3 on day 3, there was a 64 percent probability that the current therapeutic approach would fail. In these cases, one needs to reevaluate current antibiotic choice and dose, and perhaps consider other diagnostic possibilities such as an intraabdominal cause of the peritonitis. Although fungi are not a common cause of peritonitis, fungal peritonitis is associated with serious complications, such as technique failure and death. Patient survival during an episode of fungal peritonitis has been associated with early catheter removal (16), which, along with appropriate antifungal therapy, is the current treatment recommendation for fungal peritonitis. In many patients (almost one third), it is possible to replace the catheter and restart PD after the fungal peritonitis resolves (17). Prior antibiotic treatment is a predisposing factor for fungal peritonitis; therefore, antifungal prophylaxis during prolonged antibiotic use is recommended by many (18).

Cardiovascular issues and PD

Typically, PD patients receive therapy daily—most often 24 hours a day, in fact. As a result, one would think there would be an opportunity for much better BP and volume control than with CHD. Despite the continuous nature of the therapy, however, two studies showed that blood pressure was controlled in only about 30 percent of patients (in one study, 15 percent normal and about 15 percent high normal) (19, 20). Another study showed that PD patients were more likely to have signs of volume overload compared with CHD patients (35.7 percent vs 12.4 percent) and evidence of hypertension (64.3 percent vs 51.2 percent) (21). Despite these observations, in retrospective cohort studies it is hard to prove an association between quartiles of BP control and survival. However, observational studies have shown an association between ultrafiltration (UF) volume and presumably sodium removal and patient survival (22, 23). Hence the recommendation in the latest Kidney Disease Outcome Quality Initiative guidelines for adequacy of PD to "normalize BP and volume" without mentioning a specific numeric BP goal.

What is not a new observation, but is increasingly recognized as an important clinical caveat to address, is the dissociation between UF volume and the percentage of that UF volume that is sodium replete. Because of the presence of transcellular aquaporins, across which a large glucose gradient is maintained, a substantial portion (almost 50 percent) of the UF with a dextrose (glucose) dwell is sodium free. As a result of this "free water" UF volume, dialysate sodium drops. If the dwell is short (as it is with overnight cycler therapy), sodium cannot catch up with the free water by moving from blood to dialysate by diffusion. During longer dwells, the sodium can catch up with the free water. Generally, because one usually does only three or four overnight dwells, this is not of consequence, especially if a patient has any residual renal function. But if one were to do more than four dextrose exchanges over a 9-hour period, the patient could experience transient hypernatremia, stimulating thirst, and although there may be a large UF volume, about 50 percent of it would be sodium free.

One should also pay attention to the daytime dwell. If dextrose dwells are used, these long dwells are long enough for sodium to catch up with the UF volume that moved across the aquaporins. However, if the dwell is too long, in many patients the glucose gradient will have dissipated as a result of glucose absorption, and UF would have ceased. In these cases, if the dwell time is long, UF volumes may be minimal, or in fact, as a result of continuous absorption of fluid from the PD cavity (almost 1 mL/min), drain volumes could be less than instilled volumes. Alternative osmotic agents such as polyglucose solutions (icodextrin) have been developed to correct some of these issues. Icodextrin has a slow but sustained UF profile, and over 95 percent of the UF volume is sodium replete. Many of the volume-overloaded PD patients who in the past transferred to CHD because of "membrane failure" are in fact currently well treated by individualization of the therapy and changes of the prescription as needed on the basis of transport types. One does this by changing dwell times, using midday exchanges, and considering the use of alternative osmotic agents such as icodextrin. Presumably in part as a result of these nuances in sodium and water removal, historical data suggest that the relative risk of death was related to transport type (higher relative risk of death in rapid transporters, who tend to have problems with UF volume during longer dwells) (24). However, in more contemporary cohorts, where prescriptions have been adjusted and various PD solutions and submodalities of PD have been used, that association has not been found (25, 26).

In contrast to what has been observed in CHD patients, PD is likely associated with less rapid drops in BP and less transient cardiac wall motion abnormalities or cardiac stunning (27). Additionally, CHD patients are known to have transient cognitive defects associated with their treatment and an increased incidence of abnormalities in brain white matter than would otherwise be expected in age-matched control individuals. Presumably there would also be less transient brain ischemia in PD patients. Interestingly, data from the US Renal Data System suggest that there is a higher prevalence of dementia in CHD patients (28), and in a retrospective study evaluating the effect of dialysis modality on the development of dementia over time, PD patients were significantly less likely to experience dementia.

Finally, a very interesting but not unsuspected clinical observation that could result in low drain volumes has been formally described. This has to do with the fact that the concentration of dextrose or icodextrin in the dialysate fluid (say 4.25 percent dextrose or 7.5 percent icodextrin) may not be the concentration of that osmotic agent in the peritoneal cavity if a large residual volume is present when the fluid is instilled, effectively diluting the osmotic agent at instillation (29). As a result, if there was a 450-mL residual volume and 2 L of 7.5 percent icodextrin was infused, this would result in an immediate dilution of the icodextrin to about a 6.23 percent solution with resultant less UF—an important clinical caveat to add to our differential diagnosis of a low UF volume in PD patients using icodextrin.

PD membrane "failure" and the long-term patient

A historical observation about PD was that it "worked" for a few years, but then patients experienced "membrane failure," had problems with volume overload, and needed to transfer to CHD. As mentioned in the earlier discussion, this actually was often due to loss of residual kidney function and failure of the nephrology team to individualize and adjust the therapy in response, or to the patients' unwillingness to change their dialysis prescriptions or an inability to make needed dietary restrictions.

Despite that recognition, one of the most important challenges to the PD community is preservation of PD membrane integrity or prevention of "peritoneal membrane failure" over time. Peritoneal membrane failure is functionally characterized by UF failure. This is reported to occur in up to 30 percent of patients receiving long-term PD. Some of the ultrastructural changes are similar to those seen in diabetic microangiopathy. Deposition of advanced glycosylation end-products in peritoneal tissue has been described (30). It is well recognized that peritoneal fibrosis is typically characterized by mesothelial cell loss, angioneogenesis, and progressive submesothelial thickening, with an overabundance of myofibroblasts in many patients (31). The origin of the myofibroblasts, which seem to play a critical

role in these changes in PD, is controversial. Some believe that myofibroblasts originate through epithelial–mesenchymal transition of mesothelial cells, and although in vivo and in vitro data suggest that observed morphologic changes in mesothelial cells are associated with the acquisition of mesenchymal markers, few of those reported biomarkers are specific enough to prove that mesothelial cell epithelial–mesenchymal transition is the true process driving peritoneal fibrosis (32). For now, though, this is the working hypothesis.

It is well demonstrated that over time during PD, increasing numbers of active myofibroblasts are stimulated by a variety of fibrogenic cytokines, such as TGF-β1 released by dysregulated cells. There is evidence that mesothelial cells normally have a local renin-angiotensin system, which over time during PD may be dysregulated (33). The question is this: what causes this dysregulated, injured environment? Is it the result of repeated instillations of high-glucose–containing fluids or the presence of glucose degradation products or both? In vitro studies have suggested that when human peritoneal mesothelial cells are stimulated to produce vascular endothelial growth factor, incubation with an angiotensin converting enzyme or an angiotensin receptor blocker inhibits or reduces its production, suggesting a downregulation of the local renin-angiotensin system (34). Interestingly, in a retrospective observational cohort study, PD patients who were taking an angiotensin converting enzyme or an angiotensin receptor blocker for any reason were less likely to have their peritoneal membrane transport characteristics increase over time (35). It therefore seems reasonable to use one of these drugs for peritoneal, residual kidney, and cardiac protection over time in PD patients if there are no side effects and no clinical contraindication to their use.

As for the peritoneal fluids, various biocompatible PD solutions that have a neutral pH and lower glucose degradation product (GDP) content have been developed, as have solutions such as amino acid–containing fluids that have no glucose. The results of studies using biocompatible PD solutions or low-glucose (glucose-sparing) regimens have not confirmed an overwhelming clinical benefit in terms of membrane preservation over conventional PD solutions (36). These regimens seem to improve some aspects of PD health and viability but with no overall consistent clinical effect on peritonitis rates, technique survival, or patient survival. Some low-GDP solutions may be associated with greater urine volume and "preservation" of renal function, but this effect may be compounded by the small increase in peritoneal transport with their use and less peritoneal UF volume, which may have an effect on residual kidney volume. A recent prospective randomized 12-month study using low glucose exposure (amino acids, icodextrin, and glucose), low-GDP fluids compared with conventional glucose fluids found increased urine volume, less biochemical evidence of membrane damage, lower inflammatory cytokines, and higher antifibrotic markers in patients using these fluids than in patients using conventional dialysate. Further studies are needed.

Conclusions

The use of PD in the United States is growing. This is likely driven by clinical outcome studies suggesting equal or better early survival in patients using PD than in those using CHD and by the financial realities of a bundled payment structure. It is recognized that the ability to individualize each patient's PD prescription is helpful to optimize certain patient outcomes. To date there are no data to show that this recent acceleration in PD use has been associated with any overall detriment in patient outcomes.

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Online Hemodiafiltration

By Francisco Maduell

Although the physical and chemical concepts of diffusion and convection are well known, dialysis has been carried out mainly by diffusion during its first four decades. This form of dialysis, hemodialysis (HD), has ensured the survival of millions of patients with advanced kidney disease worldwide and has met the increasing needs generated in the 50 years since dialysis was considered for long-term renal replacement therapy.

The delay in incorporating convection techniques as routine treatment has technological and economic reasons. Hemofiltration (HF) or hemodiafiltration (HDF) modalities require the use of dialyzers of high permeability and, at the same time, monitors with volume control and a dual pump. Replacement fluid is a further cost, is the main reason for abandoning HF, and was a key constraint on the initial HDF technique, with volumes ranging between 3 and 10 L. In the 1990s, the introduction of online HDF techniques using the dialysis fluid itself as a replacement solution has meant a revolution in HD units. It has taken another 10 years to renovate and upgrade water treatment, introduce specific monitors, and incorporate safety filters to ensure ultrapure dialysate.

What is hemodiafiltration?

The European Dialysis working group (EUDIAL) revisited the definition of hemodiafiltration (1) as the blood clearance treatment that combines diffusive and convective transport using a high-flux dialyzer with an ultrafiltration coefficient (KUF) >20 mL/mm Hg/h/m^2, a sieving coefficient for ß2-microglobulin >0.6, and a percentage of effective convective transport greater than 20 percent of the total processed blood. Convection volume was defined as the sum of the replacement volume and the intradialytic weight loss achieved.

Can I provide online hemodiafiltration?

To answer this question, complete the checklist in Table 1. If the answer to all of the questions is yes, you are able to provide this treatment modality. If the answer to one or more of the questions is no, the treatment cannot be started until each point has been resolved. This checklist does not include training, because the current technology has been greatly simplified and is easy to use.

Why should we systematically implement online hemodiafiltration?

Online HDF (OL-HDF) can be indicated for all patients receiving hemodialysis, because there are no contraindications. Online HDF techniques constitute progress toward renal replacement therapy that is most similar to the native kidney. These techniques offer a higher clearance of uremic substances with a greater range of molecular size.

The possible clinical benefits that convection techniques can provide are better control of hyperphosphatemia, malnutrition, inflammation, anemia, infectious complications, joint pain, amyloidosis associated with dialysis, intradialytic tolerance, insomnia, irritability, restless leg syndrome, polyneuropathy, and itching.

Does online hemodiafiltration improve survival?

Observational studies, adjusted for demographic and comorbidity factors, have shown that a lower risk of death is associated with online HDF (2–5). In addition, three large prospective randomized clinical trials (RCTs) have been conducted to compare survival outcomes in prevalent patients. The CONTRAST study randomized 714 patients to low-flux HD or OL HDF and at the end of the study the two groups showed no difference in survival (6). Similarly, in the Turkish HDF study, 782 patients were randomized to HF HD or OL HDF and the outcome was not affected by treatment allocation (7). However, the ESHOL study randomized 906 patients to HF-HD or OL HDF, and the allocation to OL HDF was associated with a 30 percent reduction in all-cause mortality (8).

Recently, two meta-analyses, including the three RCTs mentioned above, have confirmed that OL-HDF increases overall and cardiovascular survival. Online HDF was associated with a reduction of 13 percent to 16 percent in all-cause mortality and 25 percent to 27 percent in cardiovascular mortality (9–10).

Association between survival and convective volume

In all large RCTs, the connvective volume seemed to be an important issue. A post hoc analysis of the CONTRAST study showed that in the group of patients with the highest delivered convection volume (upper tertile >21.95 L), mortality was 39 percent lower than in patients randomized to LF-HD (6). In a Turkish study, the median value of substitution volume in the OL-HDF group was 17.4 L, and when patients were stratified according to this threshold, those in the high-efficiency OL-HDF group were associated with a 46 percent risk reduction for overall mortality and a 69 percent risk reduction for cardiovascular mortality (7). In post hoc analyses of the ESHOL study, mortality in the intermediate tertile (23.1–25.4 L per session) and upper tertile (>25.4 L) was significantly lower than that in patients randomized to HD: 40 percent and 45 percent risk reduction for overall mortality, respectively (8).

Convective dose prescription

Convective target volume should therefore be the maximum possible for the individual characteristics and parameters of each patient dialysis. Based on the results of secondary analyses of the main clinical trials, the current recommendation of the optimal dose of OL-HDF, in postdilutional mode with a thrice-weekly treatment schedule, would be a convective volume >23 L per session. However, bear in mind that this recommendation is based in secondary analysis, and therefore there could be a selection bias. Patients receiving greater convective volume are those in better overall condition, with good vascular access and less diabetes or cardiovascular disease. In the absence of more conclusive scientific evidence, it seems a reasonable and affordable recommendation that should be confirmed with future clinical trials.

How to optimize online hemodiafiltration

Vascular access

A native fistula is the best option for all HD modalities as well as for OL-HDF. However, the use of a native fistula or graft has decreased because of greater patient age and the increased prevalence of cardiovascular disease and diabetes. The use of a catheter means a lower blood flow (Qb) and convective volume. In a multicenter study, only a third of the patients with catheters achieved a minimum of 21 L of replacement volume target (11). It's important to consider that patients with catheters should increase the duration of dialysis to achieve an adequate dialysis dose (additional 30 minutes if the catheter is used in the normal position and 1 hour if it is in a reversed position) (12). Therefore, catheter use should not be seen as an obstacle for HDF, but increasing dialysis duration must be considered.

Blood flow

The main limiting factor for convective volume is Qb. In postdilution mode, the maximum recommended infusion flow is 33 percent of the Qb value. Achieving adequate convective volumes may be complicated in patients with limited Qb. Some authors have suggested that the prescription of Qb is more a matter of treatment policy in each dialysis unit than the characteristics of the patients themselves (13).

Dialysis machine

New dialysis machines that allow an automatic infusion flow (Qi) to maximize the convective volume have reduced the risk of hemoconcentration and have increased convective volume (14–15).

Dialyzer

Online HDF needs high-flux dialyzers. Currently, dialyzers are available with large convective capacity, with KUF between 40 and 100 mL/h/mm Hg. This means that with a transmembrane pressure of 200 mm Hg, allowing Qi of 133 to 333 mL/min, Qi is much higher than those that can actually be used. Therefore, a dialyzer with KUF > 45 mL/h/mm Hg is not a limiting factor in the convective volume, and the differences obtained in the purification capacity would be minimal.

Dialysis duration

Increase in the duration of dialysis will always be a valid alternative to increase in convective volume.

Is it time to change from diffusion techniques to online hemodiafiltration?

We are fully convinced that now is the time to change to convective techniques. First, the available scientific evidence supports that this treatment increases overall and cardiovascular survival. Second, technological develop-

Table 1. Checklist to evaluate whether a dialysis unit can provide online hemodiafiltration

Question	Yes	No
Do you have proper water treatment for ultrapure water?		
Do you have access to high-flux dialyzers?		
Do you have appropriate machines for OL-HDF?		
Can you use two safety filters on these machines to obtain ultrapure dialysate?		
Can you request monthly microbiological cultures and endotoxin determinations?		
Do you have adequate financial reimbursement?		

Abbreviations: HDF = hemodiafiltration; OL = online.

ment in water treatment, advances in monitors, and the widespread use of synthetic high-flux dialyzers, make this a feasible proposition. Finally, online HDF provides possible clinical benefits, and we have found no published literature showing any undesirable effects.

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Continuous Renal Replacement Therapy: The Rise of the New Machines

By Lakhmir S. Chawla

Continuous renal replacement therapy (CRRT) is relatively young; the first continuous venovenous CRRT systems were deployed widely in the late 1990s. The early machines were an enormous improvement over continuous arteriovenous systems. However, the early machines did not have the corresponding accessories available, and many nephrologists can recall "brewing" lactate-buffered dialysis and replacement solutions to operate CRRT in the early days. Some of us even resorted to using peritoneal dialysate in CRRT. In the past 15 years, the need for customized fluids has been rare, and multiple bicarbonate buffered commercial solutions are now available. In addition, the accessories for short-term dialysis such as double-lumen catheters, anticoagulation options, and replacement fluid solutions have all been upgraded over the past 15 years. Now, CRRT, which was once a laborious and complex procedure, has become much easier and safer. So what does the field need now? Next-generation machines.

The first-generation CRRT machines were the Prisma and the Diapact. At the time, these machines were embraced because of their ability to perform venovenous procedures more safely. During this time, the primary goal was to get control of the patient's volume and electrolytes without hemodynamic instability. The publication of the "Ronco paper" in *The Lancet* in 2000 pushed many clinicians to try to achieve a higher dose of CRRT.

These first-generation machines did not have flow capacities for blood or effluent flow rates that met the needs of many clinicians, and the second-generation machines were brought into the intensive care unit with the capacity to achieve these higher flow targets. After publication of the Randomized Evaluaton of Normal versus Augmented Level of Replacement Therapy trial and Acute Renal Failure Trial Network, the consensus dose for CRRT was set at 20 to 25 mL/kg/h. However, questions about hemofiltration versus diffusion remain unanswered, and some still believe that extended daily dialysis is adequate compared with CRRT.

In any case, for most clinicians in the United States, CRRT is performed with the PrismaFlex (Baxter Medical), the NxStage System One (NSO, NxStage Medical), or the Diapact System (B-Braun). Both PrismaFlex and NSO have the ability to run much higher effluent flow rates. Both platforms can also perform plasmapheresis, and the PrismaFlex can be used with the MARS system (Gambro) to conduct albumin dialysis. The key technological differentiator of the NSO compared with the PrismaFlex and the Diapact System is its use of a disposable cartridge containing all of the blood and fluid pathways, including a volumetric fluid management system. This volumetric system balances fresh replacement fluid or dialysate with effluent coming from the dialyzer and removes excess fluid (net ultrafiltration) from the patient. The PrismaFlex and the Diapact System both use gravimetric scales. The PrismaFlex machine features five pumps (blood, dialysate, pre–blood pump replacement solution, post–blood pump replacement solution, and effluent), four scales (one each for effluent and dialysate, two for replacement solutions) and a disposable set with preconnected high-flow dialyzers and fluid circuitry. The Diapact system has three pumps with a wide range of blood flows and dialysate flows. Fluid handling and ultrafiltration control is gravimetric, with one scale.

But now the new machines are coming. A looming question is whether these current platforms are sufficient or whether new capabilities and features are required. The names and timelines of the new machines have not been officially announced, but at the bedside we can expect new versions of the PrismaFlex and the NSO in the next 24 months. In addition, Spectral Medical, Inc., has indicated its intention to introduce a CRRT machine to the North American market in the next 18 months, called the S.A.M. (Spectral Apheresis Machine). The S.A.M system uses a synchronized piston pump system run by four internal cam shafts that also run the pump clamps. The S.A.M. system is a small, easy-to-use, open platform for CRRT and hemoperfusion. In the pediatric world, the CARPEDIEM machine (Bellco), which debuted in Europe, looks to enter the US market. CARPEDIEM was specifically designed for neonatal CRRT and has very low priming volumes, blood flow rates as low as 5 mL/min, and incredibly accurate scales (error = 1 g), making it appealing for use in low-weight children as well.

What features can we expect with these new machines, and will the new machines bring features to the bedside to improve only delivery of the therapy or will they also have new capacities to improve outcomes? Inasmuch as the new machines and their new features remain unknown, I conducted an informal poll at the Critical Care Nephrology meeting in Vicenza, Italy, in June 2015 and asked which new features were most desirable. The top answers were reduced cost, smaller footprint, increased versatility, and portability. Interestingly, many thought leaders said the addition of an online monitor for hematocrit, calcium, or both would be an important advancement. In short, the new machines are coming soon, and we can hope that the manufacturers of the new devices will deliver.s

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Individualization of Vascular Access Care: Dream or Reality?

By Prabir Roy-Chaudhury MD, PhD

Scope of the problem

Hemodialysis vascular access is without question the lifeline for the more than 400,000 patients undergoing hemodialysis in the United States. Unfortunately, because of the high incidence of dialysis vascular access dysfunction, it is also the "Achilles heel" of hemodialysis (1, 2). There are currently three main forms of permanent dialysis vascular access, each of which have their pros and cons.

Arteriovenous fistulae (AVFs) are the preferred form of permanent dialysis vascular access because of their prolonged long-term survival and lack of infection. Indeed, the Fistula First initiative has increased the current AVF prevalence from under 30 percent to over 60 percent in the United States. The main complication of AVFs is a very high failure-to-mature rate (defined as the inability of the AVF to increase blood flow and diameter adequately to support hemodialysis). Currently, as many as 60 percent of AVFs are unsuitable for dialysis between 4 and 5 months after surgery (3). Some of these failures could be due to the placement of AVFs in patients with small vessels or with other predictors of AVF failure. The main reason for AVF maturation failure at a pathogenetic level is likely a combination of an aggressive neointimal hyperplasia (myofibroblast and smooth muscle cell ingrowth from the media) combined with a possible lack of outward remodeling (dilatation) (1, 4).

Arteriovenous grafts (AVG), by contrast, do not have these early failure-to-mature problems, and over 90 percent of surgically created AVGs can in fact be used for hemodialysis within the first 6 weeks after surgery. The main problem with AVGs, unfortunately, is a predictable stenosis at the graft–vein anastomosis resulting from neointimal hyperplasia, which is responsible for a dismal 1year primary patency of only 23 percent.

The least desirable form of permanent dialysis vascular access is the tunneled dialysis catheter (TDC), which carries a huge morbidity and mortality burden as a result of catheter-related bloodstream infections; fibrin sheath formation, which results in inadequate blood flow; and central vein stenosis. Despite the significant increase in both morbidity and mortality and the cost associated with TDC dysfunction (5), almost 80 percent of new (incident) patients starting hemodialysis do so with a TDC.

Current vascular access care paradigms

An important focus of the broader vascular access community—physicians, nurses, hospitals, and payers (particularly the Centers for Medicare and Medicaid Services)—over the past decade has been on the Fistula First initiative. This initiative, which began over 10 years ago, has been amazingly successful in that it has increased the AVF prevalence rate from under 30 percent to over 60 percent currently (6). Whereas the Fistula First initiative was clearly the need of the day when the AVF prevalence rate was low, it is unclear whether the same drivers are still in play, with the current AVF prevalence rate of 61 percent nationally. In particular, the higher AVF prevalence suggests that rather than a one-size-fits all approach, it may be time to move toward a more individualized approach to vascular access care (7, 8).

Stratifying patients using demographic, clinical, and biologic parameters

Several factors are currently thought to be associated with a higher incidence of AVF maturation failure in particular. They include small arteries (<1.5–2 mm) and veins (<2.5–3 mm), female gender, obesity, the presence of peripheral vascular disease, older age, and African American ethnicity. The availability of these factors does not appear to have had a significant impact on AVF maturation, however, which could result from the poor predictive power of these criteria or, alternatively, the lack of a unified approach to the application of this information to routine clinical vascular access care. Thus, we are still left with multiple instances wherein an AVF created in an older patient or in a patient with small vessels undergoes successful AVF maturation, whereas an AVF created in a younger patient or in a patient with larger vessels fails to mature. In an attempt to address this specific issue, the Hemodialysis Fistula Maturation Consortium, funded by the National Institutes of Health, has collected extensive clinical, demographic, biologic, and process of care data in over 600 patients receiving a new AVF and is in the process of linking some of these data with AVF maturation success or failure (9).

Outside of AVF maturation, however, we have absolutely no clinical predictors of AVG success or failure, for example, nor of the factors that may be able to predict a good response to angioplasty with or without stent placement in patients with AVF and AVG stenosis. We therefore believe that it is essential to develop high-quality clinical and biologic predictors of dialysis vascular access dysfunction in such a manner that future patients receiving a new dialysis vascular access or undergoing an angioplasty with or without stent placement could be stratified into high-risk and low-risk groups based on a combination of such predictors. Some examples of specific biologic predictors, in particular, could include genetic polymorphisms, flow-mediated dilatation, and aortic pulse wave velocity.

Targeting high-risk patients with technology and process of care interventions

The development and validation of high-quality clinical, demographic, and biologic predictors for dialysis vascular access dysfunction (in the context of both initial surgical placement and later endovascular and surgical intervention) could result in several important downstream effects.

First, it is likely that as we develop novel therapies for dialysis vascular access dysfunction that can reduce neointimal hyperplasia, enhance outward remodeling, or reduce postangioplasty restenosis, these therapies could be preferentially used in patients at high risk for dialysis vascular access failure.

Second, such an enhanced "predictor panel" could also be used to individualize the initial choice of vascular access, in that patients at high risk of AVF maturation failure could receive an AVG instead. Such a choice could potentially also reduce the current epidemic of TDC use during prolonged periods of AVF maturation.

Last but not least, patients at higher risk of dialysis vascular access dysfunction could be placed into a more intensive "process of care" pathway in that they could be fast tracked for early surgery and more aggressive follow-up with dedicated vascular access coordinators.

Putting it all together

We strongly believe that we need to move away from a one-size-fits-all paradigm into a construct wherein we try to individualize vascular access care in such a manner that we place the right access in the right person at the right time (Figure 1). To do this, however, we desperately need high-quality and well-validated predictors, particularly those that are derived from the biologic aspects of vascular access dysfunction.

Individualizing dialysis vascular access care could significantly reduce the morbidity and mortality burden (repeated endovascular/surgical interventions and prolonged TDC use with all its attendant complications) associated with dialysis vascular access dysfunction, and as a result improve the quality of life of our hemodialysis patients. In addition, as we move into an era of bundled dialysis payments, individualization of dialysis vascular access care could also result in significant savings in health care costs: smart medicine by any other name.

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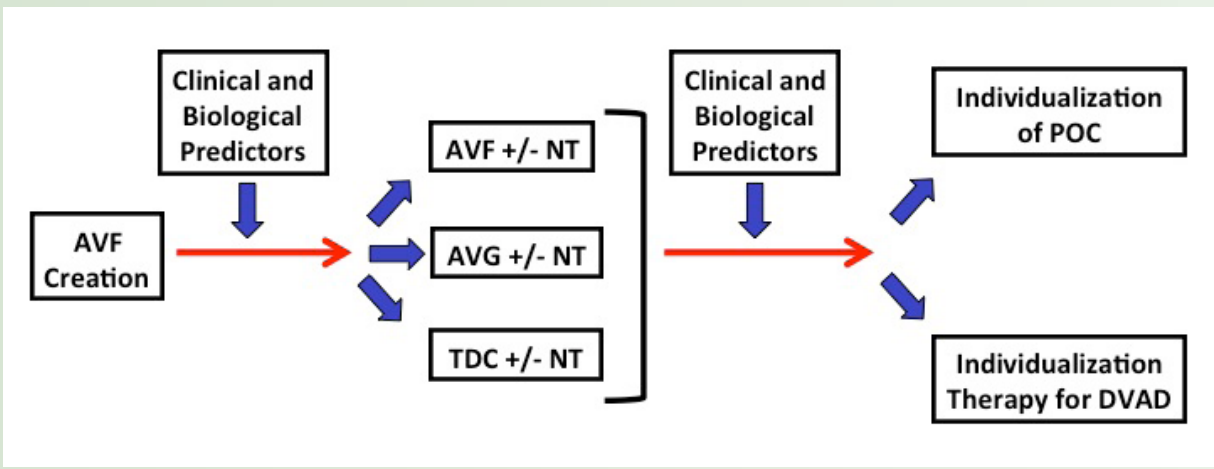
Figure 1. Individualization of dialysis vascular access care



The availability of high-quality clinical and biologic predictors could help to individualize every aspect of vascular access care from the selection of the right vascular access type in a particular patient to the application of targeted process of care and novel therapies to treat dialysis vascular access dysfunction in selected patients.

Abbreviations: AVF = arteriovenous fistula; AVG = arteriovenous graft; DVAD = dialysis vascular access dysfunction; POC = process of care; NT = new therapies; TDC = tunneled dialysis catheter.

Evolution of the Management of AKI in Neonates

By Claudio Ronco and Zaccaria Ricci

1983–1988: Technology and bioengineering

We in Vicenza began studies on buffers in peritoneal dialysis (PD), leading the pathway toward the use of bicarbonate in fluids (1–3). We analyzed the pathophysiologic pathways of neurotransmission, measuring several substances in the cerebrospinal fluid before and after dialysis (4, 5). In those days, the pressure to shorten hemodialysis treatments provided the impetus for studies on dialysis tolerance. We therefore focused on developing technology to make short dialysis efficient and safe (6). We studied fluid mechanics and flow distribution in dialyzers and mechanisms of solute transport in hollow fibers, and we applied all of this information to support rapid hemodialysis (7) and continuous arteriovenous hemofiltration (CAVH) (8). We developed new filters (9), described the adsorption process onto the membrane, and made the first filters with two ports in the filtrate compartment so that we could perform the first hemodiafiltration treatment (10). At the same time, we developed new fluid balance devices to be applied in intensive care patients (11).

1989–1995: Adequacy beyond Kt/V and the birth of critical care nephrology

During the years after the rapid evolution of dialysis and consequent technologic improvement, we started to consider that urea was just one aspect of treatment adequacy, and we began to promote a more holistic approach to the patient. In 1992, I felt compelled to start exploring the true integration between intensive care medicine and nephrology for better outcomes in critically ill patients. In 1998, Rinaldo Bellomo and I published "Critical care nephrology: the time has come" (12). This editorial, together with the first textbook on critical care nephrology (13), paved the way toward a new modern discipline. In the meantime, other studies were published by our group on new hemodialysis membranes, the new low-flux polysulfone (14), the use of adsorption (15), and the mechanics of cross-filtration in hollow fiber dialyzers (16). These and other studies paved the way for the Cardio-Renal Pediatric Dialysis Emergency Machine (CARPEDIEM).

2006–2010: The years of multiple organ support therapy, the wearable artificial kidney (WAK), and cardiorenal syndrome

Once the research group had been established in Vicenza, a continuous rotation of fellows made the Vicenza center a vibrant and energetic environment for new projects. We had already proposed the concept that although a single organ failure like acute kidney injury (AKI) requires specific organ replacement and thus dialysis/hemofiltration, multiple organ dysfunction syndrome in the critically ill patient may require multiple organ support therapy (MOST) (17). Thus, we advocated the transformation of the continuous renal replacement therapy (CRRT) machine into a platform for any extracorporeal therapy that can provide organ support. Techniques such as hemodiafiltration for the kidney, slow continuous ultrafiltration for the heart, plasmafiltration and albumin dialysis for the liver, and extracorporeal CO_2 removal for the lung were conceived and clinically applied with success (18).

2011–2013: The CARPEDIEM project (Cardio-Renal Pediatric Dialysis Emergency Machine): a journey into pediatric nephrology

In 1984, we pioneered new techniques for neonates: CAVH. We published a series of four neonates treated with an extracorporeal circuit in which blood was circulated through a permeable filter by the pressure gradient generated by the heart (19). Our expertise with the technique in adults and in bioengineering of hollow fiber hemodialyzers allowed us to open the way to pediatric hemofiltration, thanks to the development of minifilters—a scaled-down version of adult filters used for artificial kidney technology (20). In the neonate, it was important to develop a tool with appropriate dimensions and extremely low extracorporeal volumes; the neonate has approximately 300 mL of blood in the body. Shifts of even small volumes into the extracorporeal circulation can create major hemodynamic derangements (2).

Figure 1. First continuous arteriovenous hemofiltration (CAVH) treatment at San Bortolo Hospital

Our experience suggested that the simplicity, rapid application, and good clinical tolerance demonstrated by CAVH in adults could make it a reliable treatment also for infants and children (19). In these patients, the technique could offer special advantages in terms of low priming volume of the extracorporeal circuit, low heparin requirements, low blood flow, and slow continuous removal of isotonic fluid. We treated four small infants with a modified CAVH circuit with shortened blood lines and connected the small filter (Minifilter) and the circuit to an artery and a vein (19). Such a circuit was able to run for 48 to 72 hours in the fourth patient treated in Vicenza for the first time in the world. Heparin and substitution fluids were administered according to the fluid balance requirements. An average ultrafiltration rate of 0.9 mL/min was achieved by this pioneering system.

Figure 1 shows the image of the first CAVH treatment carried out at the San Bortolo Hospital in Vicenza. The results in the four patients were subsequently published as the first application of CAVH in neonates (19). As a consequence, CAVH in neonates became a routine treatment in the world during the following years. The continuous evolution of the technique in the adult led to modified and specific machines with special blood and ultrafiltrate pumps that were designed to optimize the performance of the extracorporeal circuit (21). These machines, however, have proved to be suboptimal for pediatric use, even in the presence of customized circuits. In fact, the current equipment is mostly used off label in patients <15 kg of body weight and often provides significant challenges in their neonatal application (2). A major obstacle, in fact, is the small size of the catheter used in the very small patient and the low accuracy of flow control in the blood circuit and fluid balance control in the dialysate circuit.

The increase in the incidence of AKI and its association with poor outcomes in the general population (22) has led to a call for action to make an early diagnosis, institute new preventive measures, and implement new therapies to improve clinical outcomes (22). In fact, increased focus on AKI has occurred in adult patients, and to a lesser extent in children, with the development of standardized AKI classification systems (23), assessment of novel AKI biomarkers (24), and assessment of the association between AKI and the development of chronic kidney disease (25). However, such progress has not been made for infants and neonates. As a result, the National Institute of Diabetes and Digestive and Kidney Disease convened a workshop in 2013 (26) to review the state-of-the-art knowledge of AKI in neonates and to determine the feasibility of studying this group in an organized prospective manner.

In children, AKI is a complicated clinical syndrome requiring careful clinical management. In recent years, despite significant advances in critical care technology, a truly pediatric CRRT system has not been developed (2). Current CRRT machines present significant limitations for children, and in some cases, severe complications have occurred (27).

In current practice, clinical application of dialysis equipment is adapted to smaller patients, with great concern about outcomes and side effects (28). Whereas critically ill adults receive renal support with modern devices and very strict safety features, smaller children must rely on very accurate delivery of therapy, especially where fluid balance is concerned. Yet current CRRT machines are not designed to treat a small infant with accurate blood flow rates in the range of 10 to 50 mL/min and hourly ultrafiltration error <5 g/h (2). The accuracy of current systems does not meet these tolerances: a recent analysis of most commonly used machines in the adult setting showed balance errors in the range of 20 to 190 g depending on the machine and treatment flow rate (29).

CRRT devices also have different "reaction times" before a fluid balance error occurs (in the range of 10 to 20 seconds). In a worst-case scenario, more than 500 mL could be excessively removed from a patient in only a couple of minutes after three or four unchecked, alarm overrides (29). Remarkably, third-generation machines automatically stop CRRT sessions when a fluid balance error (typically 60 to 500 mL) has been reached within the (adjustable) time unit (typically 3 hours) (21). Before this feature was applied, fatal errors occurred in the very small child. Furthermore, because manufacturers of dialysis or CRRT machines do not perform specific tests for treatments in patients smaller than 10 to 15 kg, and safety features in these patients are not specifically created, legal concerns may arise when operators decide to prescribe these therapies (2). Thus, although current CRRT machines have been equipped with "modified" or

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AKI in Neonates

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"adapted" circuits for children, they are not reliable for patients weighing <15 kg. Moreover, a specifically designed neonatal machine had never been conceived. The small number of cases, together with the limited interest by industry in developing a fully integrated device specifically designed for small children, made AKI/acute renal failure in infants and neonates an "orphan disease" (2).

With this in mind, in 2008 we undertook a new journey into this area of "orphan" medicine to develop dedicated technology. We started a fundraising campaign to engage a team of experts to develop a miniaturized device for renal support in the neonate. The CARPEDIEM project was designed to create the conceptual basis for renal replacement therapy equipment specifically dedicated to newborns and small infants in a weight range of 1.5 to 10 kg and with an approximate body surface area of 0.15 to 0.5 m^2. In these patients, the total blood volume ranges from <200 mL to about 1 L, meaning that total body water content varies from 1 to 5 L. In such conditions, circuit priming volumes should be reduced to a minimum level and roller pumps should be able to run at slow speeds, guaranteeing the integrity of lines (small roller pumps running small tubes are expected to cause a quick decline in their performance) and maintaining an excellent level of flow and balance accuracy. The ambition of the CARPEDIEM project was to reconsider the technical and clinical expertise accumulated during the pediatric CAVH era and to design, with the help of modern miniaturization engineering skills, the first neonatal CRRT device. The project was carried out with the collaboration of many experts, including Luciano Fecondini (Medica, Medolla, Italy) and Domenico Cianciavicchia (Bellco, Mirandola, Italy), together with our engineering team leader, Francesco Garzotto, who conceived and built the machine.

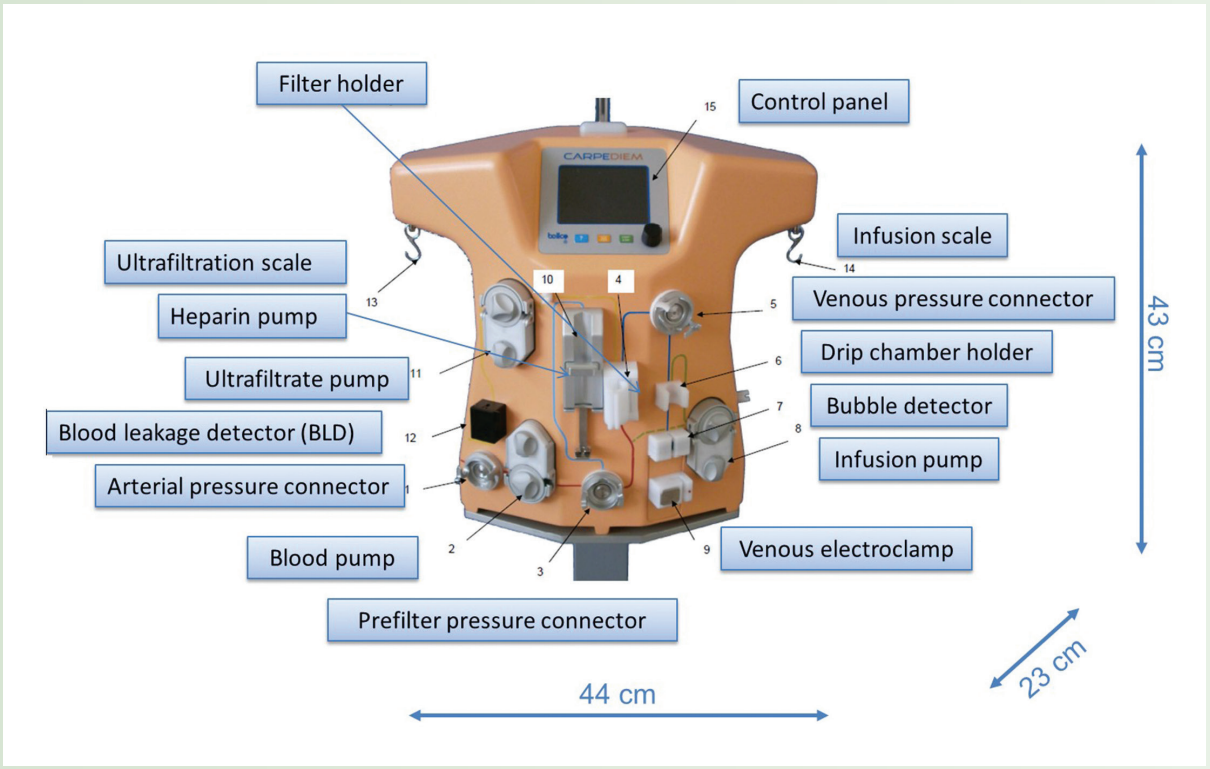
A prototype was created in record time and immediately tested in our laboratory. The machine was subsequently manufactured by Bellco. CARPEDIEM received the European Community (CE) mark in 2012 and, after thorough testing in the International Renal Research Institute of Vicenzia, was licensed for in vivo use in June 2013. Incredible effort and an enormous amount of energy, work, and passion has been the basis for the development of CARPEDIEM, and finally the technology was available for our infants with AKI (2).

The new system

CARPEDIEM is a combination of hardware, software, and disposable circuits specifically dedicated to neonates and small infants with a weight range of 2.0 to 9.9 kg and a body surface area of 0.15 to 0.5 m^2. Miniaturized circuits with reduced priming volume (minimum, 27 mL including filter) and new roller pumps were created to run continuously at flows as low as 1 to 50 mL/min. Ultrafiltrate and replacement fluid pumps have the same level of accuracy, running at 0 to 10 mL/min and finely regulated by two precision scales accurate to 1 g (Figure 2). Three configurations were made available with filters of different surface areas to adjust for patient size (0.0075, 0.0150, and 0.0250 m^2). The machine can perform CVVH in predilution, postdilution, and mixed predilution-postdilution plasma exchange, blood exchange, and continuous venovenous hemodialysis or single-pass albumin dialysis.

All of these specifications were thoroughly tested and confirmed in several sessions of in vitro laboratory testing performed by four independent operators. Circuits were run for 24 hours, and no significant changes in flow accuracy were observed with the use of 4-French and 7-French dual-lumen catheters. We observed excellent accuracy of blood pump flow rate, with an error always <10 percent. The rate of reinfusion/dialysis flow ranged from –8 percent to +7.5 percent. Importantly, whereas ultrafiltration accuracy always remained within the limit of 1 g/h, no significant variation in relation to different transmembrane pressure and filtration rates was observed (2). Microhemolysis was evaluated by measuring the normalized (by hematocrit) index of hemolysis. We tested three different assembly lines and dialyzers in triplicate at maximum blood flow for 10 hours. The observed microhemolysis was lower than 10.7×10^{-4}, and no difference was observed for the three types of tested circuits.

Figure 2. Components of the CARPEDIEM machine



2013: The first CARPEDIEM treatment in the world

A newborn girl had a subgaleal hemorrhage resulting from vacuum extraction and consequent hemorrhagic shock. The patient received several transfusions (28 units of packed red cells and platelets); she was intubated and mechanically ventilated. She had severe thrombocytopenia, acidosis, and severe fluid overload (60 percent of baseline body weight; body weight at birth, 2.9 kg; body weight at start of CRRT, 5.2 kg) with hyponatremia.

On day 2, a 4-French dual-lumen catheter was surgically placed into the femoral vein because of the lack of any other possible vascular access resulting from severe edema. Because she had oliguric AKI, she was given postdilution CVVH with the CARPEDIEM machine. The blood pump flow rate ranged from 9 to 13 mL/min, and daily clearance ranged from 2.2 to 2.8 L (a volume exchange close to the patient's total body water). The extracorporeal priming volume of the circuit was 27 mL, allowing maximal hemodynamic tolerance (Figure 3). Whereas creatinine and fluid overload began to be slowly but effectively corrected (Figure 4), the baby experienced severe hyperbilirubinemia (up to 54 mg/dL) resulting from combined liver dysfunction, and the hemofiltration treatment was subsequently alternated with other modalities aimed at bilirubin removal such as blood exchange in three sessions with 475 mL blood volume exchange at an isovolumetric exchange rate of 5 mL/min, single-pass albumin dialysis in three sessions of 10 hours with 4 percent albumin dialysate, and finally plasma exchange in four sessions with 670 mL plasma volume exchange. CVVH with additional bilirubin-targeted treatments led to progressive normalization of the bilirubin levels (Figure 5). The patient was supported with parenteral nutrition and supplementation with calcium, phosphate, and intravenous infusion of antibiotics and antifungal drugs because of her positive bacterial and fungal cultures. After 7 days of CRRT, her urine output partially recovered to 1.2 mL/kg/h and ultimately reached 3.2 mL/kg/h at 20 days. Hemofiltration was discontinued 25 days after the start of renal replacement therapy. Three days later, she was extubated, and she started to advance to complete oral alimentation. The extracorporeal treatment was carried out for 25 days, constituting more than 400 hours of extracorporeal circulation, stabilization of vital indicators, and correction of fluid overload, in conjunction with stabilization of serum creatinine at 2.8 mg/dL. After she reached her ideal body weight, she subsequently achieved physiologic weight gain, always while daily fluid balance was being monitored.

Finally the neonate was considered to be in stable condition, breathing normally without supplemental oxygen, making adequate amounts of urine, and displaying normal liver function, and she was therefore discharged from the intensive care unit. Twenty days later she was discharged from the hospital. The patient still had significant chronic kidney dysfunction, with a serum creatinine of 2.2 mg/dL. However, without a dedicated CRRT platform, renal replacement therapy would have been impossible because of technical and clinical contraindications to PD and inability to achieve a reliable vascular access for the use of traditional machines. We hypothesize that an inevitable fatal outcome would have occurred a few days after birth.

The CARPEDIEM technology applied in this case report represents a potential paradigm shift in the treatment of the neonate with AKI. Whereas PD will remain an important therapy for the uncomplicated case of neonatal AKI, the ability to accurately prescribe clearance and fluid balance will usher in a new era of renal replacement therapy and will provide a method of renal

Figure 3. The CARPEDIEM machine

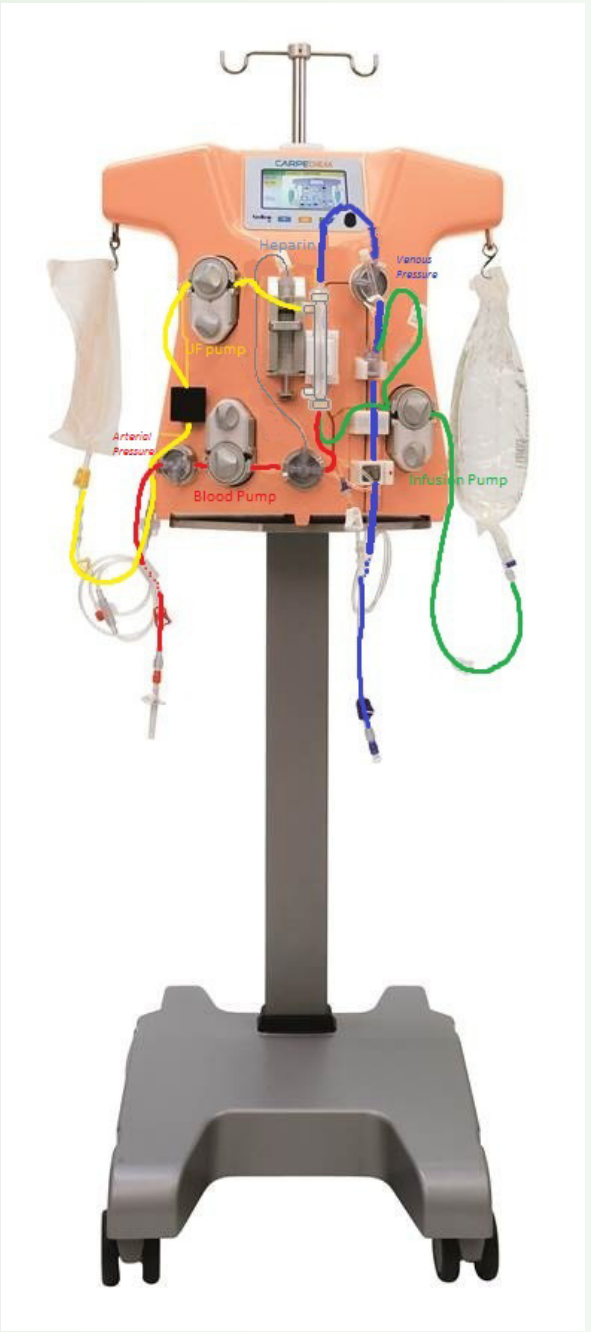


Figure 4. Fluid management and percent fluid output

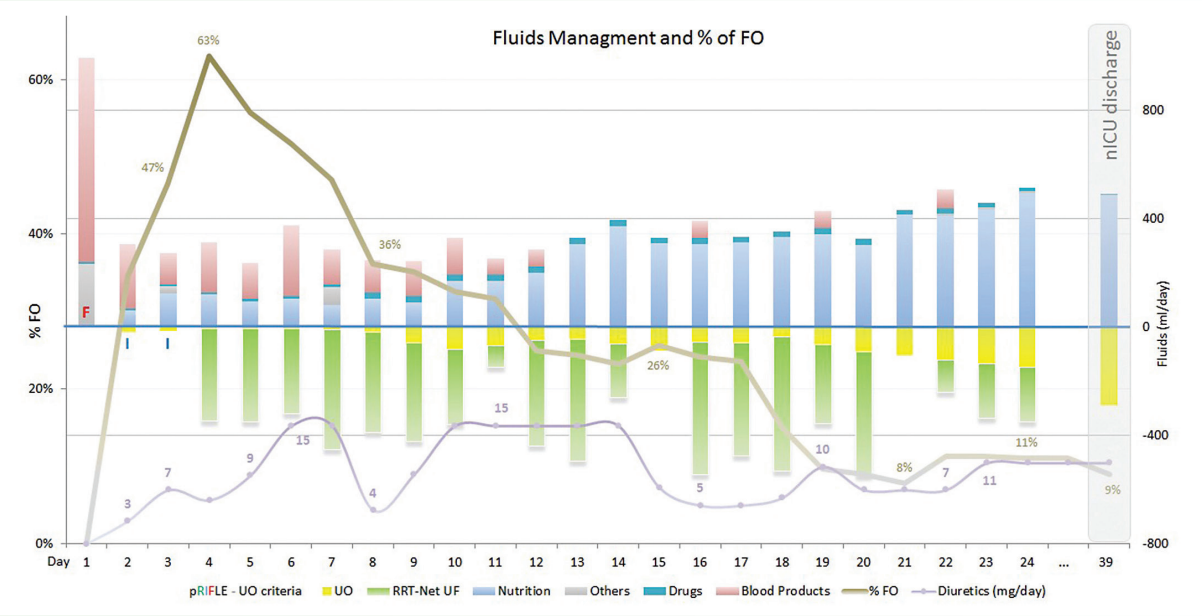
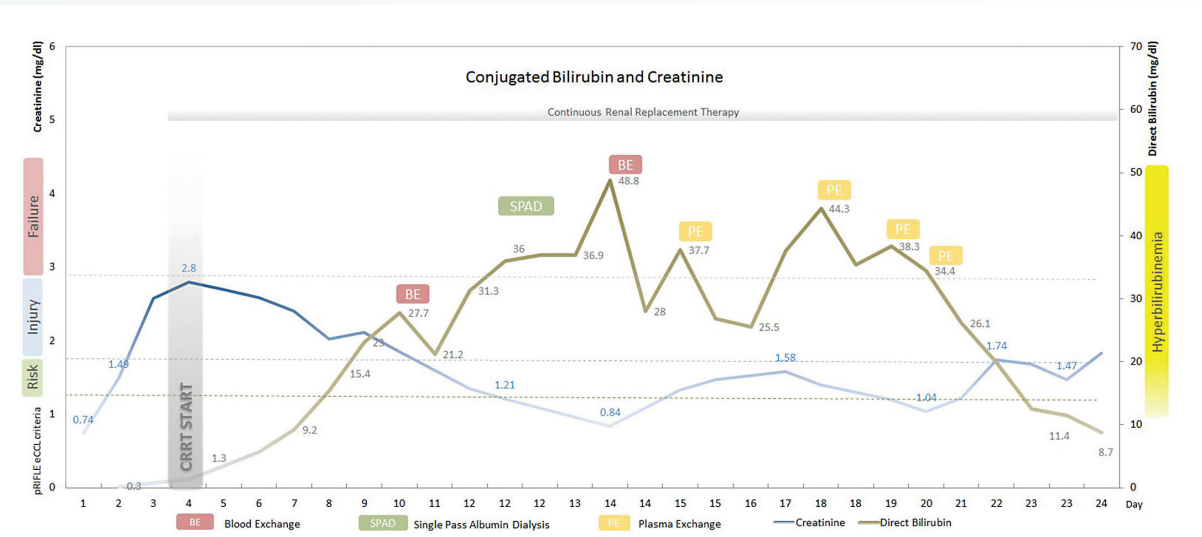


Figure 5. CVVH with additional bilirubin-targeted treatments



supportive therapy in neonates with common technical contraindications to PD. In addition, the ability to combine extracorporeal therapies, such as plasma exchange, single-pass albumin dialysis with CRRT extends the spectrum of support to critically ill infants. The CARPEDIEM technology is the first CRRT platform designed and developed for small pediatric patients, and very likely this machine will change the destiny of many infants and children.

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AKI in Neonates

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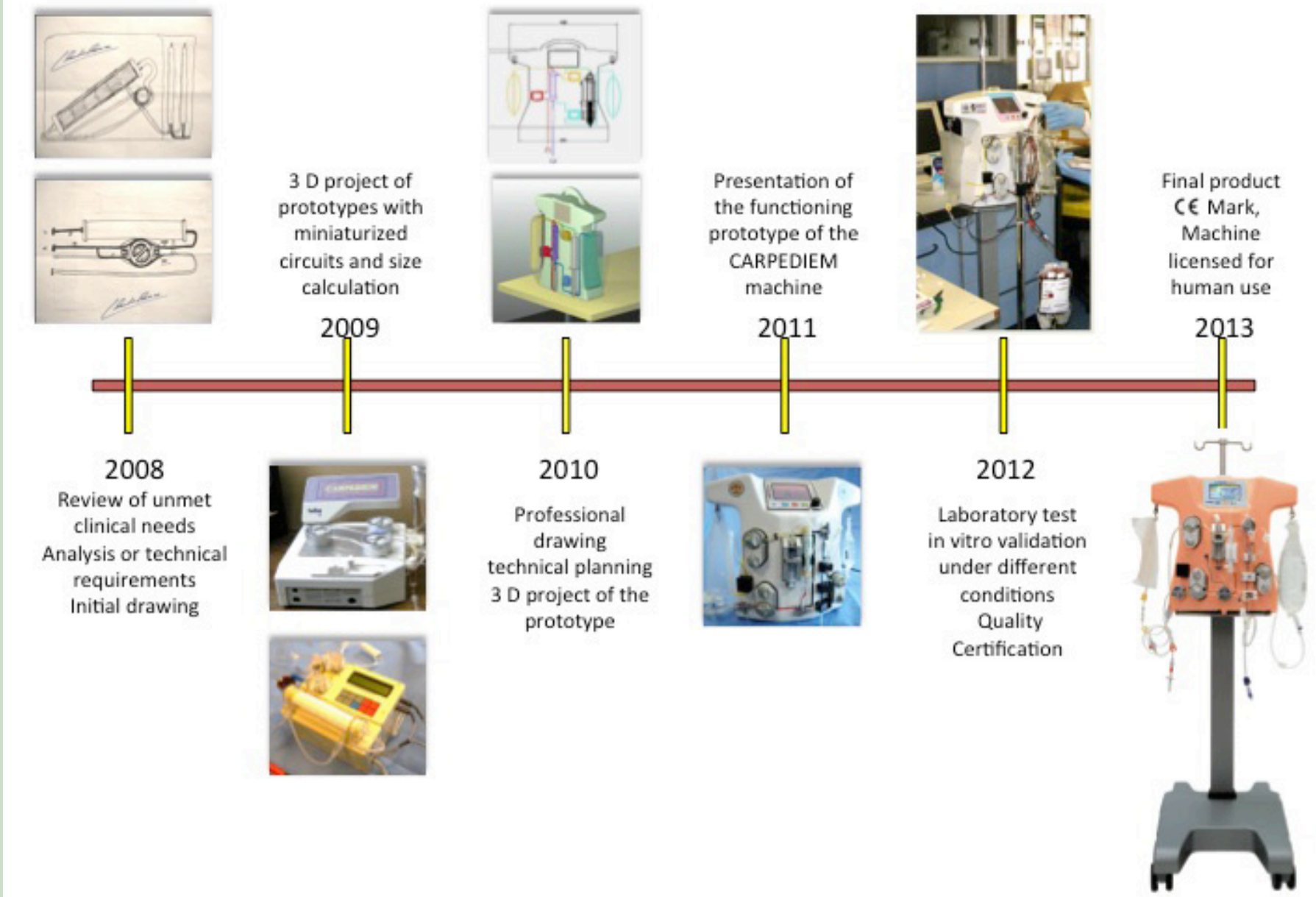
Figure 6. Timetable in development of the CARPEDIEM machine



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Adaptability: *The Business of Medicine*

By Robert Provenzano

Health care reimbursement is undergoing a fundamental change from volume-driven to value-driven care. The Patient Protection and Affordable Care Act of 2008 has marshaled this transformation in the dominant payment model. This legislation, as yet unproven in its benefits, has placed disproportionate burdens on medical practices, challenging the business models on which they are built.

This new practice stressor is compounded by the continued roll-out of reporting metrics, electronic medical record requirements, and a windfall of power granted to hospitals by accountable care organizations, which are population risk vehicles that have driven hospital consolidation into mega–health care systems to mitigate this risk. Physicians, faced with little to no ability to compete in this space, quickly became hospital employees: primary care physicians first, followed by high-revenue subspecialists (oncologists, cardiologists, orthopedists), who all have recently seen their outpatient procedure reimbursement gutted, destroying the business models that had sustained them for years. The hospital strategy is to create seamless care models over wide geographic areas and to manage risk by serving large populations while controlling and directing physicians' care, with the hope of linking this to higher care quality and therefore higher value.

Although one may quibble over the details or the wisdom of this approach, given how the Patient Protection and Affordable Care Act is constructed, this scenario is rapidly gaining ground.

What does this mean for nephrologists? How can we respond? Do we have a strategic advantage over our hapless colleagues? Maybe.

Nephrology practices have had an advantage in that the majority of our income has not been linked to hospital care. Rather, ESRD care and medical director reimbursement have contributed up to 60 percent of nephrologists' total compensation, as reported in the 2013 Renal Physicians Association benchmark survey. This fact not only has made us less attractive to hospitals but has created a potential opportunity for continued independence and success. To accomplish this, practices will be required to get serious about how they greet this opportunity.

First, practice leadership must accept and manage their "practice" as a business and treat it as such. Our product (commodity) is "care" that has a defined payment, eroded directly and indirectly for years. In the past, as reimbursement for the "commodity" was eroded we responded by increasing the volume of care. Not only is this unsustainable, not focused on quality, and inconsistent with the new payment models, but also practices rarely even knew the price of providing the commodity they were marketing. Additionally, practices were rarely focused on business processes and less rarely performed those business processes professionally. Revenue cycle management, contract negotiation, coding and billing, credentialing, personnel management, and related activities consumed disproportionate resources and revenue, were performed by nonprofessionals, and had little or no structure. Hospitals often touted as a major selling point their ability to provide these services at scale and to alleviate physicians' distraction.

Nephrology practices—regardless of their size—should look carefully at what practice services they require to remain competitive, what these services actually cost, and what value is delivered. The economy of scale for providing services in large practices (>25 physicians) cannot be delivered by smaller practices. This is one of the more basic business decisions to make: do I "build it or buy it?" For practices with fewer than 25 physicians, look to buy services. Professional management companies have reported practice savings of up to 30 percent.

Once you get your house (business) in order, you can focus on remaining competitive in our current environment.

The next step is to seek out partners that enhance your presence in the market. For nephrologists, like it or not, I am talking about dialysis providers. We like to tout that we are independent, and we are to some extent, but realistically we serve as medical directors, use facility services for our patients, and may participate in joint ventures or real estate ownership. Let's call it co-dependency. We need one another. Given that the Centers for Medicare & Medicaid Services has publicly stated that 50 percent of reimbursement will be value driven by 2017 and 70 percent by 2020, developing a partnership is critical to our continued survival. Partnership with dialysis providers is a natural step because we already have a business relationship. Given that dialysis providers cannot and do not practice medicine, and for the most part nephrologists no longer own or operate dialysis facilities, the smart move is obvious.

Understand how care must evolve in the population you serve. Identify the problem, such as chronic kidney disease, and manage it with the intent of slowing progression to ESRD. If ESRD is not avoidable, focus on preemptive transplantation. If not transplantation, then appropriate education and preparation for home modalities, arteriovenous fistula placement, and other such measures will be expected during this transition.

Your practice operations must also evolve. Do you have protocols for avoiding use of the emergency department? Are patients with health problems routed from dialysis facilities to the emergency department or to your offices? Are you using physician extenders to free you up for physician-centric care? Is your practice capable of seeing hospitalized patients within 72 hours of discharge?

I know what you are thinking: only large practices can do this. True: they can and often do, without much assistance. Smaller practices can too, with strategic partnerships with local or regional larger practices, in collaboration with dialysis providers, or in other business vehicles such as independent practice associations.

In conclusion:

1. Your practice is a business; treat it as such.
2. The environment your business must compete in has changed and is changing drastically.
3. Get you house in order—make sure your business operation services are maximizing your return. If you are unsure, get a professional practice assessment.
4. Seek out strategic partnerships, given the expectations of payors and patients.
5. Educate yourself; how can you retool practice operations? How can you better manage the costs of care?

There is no reason you cannot remain independent providers of renal care if you take a breath, seek out expert advice, remain open-minded, and are open to trying things out of your comfort zone.

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Industry Spotlight

Dialysate Drug Maintains Hemoglobin Levels

Triferic, a drug approved for iron delivery through dialysate, has met its primary endpoints in two phase 3 CRUISE studies (CRUISE 1 and 2), according to published data in *Nephrology Dialysis Transplantation* (1). Manufactured by Rockwell Medical (Wixom, MI), Triferic is the only drug so far in the US to win approval from the US Food and Drug Administration (FDA) for delivery via dialysate to replace iron and maintain hemoglobin in patients undergoing hemodialysis. Approval came in January 2015, and the two postapproval safety and efficacy studies were recommended but not required.

The primary objective of the CRUISE studies was to determine whether regular administration of Triferic via dialysate could maintain hemoglobin concentrations by optimizing iron delivery and maintaining iron balance.

A total of 599 patients participated in both studies, with 290 randomized to receive Triferic and 295 to receive placebo. The patients completed the phase 3 study when they met prespecified anemia criteria or went 48 weeks without reaching the criteria levels.

The primary endpoint was the mean change in hemoglobin from baseline to the end of treatment.

In both studies, the study drug met the primary endpoint with a treatment difference of 0.4 g/dL in hemoglobin concentration in the Triferic group ($p = 0.011$ for individual studies, 95% confidence interval 0.1–0.6 g/dL) compared with the placebo group; hemoglobin levels held steady in the Triferic group but declined in the placebo group, Rockwell Medical noted. The safety profile of Triferic was similar to that in placebo-treated patients; both groups experienced similar percentages of adverse events, Rockwell Medical said.

Steven Fishbane, MD, lead author of the study, nephrologist and chief of the division of kidney diseases and hypertension, North Shore University Hospital and Long Island Jewish Medical Center, noted, "Triferic is administered at each dialysis session and its iron is immediately donated to transferrin, very similar to the slower, natural way iron is used in the body to maintain hemoglobin." He said that patients undergoing dialysis have been treated almost exclusively with intravenous iron for iron replacement, which "injects a large amount of iron directly into the bloodstream and gets sequestered in the liver, resulting in higher and higher ferritins."

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Practice Pointers

The Wearable Artificial Kidney

This month, *Kidney News* interviews Victor Gura, MD, developer of the wearable artificial kidney.

Victor Gura, MD

KN: Please tell us something about yourself.

Victor Gura: I was born and raised in Buenos Aires, Argentina, and graduated from the National University of Buenos Aires Medical School. There was a lot of turmoil in Argentina in those days, so I decided to leave. I went to Israel, where I did my internship, residency, and renal fellowship. Then I came to the United States and did a second renal fellowship. I then worked in private practice until I decided to get back into research and develop the wearable artificial kidney (WAK). Currently I devote a major part of my time to this endeavor.

KN: How did you come up with the idea of the WAK?

Victor Gura: The outcomes of long-term dialysis treatment were disappointing—and remain so to this day. The poor quality of life, premature mortality, and plight of patients with ESRD drove me to look for a better way to treat them. In the late 1990s, there was a mounting body of literature praising the many benefits of daily dialysis: less morbidity, better quality of life, and potentially less premature mortality.

It became obvious that longer treatment time is crucial and that unless we could do much longer and more frequent treatments, clinical outcomes were unlikely to improve. On the other hand, daily dialysis or dialysis for longer sessions remains impractical for the vast majority of ESRD patients. I could not implement daily dialysis for most of my patients because it would cost money we did not have, there was no way we could double the number of dialysis chairs available, there were not enough nurses, and patients in general are loath to spend more time tethered to a machine.

KN: How long have you been working on the WAK since you first conceptualized it?

Victor Gura: I started this project in the summer of 2001.

KN: Please differentiate the WAK from current modes of renal replacement therapy.

Victor Gura: The WAK is designed to be worn on the patient's body so that it provides continuous renal replacement 24/7. In its current version it weighs about 11 pounds, but it delivers 168 hours per week of blood filtration, just as the native kidneys do, instead of filtering the blood for only 9 to 12 hours a week, as is done today. Because it works on batteries and requires only about 400 mL of water, it does not require a hookup to an electrical outlet, nor does it require about 40 gallons of fresh water, as current machines do. Because of the small amount of water required, the use of intravenous-quality sterile water is then feasible and affordable. This water quality is superior to the quality of ultrapure dialysate used in Europe and far better than the quality of water used in the United States.

Ultrafiltration at physiologic rates of fluid removal would virtually eliminate the hemodynamic problems we so often see in patients requiring removal of large amounts of fluids in a short time. Inasmuch as the WAK also maintains adequate homeostasis of electrolytes while removing excess salt and phosphorus, we expect to liberalize diet and fluid intake and reduce the "pill burden" on patients. We hope to demonstrate that the WAK will improve the outcomes of long-term dialysis in terms of quality of life, mortality, and costs.

KN: What obstacles and challenges have you encountered since you started working on it?

Victor Gura: Lack of funding was and remains the main obstacle. When the project started, I encountered a lot of contempt and disbelief. Many thought I was a lunatic Don Quixote, taking on the windmills. The WAK was then the subject of a few jokes, a lot of cynicism, and lack of support from traditional funding sources. Since then we have gained a lot more credibility. However, there is no support from the dialysis industry. We have had no venture capital support even after winning the US Food and Drug Administration (FDA) Innovation 2.0 Award.

KN: What was your experience with animal studies?

Victor Gura: Initially I wanted to do an animal trial on dogs because of my previous experience with uremic models in this species. However, this idea was rejected by the Institutional Review Board for Animal Use. They feared problems with groups that oppose experimentation with animals and said that if we used pigs instead, there would be less opposition. The uremic animal model in pigs was not described in the literature, so we had to create one. We encountered some surprises: we discovered that pigs become very uremic and hypercatabolic immediately after the ureters are ligated. We also found out that pigs require a much higher dose of heparin related to body weight in comparison with humans of similar body weight.

KN: What was your experience with the first human clinical trial and experience?

Victor Gura: As we concluded the pig study in Los Angeles, Claudio Ronco showed up in my laboratory and told me that he had heard from my late friend Hans Dietrich Polaschegg that we had a working WAK model. Claudio was bold enough to believe in this project, so he invited my team to work in Italy.

We did the first human trial at San Bortolo Hospital in Vicenza, Italy, in collaboration with Ronco's team. We treated 6 patients with the WAK configured for ultrafiltration only for up to 6 hours, with no adverse effects. The device worked as expected. As this work was published, Andrew Davenport of the University College London Center for Nephrology, Royal Free Hospital, offered to do in London a second human trial but this time with the WAK fully configured for hemodialysis. We treated 8 patients for up to 8 hours with no adverse effects. The data from this trial also indicated that the device does in fact work as expected. We are using the same prototype in our first human trial in the United States for up to 24 hours in Seattle, Washington, in collaboration with Jonathan Himmelfarb and his team. In both studies we used a most rudimentary prototype, which needs a lot of improvement, and we will have to develop and miniaturize the WAK further before we launch the next human trial.

KN: What made you persevere in pursuing the WAK?

Victor Gura: My first thought is that I am stubborn. I think that my wife would agree with that. But to be serious, I have a profound belief that this is the right thing to do, and I have a strong commitment to persevere and get the project completed. I think that as nephrologists we have an obligation to innovate, and we owe that to dialysis patients.

It seems to me that as a nephrology community of physicians, academics, and industry, we have failed for decades to innovate in this field, and we have became complacent. We have done little to bring to bear on the technology of dialysis equipment the enormous progress achieved in other technology fields for the past 6 decades since Kolf invented the dialysis machine. All kinds of technologies around us have become miniaturized, but no one has done enough to miniaturize the WAK. The plight of patients with ESRD must be alleviated, and we need to be creative enough to make that happen. I believe in what I am doing, and I will continue to work very hard to prove it. I was lucky enough to be guided by a wonderful group of mentors and colleagues, and I am very lucky to be supported by my wonderful wife and friend.

KN: Please tell us what is the latest news with the WAK.

Victor Gura: The first human trial has been completed. It seems that we will have a large amount of data to contribute in the field of innovative technology for ESRD. That data must undergo peer review before it is divulged to the public. As such, we will first announce these data in a peer-reviewed scientific forum and publish the study in a peer-reviewed journal.

KN: How do you see the future of WAKs?

Victor Gura: The WAK will undergo considerable improvements based on the lessons learned in our latest trial. We know much more now about what works in the WAK and what needs improvement. There is a lot to do, but based on what we already know, we hope to bring about a better alternative for the treatment of ESRD. Although it is too early to predict which patients will choose the WAK, we are inundated with patients' requests from around the world to use the WAK.

KN: What do you think about its applicability to patients in underdeveloped countries?

Victor Gura: The world cannot afford dialysis for all those who need it. We must reduce the cost of dialysis and make it more affordable to underserved populations around the globe. Underdeveloped countries are in dire need of affordable dialysis. Also, by reducing the morbidity associated with ESRD, we may decrease the economic burden of kidney failure. We hope that ESRD patients will require fewer procedures and fewer drugs and will go to the hospital

much less often. We have not yet met those needs for more affordable and better technologies, but it is abundantly clear that many people in underdeveloped countries perish because no dialysis is available or there is no money to pay for dialysis.

KN: Tell us about the WAK foundation: http://wakfund.org/.

Victor Gura: The WAK foundation is a 501(c3) public charity established for the purpose of funding WAK research in academic centers of excellence around the country with the hope of accelerating the development of the WAK and making it available to patients as soon as possible. The officers of the foundation are kidney patients. The first trial in the United States, conducted in Seattle, was funded by charitable gifts.

KN: Are there ongoing trials in other countries?

Victor Gura: Not at the present time. The FDA and our team have agreed to carry out clinical trials in the United States only. This was a requirement of the FDA Innovation 2.0 competition.

KN: If you had an opportunity to turn back the hands of time, what would you change? Or not change?

Victor Gura: Change? I would be much more cautious about accepting investments from business people who attempt to take control of a project in a field where they have no previous experience. I would not become a public entity again by reverse merger. That was a major mistake. Not change? I would pick my associates very carefully, and be fiercely loyal to those who do the actual work and support the project. I would accept setbacks as opportunities to learn and improve.

KN: What would you advise younger colleagues as they learn from your experiences?

Victor Gura: Be mindful of the company you keep, because you are only as good as the co-workers you associate with. Don't be afraid to come up with good ideas. If you decide to innovate in your field, make sure that you identify an unmet need, develop a plan to answer such a need with a solution, and be prepared to work very hard to make it happen. If you believe in what you do, do not allow disbelief and contempt to prevent you from doing what you believe is right. One of my favorite quotes is this: "Those who say it can't be done are usually interrupted by those doing it."

Findings

Fewer Long-Term Cardiovascular Events with Intensive Glycemic Control

Ten years later, patients with type 2 diabetes assigned to intensive glucose-lowering therapy have fewer major adverse cardiovascular events but no reduction in cardiovascular mortality, according to a study in the *New England Journal of Medicine*.

The study reports extended follow-up data on patients enrolled in the Veterans Affairs Diabetes Trial. In that study of 1791 veterans with type 2 diabetes, intensive glucose-lowering therapy did not reduce the rate of major cardiovascular events at a median 5.6 years' follow-up. For the primary outcome of major cardiovascular events, follow-up (median, 9.8 years) was available for 703 patients assigned to intensive therapy and 688 assigned to standard therapy. For the secondary outcomes of cardiovascular and all-cause mortality, the analysis included 837 and 818 patients, respectively (median, 11.8 years).

The median glycated hemoglobin levels during the trial were 6.9 percent in the intensive therapy group and 8.4 percent in the standard therapy group. Three years after the study ended, the difference was only 0.2 to 0.3 percentage points. At long-term follow-up, the risk of major cardiovascular events was significantly lower in the intensive therapy group: hazard ratio 0.83, with an absolute risk reduction of 8.6 events per 1000 person-years.

Neither cardiovascular nor overall mortality was significantly different between groups. The effects of intensive glucose control were similar for patients at higher versus lower cardiovascular risk.

Intensive glucose control may reduce the long-term risk of major cardiovascular events in older patients with long-standing type 2 diabetes, the results suggest. However, there is no reduction in the risk of death, overall or from cardiovascular causes. The potential benefits of intensive glycemic control should be weighed against the burdens and side effects of the specific treatment being considered, the researchers conclude [Hayward RA, et al. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2015; 372:2197–2206].

"Simple Strategy" Reduces AKI Risk during Cardiac Surgery

A preoperative "remote ischemic preconditioning" step substantially lowers the risk of acute kidney injury (AKI) in high-risk cardiac surgery patients, reports a study in the *Journal of the American Medical Association*.

The randomized trial included 240 patients undergoing on-pump cardiac surgery at four German centers. All were considered at high risk for AKI based on a Cleveland Clinic Foundation score of 6 or higher. The intervention group underwent remote ischemic preconditioning, administered by blood pressure cuff inflation after the induction of anesthesia. The protocol consisted of three cycles of 5-minute ischemia and 5-minute reperfusion in one upper arm. Control individuals underwent a sham intervention.

Based on the Kidney Disease: Improving Global Outcomes criteria, AKI occurred in 37.5 percent of patients assigned to remote ischemic preconditioning versus 52.5 percent of control individuals. Preconditioning was also associated with less need for renal replacement therapy: 5.8 versus 15.8 percent, and less time in the intensive care unit, 3 days versus 4 days.

There was no difference in stroke, myocardial infarction, or death. The release of two AKI biomarkers, urinary insulin-like growth factor–binding protein 7 and tissue inhibitor of metalloproteinases 2, was reduced in the intervention group. There were no reported adverse events.

Remote ischemic preconditioning may activate natural defense mechanisms that can protect the kidney during subsequent inflammatory or ischemic stress. Previous small studies of remote ischemic preconditioning to prevent AKI have yielded conflicting results.

This multicenter trial showed a 15 percent absolute reduction in AKI among high-risk cardiac surgery patients undergoing remote ischemic preconditioning. The authors call for further study of this "simple and promising strategy" to protect the kidneys and improve postoperative outcomes [Zarbock A, et al. Effect of remote ischemic preconditioning on kidney injury among high-risk patients undergoing cardiac surgery: a randomized clinical trial. *JAMA* 2015; 313:2133–2141].

Common Kidney Function Tests Predict AKI Risk

Widely assessed kidney function measures are consistently and strongly related to the risk of acute kidney injury (AKI), independently of other risk factors, according to a pair of meta-analyses in the *American Journal of Kidney Diseases*.

One analysis included eight general population cohorts and five chronic kidney disease (CKD) cohorts participating in the CKD Prognosis Consortium. Potential predictors of AKI hospitalization were evaluated, including diabetes and hypertension, estimated GFR (eGFR, calculated by the 2009 CKD Epidemiology Collaboration creatinine equation), and urine albumin-to-creatinine ratio (ACR).

With and without diabetes or hypertension, low eGFR and high ACR were associated with higher AKI risk. Diabetic patients were generally at higher AKI risk than were nondiabetic patients at any level of eGFR, although the difference was less pronounced in the lower range of eGFR. A similar pattern was noted for ACR. Hypertensive patients were at higher risk than were patients without hypertension, although the risks were comparable at eGFR levels less than 60 mL/min/1.73 m^2 and ACR values greater than 30 mg/g.

The second meta-analysis evaluated the AKI risk associated with eGFR and ACR in terms of age, race, and sex. Acute kidney injury occurred in 1.3 percent of the general population cohort members (mean follow-up time, 4 years) versus 2.6 percent of CKD cohort members (mean follow-up time, 1 year). Again, both test results were strongly associated with AKI. Older age and male sex were significant risk factors for AKI, although the associations were weaker in the presence of CKD. For African Americans, AKI risk was elevated at higher eGFR levels and at most ACR levels.

The results suggest that common laboratory measures of pre-existing kidney health could be the strongest predictors of AKI risk—even more so than diabetes, hypertension, age, race, and sex. The researchers conclude, "These results suggest the primacy of low eGFR and high ACR in AKI risk stratification—an observation that could guide preventative efforts" [James MT, et al. A meta-analysis of the association of estimated GFR, albuminuria, diabetes mellitus, and hypertension with acute kidney injury. *Am J Kidney Dis* 2015; doi:10.1053/j.ajkd.2015.02.338; and Grams ME, et al. A meta-analysis of the association of estimated GFR, albuminuria, age, race, and sex with acute kidney injury. *Am J Kidney Dis* 2015; doi:10.1053/j.ajkd.2015.02.337].

Industry Spotlight

Sanofi Tackles Diabetes

French drugmaker Sanofi recently reported on two developments in diabetes drug development: results of a successful clinical trial of a Sanofi drug combined with another drug to lower hemoglobin A1c levels and a new partnership that intends to create a stem cell–based drug to treat diabetes.

Sanofi's drug insulin glargine (Lantus) taken in combination with lixisenatide (Lyxumia, Zealand Pharma, Copenhagen) successfully lowered hemoglobin levels in patients with type 2 diabetes compared with either drug administered alone. The combination drug, called LixiL, is injectable.

According to Zealand, a global licensing agreement is in place with Sanofi that covers lixisenatide and any combination products that include lixisenatide, and specifies that Sanofi is responsible for all development and commercialization including the financing.

Sanofi is also teaming up with German biotech firm Evotec to develop stem cell–based treatments for diabetes, under a deal that could earn Evotec more than €300 million ($327 million), Reuters reported in early August.

Philip Larsen, MD, PhD, Sanofi's global head of diabetes research and translational science, noted: "Combining Sanofi's and Evotec's beta cell and stem cell expertise in drug discovery and development will enable optimal exploitation of the potential of stem cell–derived human beta cells for therapy and drug screening in diabetes."

Cord Dohrmann, MD, chief scientific officer of Evotec, said that the use of human stem cells in drug discovery and development is rising and "will increasingly shift the landscape from symptomatic treatments to disease-modifying therapies also in diabetes."

Under the agreement, Evotec will receive different tiers of payments depending on the firm's success in meeting targets set for development, regulatory. and commercialization purposes, Reuters noted.

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