ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

KidneyNews

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Epigenetics may help unravel kidney disease complexities

By Cathy Yarbrough

Could the progression of kidney disease be explained by changes in gene expression triggered by such environmental factors as diet, stress, or exposure to the carcinogens in cigarette smoke? Could epigenetic mechanisms explain the occurrence of hypertension, diabetes, and chronic kidney disease in one monozygotic twin but not his identical twin brother?

Epigenetics refers to the stable, heritable changes in the genome's function that influence, but do not alter, the nucleotide sequence of an organism's DNA. In the past several years, this relatively new field has grabbed some of the scientific spotlight from the search for genes in the 3 billion chemical bases of the human DNA code.

"Traditionally, it has been assumed that only the DNA sequence can account for the capability of normal traits and diseases to be inherited," said Ari Petronis, PhD, senior scientist in the neuroscience department and head of the epigenetics laboratory at the University of Toronto. Petronis is also an associate professor with the department of psychiatry at the university.

"Over the last several decades, there has been an enormous effort to identify specific DNA sequence changes predisposing people to psychiatric, neurodegenerative, malignant, metabolic, and autommune diseases, but with only moderate success," said Petronis. Petronis was one of the speakers at a Renal Week symposium last year on "The Epigenetic Epidemic: Understanding the Grammar of Genetic Language."

The lack of "significant breakthroughs," Petronis said, likely is based on the fact that while a "DNA sequence-oriented

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Dry Weight—An Old Concept Whose Time Has Come

Control Volume to Control Blood Pressure…and Possibly Cardiovascular Morbidity

By Timothy O'Brien

Looking for a new approach to controlling blood pressure and cardiovascular risk in dialysis patients? It's not the latest blood pressure drug—in fact, it may reduce or avoid the need for antihypertensives. It's a concept that's familiar to nephrologists, if sometimes overlooked: probing, achieving, and maintaining dry weight.

Getting to dry weight may improve patient outcomes, a growing body of evidence suggests. But it doesn't make life easier for dialysis center doctors and nurses—or patients, for that matter. "Probing dry weight is not the most convenient thing for the nephrologist to do," said Rajiv Agarwal, MD, of Indiana University School of Medicine in Indianapolis. "It's like changing diet, or exercising or making lifestyle changes…that's always harder than prescribing a pill."

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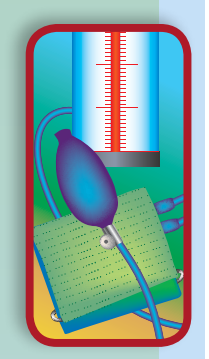


JAMES D.
Age: 56
Time on dialysis: 6 mo.
Lateral abdominal

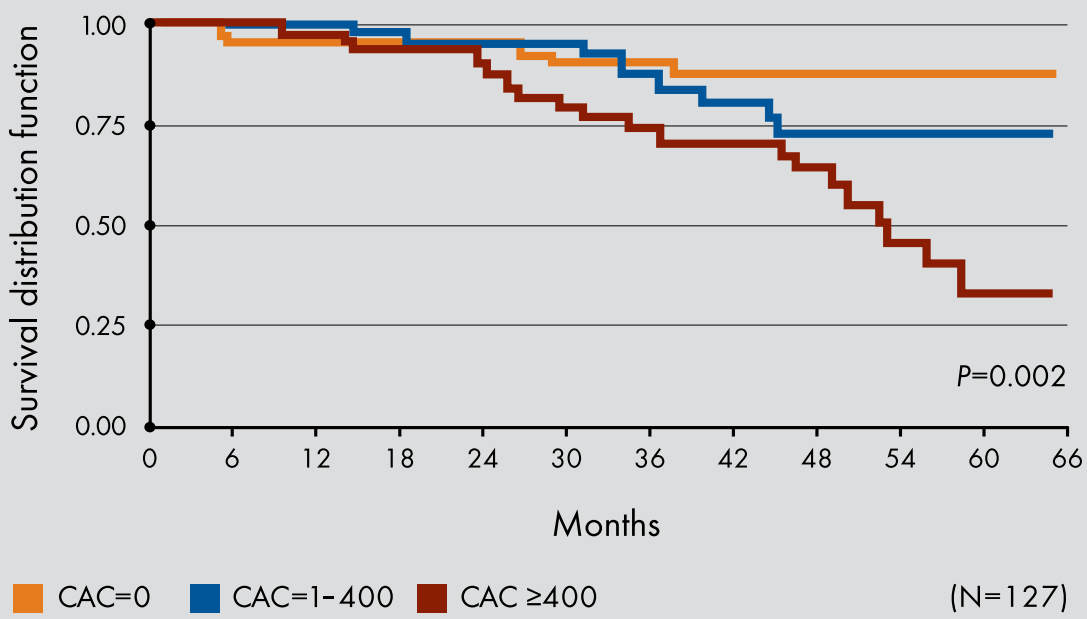
Ca^{+2}ution

64% of new dialysis patients[1] and 83% of prevalent dialysis patients[2] have been shown to have calcification.

2009 KDIGO guidelines[3] for CKD-MBD state:

The presence and severity of cardiovascular calcification strongly predict cardiovascular morbidity and mortality in patients with CKD.

A study by Block *et al* evaluated adjusted survival by baseline coronary artery calcification (CAC) score[4]*



*Multivariable adjusted (age, race, gender, diabetes).
P value represents significance across all 3 groups.

KDIGO suggests restricting calcium dose in the presence of[3]:

- **Persistent/ recurrent hypercalcemia†**
- **Arterial calcification**
- **Persistently low PTH levels**
- **Adynamic bone disease**

†KDIGO recommendation.

References: **1.** Spiegel DM, Raggi P, Mehta R, et al. Coronary and aortic calcifications in patients new to dialysis. *Hemodialysis Int.* 2004;8:265-272. **2.** Raggi P, Boulay A, Chasan-Taber S, et al. Cardiac calcification in adult hemodialysis patients: a link between end-stage renal disease and cardiovascular disease? *J Am Coll Cardiol.* 2002;39:695-701. **3.** Kidney Disease: Improving Global Outcomes (KDIGO) CKD–MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD–MBD). *Kidney Int.* 2009;76(suppl 113):S1-S130. **4.** Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. *Kidney Int.* 2007;71:438-441.

genzyme
Renal

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Epigenetics

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paradigm" has been very productive in classical genetic disorders such as sickle cell anemia and Huntington's disease, it is not the best tool for studying complex non-Mendelian diseases.

Epigenetics perhaps will prove to be the tool that will enable scientists to illuminate the molecular origins of chronic disease and identify epigenetic-based therapies for halting the progression of these diseases.

"Such epigenetic drugs would be novel, potentially possessing substantially higher therapeutic potential and much lower rates of adverse effects in comparison to current symptomatic treatments," Petronis wrote in a 2008 *Annual Review of Pharmacology and Toxicology article*.

Scientists recently have identified epigenetic modifications that are associated with kidney disease, diabetes, hypertension, cardiovascular disease, and many cancers.

Like genes, epigenetic mechanisms are critical to an organism's healthy development and functioning. However, if a gene is mutated or is misregulated by an epigenetic factor, the organism's normal functioning will be disrupted, and disease can result.

While gene mutations cannot be repaired, epigenetic modifications are potentially reversible. By tapping regulatory epigenetic mechanisms, such as DNA methylation, scientists may be able to prevent or reverse kidney cell damage by silencing or activating the expression of specific genes.

DNA methylation, perhaps the best studied epigenetic mechanism, originates with an environmental or lifestyle effect on the body that mobilizes a group of methyl molecules to attach to a particular gene's control segment.

This attachment—or epigenetic "tag"—alters the three-dimensional structure of the chromosome on which the particular gene resides. The gene's DNA is either silenced or activated. (View a scientific illustration of epigenetic mechanisms at http://nihroadmap.nih.gov/epigenomics/epigeneticmechanisms.asp)

Although a relatively new field, epigenetics of human disease thus far has contributed to the development of four U.S. Food and Drug Administration-approved medications, all in oncology. For the treatment of chronic kidney disease, scientists hope to create drugs that de-methylate genes with harmful methyl tags, or restore health-promoting methyl tags to specific genes.

"Epigenomics represents the next phase in our understanding of genetic regulation of health and disease," said Francis Collins, MD, PhD, director of the National Institutes of Health (NIH), which last September awarded 22 five-year grants, totaling $62 million, to fund epigenetics research.

"These awards will address the extent to which diet and environmental exposures produce long-lasting effects through changes in DNA regulation," Collins said. Epigenetics "is expected to profoundly alter the way we understand, diagnose, and treat disease."

Among the recipients of the NIH grants is Katalin Susztak, MD, PhD, who is trying to determine whether new diagnostic and prognostic markers for progressive renal disease will be revealed by gene expression studies coupled with epigenomics analysis.

"These studies would describe for the first time epigenetic modification in the kidney and help us to understand the complex regulatory network that leads to progressive loss of renal function," said Susztak, associate professor of medicine at Albert Einstein College of Medicine. "The availability of large numbers of well characterized human tissue samples with the corresponding gene expression data puts us into a unique position to achieve these goals."

Epigenetic changes may explain diabetes' rank as the leading cause of renal failure. "People with diabetes who control blood glucose levels develop fewer complications," said Susztak. "But they still face a greater risk for kidney failure and other complications—probably because their bodies remember periods from long ago when their glucose was not well controlled."

Assam El-Osta, PhD, has found strong evidence that epigenetic mechanisms trigger hyperglycemic memory.

His studies at the Baker IDI Heart and Diabetes Institute in Melbourne, Australia, determined that transient hyperglycemia induces long-lasting epigenetic changes in the gene coding the transcription factor NFκB-p65. El-Osta and his colleagues published the results in the *Journal of Experimental Medicine* in 2008 and *Diabetes* in 2009.

These epigenetic changes led to the overexpression of NFκB-p65 as well as genes coding the pro-inflammatory markers that have been implicated in the development of vascular complications, El-Osta said. Even when sugar levels returned to normal, the epigenetic-induced gene modifications persisted. These findings suggest that spikes of hyperglycemia may be a risk factor for diabetic complications independent of a patient's mean levels of glycemia, measured as hemoglobin A1c (HbA1c).

El-Osta attributes the epigenetic persistence to "startling changes" to histone 3 (H3) methylation that were maintained for at least six days when endothelial cells were returned to normoglycemic conditions.

Histones are not just the structural protein spools around which DNA is wound in the cell nucleus. They are among the key players in epigenetics.

Methylation at specific lysine residues of histones H3 and H4, two of the four basic histone proteins that form higher order nucleosome structures, can determine whether a gene remains accessible to the transcription machinery or whether it is silenced into tightly packaged heterochromatin, said Gregory Dressler, PhD, collegiate professor of pathology at the University of Michigan.

"Such epigenetic modifications of histones could account for a heritable cellular memory during embryonic development and could greatly affect gene expression patterns in diseased and aging cells," said Dressler.

Dry Weight

Continued from page 1

Writing in this month's *Clinical Journal of the American Society of Nephrology*, Agarwal and Matthew R. Weir, MD, of the University of Maryland in Baltimore believe that getting to dry weight to avoid hypervolemia can control blood pressure with fewer or no antihypertensive drugs—and perhaps make inroads against the high cardiovascular morbidity and mortality in dialysis patients.

Dry weight: what is it…and how do we get there?

The dry weight concept is familiar to nephrologists, even if definitions have shifted over the years. Dry weight is the patient's weight immediately after dialysis, when excess fluid buildup has been removed. It's the lowest weight the patient can achieve without developing symptoms of hypotension or hypovolemia.

But defining dry weight and achieving it are two different things. "Probing dry weight—trying to get to an appropriate volume in a given patient—is difficult to do," Weir said. He thinks nephrologists often take the easy way out. "Rather than let the patients get uncomfortable as they probe for dry weight, they say, 'Let's just give them blood pressure medicines to get their blood pressure to a desirable level, and call it a day.'"

The problem is that this leads to chronic volume overload and over time to cardiac remodeling—and a heightened risk of congestive heart failure and other adverse events. "So even though you may control somebody's blood pressure by throwing more medicine at it, the fact that they are volume expanded and centrally 'stretched out' may facilitate the development of heart disease," Weir said.

Probing dry weight can break this cycle of hypervolemia. Agarwal and Weir suggest a gentle approach, setting the ultrafiltration goal a little higher without changing the dialysis time—or better yet prolonging dialysis time, allowing for slower ultrafiltration. "Weight is reduced by a very small amount—maybe half a pound at each dialysis session," Agarwal recommends. "That continues till the patient cannot tolerate it, or you have reached normal blood pressure, or whatever the goal might be for that individual patient."

That may take a while—up to several weeks. "It's an iterative process," Agarwal said. "It's more work for everyone, and it's something that's not reimbursed as such. You do this in the hope that it would improve your patient's outcomes. But there's really no reward at the end of the day for the people who are probing dry weight, compared to people who are not doing it."

Of course, there are also some associated hazards and difficulties, including a potential increase in complications related to interdialytic hypotension. Nonadherence with dialysis or reduced time on dialysis may make it difficult to achieve dry weight.

More art than science—objective monitoring can help

As chairman of a recent CMS quality meeting, Agarwal found general agreement that probing dry weight would probably be associated with better outcomes in dialysis patients. "But nobody knew exactly how to measure it, and how to translate this into an outcome measure that can be measured," he said. "It's like quantifying beauty—when you see it, you recognize it."

So for the moment, probing dry weight is more art than science. "We are just starting to recognize some of the tools that are available to us that might quantify something that is very hard to measure," Agarwal said.

One promising tool is relative plasma volume (RPV) monitoring—a noninvasive assessment of absolute hematocrit that allows real-time calculation of the percent blood volume change during dialysis. By inspecting the RPV slope—a function of the ultrafiltration rate and plasma refill rate—the nephrologist can distinguish patients who are "wet" from those who are at dry weight.

In the "Dry-weight Reduction In hypertensive hemodialysis Patients" (DRIP) trial, Agarwal's group found the RPV slopes useful in identifying patients in a volume-overloaded state (Sinha, Light, and Agarwal. *Hypertension* 2010; 55:305–311). Most importantly, "RPV slopes predicted the subsequent reduction in interdialytic ambulatory systolic blood pressure," Agarwal and Weir write. "[Patients] with the flattest slopes had the greatest decline in blood pressure on probing dry weight."

Probing dry weight to reduce blood pressure—and cardiovascular risk?

"There's some mystery out there with regard to what's the right blood pressure for patients on dialysis," Weir said. Epidemiologic studies haven't found a strong link between high blood pressure and cardiovascular events in dialysis patients—in fact, low or declining blood pressure may carry an increased risk of poor outcomes. Some studies have even found paradoxical worsening of blood pressure control in patients taking more antihypertensive drugs.

The most recent DRIP trial results (Agarwal, et al. *Hypertension* 2009; 53:500–507) suggest that probing dry weight helps to control blood pressure. Even after correcting for a placebo effect, the reduction in blood pressure was 7/3 mm Hg—substantially larger than the effect of adding an additional antihypertensive drug. "We found that reducing dry weight can actually improve the blood pressure by quite a substantial amount, within four weeks," said Agarwal. "And that effect stays for another four weeks." Achieving dry weight may eliminate or reduce the need for antihypertensive drugs and increase the effectiveness of existing drugs.

Results like these could restore interest in avoiding medications and focusing on volume-directed blood pressure control, Weir said. "The beauty of Dr. Agarwal's work is that he's now starting to drill down on the issues of whether more careful measure of central volume or change in central volume with probing of dry weight can actually be predictive of outcome," he said. "And the results have been very consistent in indicating that it probably is predictive."

What's needed now is a prospective clinical trial to see if longitudinal RPV slope monitoring can help to reduce endpoints like heart failure, stroke, and cardiovascular death, said Weir. "What I would envision would be a usual care group versus a more intensive care group, where the intensive care group has routine RPV slope monitoring, and the doctors would use that to adjust dry weight and make decisions about use of medications, etc."

The latest study by Agarwal's group, to be published soon in *Hypertension*, found that a single, cross-sectional RPV determination is predictive of mortality in dialysis patients—independent of blood pressure. "It's more fuel to our argument that we really need to get going on this," said Weir. "We need to get the message across that our traditional way of abdicating our responsibility for getting to dry weight may contribute to cardiovascular mortality."

But can we cut the salt?

There's another critical factor in the equation: controlling salt. For several reasons, reducing dietary salt is a difficult change for most patients to make. They may have salt cravings, possibly related to blunting of the taste threshold for sodium. In addition, many dialysis patients are poor and don't have access to healthier or lower salt foods. "Or if they have access, they might not be able to afford them," said Agarwal. "So low-salt diets may not fit into their lifestyle."

Yet reducing salt intake is critical to reducing weight gain between dialysis sessions—thus making it easier to achieve dry weight. "If somebody gains, say, seven or eight kilos between dialysis, and you're trying to reduce their weight by 8.5 kilos, they might not tolerate it, because that's too aggressive a rate of fluid removal," said Agarwal. "On the other hand, if they gain only one or two kilos between dialysis, you can easily and safely remove half a kilo more, without undue discomfort to the patient."

At least one expert has doubts about the prospects for controlling salt intake in the overall dialysis population. "In a perfect world, most patients who are adherent with their dialysis times and lifestyle of low sodium and protein intake have far fewer problems than those who do not," commented George Bakris, MD, of the University of Chicago. "This is true, however, with any risk factor that requires more from the patient and less from medications." He cites a study in patients with diabetes (Saydah, et al. *JAMA* 2004; 291:335–342) showing that the rate of risk factor control is much higher for hyperlipidemia, for which 75 percent of the control comes from the medication, compared to hyperglycemia, for which 75 percent of the effort comes from the patient in the form of dietary control.

"Lower sodium intake also benefits easier blood pressure control in all patients with stages 2 to 4 nephropathy with hypertension," said Bakris. Another recent study (Boudville, et al. *Am J Hypertens* 2005; 18:1300–1305) found that, for each additional increase of 300 to 500 mg/day of sodium intake above 3000 mg/day in patients with stage 4 disease, one additional antihypertensive medication was needed to control blood pressure.

"The sad part is that most people cannot maintain this low sodium intake for long periods of time in the Western world, with an average sodium intake of 6 to 10 g/day," said Bakris. "So while achieving dry weight is a very relevant concept and principle, in reality only those diligent patients who commit to a sustained lifestyle of lower sodium intake will reap the benefits of a lower pill burden."

Because it's under the nephrologist's control, reducing dialysate sodium is easier than reducing dietary sodium, especially over the long term. In addition to reducing thirst and limiting intradialytic weight gain, it can also help in achieving dry weight, although it may also contribute to intradialytic hypotension.

"It's going to be a little bit more work"

But given the potential benefits—reducing cardiac pressure and volume loading, limiting remodeling, and reducing cardiovascular morbidity—the dry weight approach is worth a try, Agarwal and Weir said. "Medication-directed approaches for blood pressure control should be a secondary consideration to manipulating the diet and dialysis prescription in order to achieve dry weight."

While the steps needed to probe and achieve dry weight aren't all that complicated, Weir acknowledges that it will take some effort to make the needed changes. "I think it's a matter of education," he said. "It's going to require a little bit more focus and attention on the staff to address means by which to individualize the approach to get to dry weight. So it's going to be a little bit more work than throwing pills at somebody. But I think it can easily be done."

Weir suggests that some clinicians may want to give RPV slope monitoring a try. "It's a simple, easy thing to do. But I think the long and the short of it is, it's going to reawaken interest in using noninvasive measures of determining appropriate blood volume for a patient, and to see if that makes a difference on cardiovascular morbidity and mortality in these patients."

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Novel Nephrology

Merriam-Webster's online dictionary defines the adjective "novel" as

1. **new and not resembling something formerly known or used, or**
2. **original or striking, especially in conception or style.**

Both definitions apply to the topics covered in this special section, which include noninvasive or minimally invasive diagnostic techniques as well as new interventions to treat disease, all of which can be performed by nephrologists.

Ambulatory blood pressure monitoring is sufficiently new that many insurers authorize payment only for the "exclusion of white coat hypertension." Jones eloquently discusses the role of ambulatory blood pressure monitoring in white coat hypertension and its opposite, masked hypertension, and the significance of the nocturnal "dip" in blood pressure with regard to long-term prognosis and end organ damage. This noninvasive technique can help predict which type I diabetic patients are at risk for kidney disease and which patients need to be monitored for left ventricular hypertrophy.

Gosmanova and O'Neill discuss the benefits of renal ultrasonography performed by nephrologists to both the patient and the practice of nephrology. Nephrologist-performed ultrasonography is convenient and provides that "clinical correlation recommended" routinely by interpreting radiologists, thus improving patient care. Equipment costs are relatively low, training and certification are available, and it's fun!

Vats explains how molecular diagnostics can elucidate the pathophysiology of genetic kidney diseases, specifically nephrotic syndrome and cystic kidney disease. Rapid and specific diagnosis of viral transplant infections using quantitative PCR assays is already improving patient care, and genetic advances may lead to personalized care and point-of-contact diagnosis in the future.

Sherbotie delivers a brief but comprehensive review of continuous renal replacement therapies, including which systems can be used for pediatric patients or therapeutic plasma exchange.

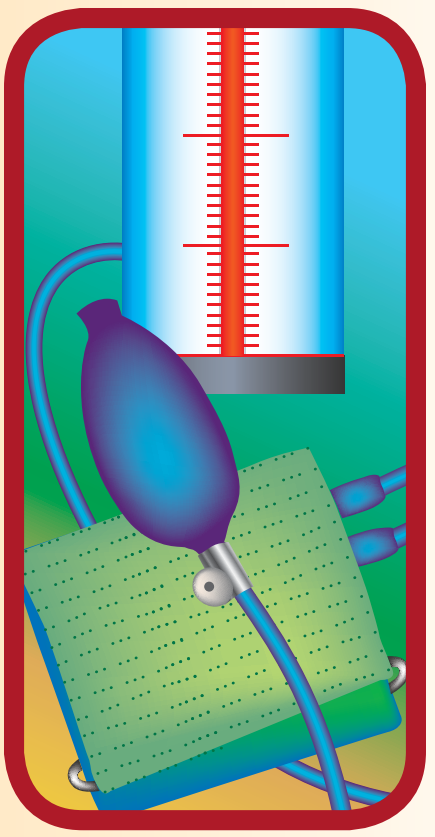
Since 2000, the American Society of Diagnostic and Interventional Nephrology (ASDIN) has worked to establish best coding practices and a comprehensive coding manual for dialysis and vascular access procedures. Pflederer outlines how the ASDIN has worked to improve the quality of care that patients receive related to vascular access, peritoneal dialysis access, and ultrasonography. He also discusses ASDIN's Procedure Outcomes Registry, an Internet database that is also available to nonmembers. Procedural certification is available through the ASDIN.

While not yet standard of care, each of these novel techniques is likely to rapidly become "best practice." A common theme is the issue of cost and reimbursement by third party payers. Costs will need to be weighed against long-term benefits as our nation's health care programs evolve. We've made considerable progress since Kolff constructed the prototypical dialysis machine from sausage casings and an automobile water pump during World War II. The techniques discussed in this section suggest that the best is yet to come. It's an exciting time to be a nephrologist.

Teri Jo Mauch, MD, PhD, is associate professor of pediatrics in the division of pediatric nephrology at the University of Utah School of Medicine.

Hypertension and Ambulatory Blood Pressure Monitoring

By Deborah P. Jones



Ambulatory blood pressure monitoring (ABPM) is a noninvasive, automated method for measurement of brachial artery blood pressure (BP) in a nonclinical setting. The two major benefits of ABPM are that the measurements reflect the diurnal pattern of BP of the individual and that data are obtained outside the clinic or hospital setting. There are excellent reviews on use of ABPM in children and adults (1–3). This article will cover the basics of ABPM—methodology, applications, and indications.

Monitors and software for ABPM are available from numerous manufacturers. Some of these have been validated. See www.dableducational.org for a list of available monitors that have been tested and the outcome of their validation. Most devices use an oscillometric method for detection of BP; however, auscultatory monitors are also available. The former are preferred by most clinicians because of the reduced likelihood for artifact. Auscultatory devices have the advantage of measuring systolic BP (SBP) and diastolic BP (DBP), whereas oscillometric monitors estimate SBP and DBP by detection of mean BP using the manufacturer's algorithm.

As with casual BP measurement, with ABPM the cuff must be adjusted to properly fit the upper arm to avoid erroneous readings. The cuff is placed on the nondominant arm and is connected to the recording device. Calibration using a mercury manometer and y-connector at the beginning of the study should be performed by trained persons. Patients are instructed to hold their arm still when they feel the cuff inflating to allow successful detection of the BP. After 24 hours, the recording device is docked to a computer with manufacturer's software to allow computation of mean 24-hour SBP, DBP, mean BP, and heart rate.

Monitors are programmed to measure BP in intervals of 15–30 minutes in most cases. The typical monitoring period lasts 24 hours. Patients are asked to record the times of various activities including bedtime and awakening. Alternatively, a standard sleep period is set from midnight to 6 a.m. Awake and sleep periods are analyzed separately and allow calculation of the nocturnal decline (dipping) in BP. Ten percent or greater is generally accepted as a normal nocturnal decline. In addition, the BP load or percent of readings greater than a designated threshold are calculated separately for awake and sleep periods and combined to yield the BP load for the 24-hour period. One may also evaluate heart rate and BP variability or other patterns in BP, one of which is the ultradian rhythm, which is shorter than the circadian rhythm within a 24-hour period. Ultradian rhythms are analyzed in periods of six to 12 hours in which variations may be the result of changes in sympathetic activity.

Normal values for ABP were initially assigned by correlating the ABP to the corresponding clinic BP threshold of 140/90, which was the definition of clinic hypertension, or from normal reference populations. More recently, normal values for ABP have been obtained using cardiovascular endpoints (4). The suggested values for normal and abnormal ABP in adults are found in Table 1. The definition of normal and abnormal ABP in children has been challenged by the paucity of hard endpoints and available reference values. The largest reference values were obtained by the German working group. Their generalizability is limited due to the homogenous ethnicity of the population sampled, which was uniformly Caucasian. However, a position paper on ABPM in children has concluded that these reference standards are currently

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Hypertension

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the best available for interpretation of ABPM in children (3).

ABP is superior to clinic BP measurement in assigning cardiovascular risk. Numerous studies in adults with hypertension (HTN), both untreated and treated, have found that abnormal ABP is independently associated with morbid and fatal cardiovascular events.

A landmark study looking at cardiovascular (CV) morbidity (defined as both fatal and nonfatal CV events per 100 patient years) evaluated baseline ABP in untreated persons with HTN. Investigators found that the rate of events was similar among normotensive controls and in individuals diagnosed with white coat HTN (0.47 and 0.49, respectively). White coat HTN (WCH) is defined as having an elevated office BP and normal ABP. The rate in hypertensive "dippers" and "nondippers" was much higher at 1.79 and 4.99, respectively (5). Nondippers refers to individuals who display absence of normal nocturnal decline.

These dramatic differences in risk persisted after controlling for age, gender, diabetes, and left ventricular mass. In a separate study of adults with treated HTN with median follow-up of five years, the adjusted relative risk of a cardiovascular event was significantly associated with both baseline systolic and diastolic HTN as measured by ABPM after adjusting for known risk factors including smoking status, diabetes, body mass index (BMI), lipid levels, and office BP (6).

With ABPM, the clinic-effect or "white-coat" effect on BP measurement is minimized. Although the significance of WCH is still debated, studies indicate that the cardiovascular risk of individuals with WCH is similar to those with normal BP or is significantly less compared to those with abnormal ABP. The only indication for ABPM currently reimbursed by the Centers for Medicare and Medicaid Services is to rule out WCH. The prevalence of WCH may vary depending on the thresholds selected. When WCH is defined as a mean daytime ABP <130/80 in untreated adults, the risk for CV disease is similar to normotensive individuals (7). Others argue that WCH confers an intermediate risk for cardiovascular disease and microalbuminuria.

Masked HTN is defined as abnormal ABP in the setting of normal clinic BP. Masked HTN has been found to increase the risk for left ventricular hypertrophy in both adults and children. Ascertainment of masked HTN is possible only when patients undergo ABPM. At-risk groups such as patients with CKD, diabetes, and post-transplantation may benefit from characterization of BP using ABPM to allow optimization of their antihypertensive treatment regimen. One pediatric study of individuals with type 1 diabetes without evidence of renal disease at baseline found elevated nighttime BP to predict the onset of microalbuminuria (8).

Generally, a decline of 10 percent from day to nighttime mean BP is considered normal. Approximately one-fourth of hypertensive adults are classified as nondippers. Occasionally BP at night is higher than during the day, a state referred to as "reverse-dipping." Hypertensive nondippers have higher rates of cardiovascular complications compared to hypertensive dippers. Nighttime BP appears to be a fairly robust indicator of prognosis. Sleep quality and quantity may impact nocturnal BP levels. When sleep is judged to be affected by the ABPM, nighttime values are not as reliable (9).

Clinic BP levels may lead to misclassification of an individual as hypertensive. Among individuals being treated for essential HTN by primary care physicians, the agreement between the assessment of BP control by office measurement and by ABPM was poor; the indication for ABPM appears to be the greatest in those who are judged to have controlled BP using clinic measurements (10).

Failure to ascertain the presence of HTN may be particularly important in the setting of CKD, in which hypertension is known to impact the rate of progression. Forty percent of adults with CKD were believed to have normal BP based upon clinic measurements yet were hypertensive based upon ABPM (11). Analysis of the baseline data from the African American Kidney Disease Cohort revealed that more than half of participants had abnormal nocturnal decline with nighttime HTN. Of those who were believed to have controlled HTN, ABPM demonstrated masked HTN in 70 percent. Even those with HTN only at night had significantly greater target organ damage (12). Among children with CKD stages 2–4, masked HTN was found in 38 percent of the participants. HTN based upon ABPM was the strongest independent predictor of left ventricular hypertrophy, not GFR (13). Reliance on clinic BP levels alone to ascertain the degree of HTN may miss an opportunity to modify a major risk factor for progression of cardiovascular and renal target organ damage, thus the utility of ABPM cannot be underestimated.

Individuals who fail to demonstrate the expected decline in BP during sleep (nondippers) may have even higher risk for cardiovascular events or cardiac remodeling compared to those with HTN who do "dip" during sleep. Among children with type 1 diabetes mellitus, loss of the normal diurnal variability in BP preceded the development of overt microalbuminuria. None of the children who developed microalbuminuria would have been considered to be hypertensive based on office measurements (8). ABPM is an invaluable tool to improve CV risk and to determine the success of therapeutic interventions in type 1 or 2 diabetics.

Trials that use ABPM to measure the treatment effect of antihypertensive medication reveal significant differences in the pharmacodynamic profile of different classes of medications that can be ascertained by analyzing the circadian BP patterns before and after initiation of treatment. Furthermore, use of ABP significantly lowers the sample size required to establish treatment effect—ABPM is consistently superior to casual measurement of BP, which is typically used as the method to measure treatment effect (14).

The cost effectiveness of ABPM has been analyzed by estimating the incidence of new onset HTN and prevalence of WCH (15). Comparing annual treatment costs with and without use of ABPM, the break-even annual cost of treatment is as low as $130. In other words, use of ABPM to distinguish which individuals are likely to benefit from initiation of antihypertensive drug therapy is likely to reduce the cost of management of hypertension because it is cost effective compared with treatments costing more than $130/year. This is much lower than the annual cost for treatment of HTN averaged over five years, which was estimated to be $580. Reimbursement by CMS averages $75 for the indication of WCH.

The cost analysis does not include the cost of the equipment for ABPM, which is approximately $10,000, nor does it include costs for software and three monitors. However, the benefit of reducing the number of individuals entering ESRD per year by slowing the rate of progression of CKD through improved identification of those with masked HTN would also be expected to significantly reduce costs of health care. Similar arguments could be made for the potential to prevent cardiovascular events.

So who should undergo ABPM? Some experts suggest ABPM for anyone with suspected HTN, pre-HTN, CKD, or diabetes, or for individuals who have had a cardiovascular event (16). Patients and physicians appreciate that ABPM provides valuable information upon which to base therapeutic decisions and experts argue that its application and insurance coverage should be extended to many more clinical indications (17).

Table 1. Reference values for ABPM in adults (4).

	24-hour	Daytime	Nighttime
Optimal BP (mm Hg)	<115/75	<120/80	<100/65
Normal BP	<125/75	<130/85	<110/70
Ambulatory HTN	≥130/80	≥140/85	≥120/70

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ULTRASONOGRAPHY:
A Skill For Nephrologists

By Elvira O. Gosmanova and W. Charles O'Neill

Since its introduction in the early 1960s, ultrasonography has become an essential part of the workup and management of patients with kidney disease owing to its safety, low cost, and the ease of visualizing the kidneys, bladder, and blood vessels. Given ultrasonography's simplicity and utility, it is curious it is not routinely performed by many nephrologists, considering that ultrasonography has become a standard procedure for many other specialists and subspecialists. This article discusses why modern nephrologists should acquire skills in ultrasonography and incorporate it into their practice. With the availability of portable, low-cost scanners and training specifically for nephrologists, incorporating ultrasonography into a practice is not a difficult undertaking.

Ultrasonography is ideally suited for imaging the kidneys and bladder, and is indicated in many situations including renal failure, hematuria, severe hypertension, pain, recurrent or refractory infection, and nephrolithiasis. Both organs are easily visualized and exhibit a limited spectrum of anatomic variation and pathologic changes. The renal cortex, medulla, and collecting system have different acoustic properties, and pathological changes are usually easily discernible and correlate well with histological findings (1).

Sonography is particularly useful in the evaluation of chronic renal failure. The finding of a small kidney or thin cortex through ultrasonography indicates irreversible damage, thereby avoiding further unnecessary workup and biopsy (2,3). Obstructive uropathy (Figure 1) and polycystic disease (as causes of renal failure) can be diagnosed or excluded with certainty, and other disorders such as nephritis, amyloidosis, and chronic pyelonephritis can be implicated. Although useful in the evaluation of acute renal failure as well, sonography is not indicated in all cases. When the clinical picture points strongly to acute tubular necrosis or volume depletion, and urinary obstruction is very unlikely, sonography adds little to the diagnostic workup (4).

Ultrasonography is indicated for acute failure in most solitary and transplanted kidneys, in which urinary obstruction is a common and unpredictable cause of renal failure (5). Sonography also plays a key role in vascular access, including placement of hemodialysis catheters, preoperative vein mapping, and evaluation of arteriovenous grafts and fistulas.

The addition of ultrasonography to a nephrology practice offers significant advantages to both the patient and the nephrologist. The most important advantage is better integration of diagnostic evaluation and patient care. Because the nephrologist is aware of the clinical situation, the ultrasound examination can be appropriately focused. Furthermore, sonographic findings often require clinical correlation, which is best provided by the nephrologist. Sonography allows the nephrologist to take a systematic approach to the patient with either acute or chronic renal failure. A rapid increase in serum creatinine with minimal or no calyceal dilatation effectively rules out urinary obstruction as a cause of acute renal failure. Hydronephrosis in the absence of bladder distension indicates ureteral obstruction. Swelling of the renal cortex in conjunction with a history of an inciting event or the presence of granular casts in the urine indicates acute tubular necrosis, while enlarged, echogenic kidneys in conjunction with hematuria are indicative of nephritis.

In a patient with nephrotic syndrome and acute renal failure, swollen, echogenic kidneys may instead indicate renal vein thrombosis, particularly if there is new onset hematuria or the renal vein is prominent with luminal echoes. Unilateral cortical atrophy with hypertension and unremarkable urinary sediment should raise suspicion for renovascular disease. Sonography can usually identify the cause of poor fistula maturation. The continual feedback from clinical correlation allows nephrologists to develop expert interpretive skills.

Another readily apparent benefit is improved patient care. Ultrasonography can be performed within minutes of evaluating a patient with acute renal failure, expediting the diagnosis and therapy of urinary obstruction. Studies can be performed at the bedside or in the outpatient clinic or office, avoiding scheduling appointments with and patient travel to the radiology department. Kidney biopsy can be performed entirely by the nephrologist, avoiding delays associated with scheduling and transportation and resulting in expedited diagnosis and treatment. Urinary retention can be excluded noninvasively, eliminating the discomfort of catheterization. Additionally, the same ultrasound equipment (with a different transducer) can be used to guide insertion of central venous catheters for hemodialysis and to evaluate dysfunctional arteriovenous grafts and fistulas.

Another benefit of ultrasonography in kidney care is increased physician efficiency. This is most apparent with renal biopsies, which can be performed at nephrologists' convenience without additional arrangements. In the outpatient setting, delays associated with scheduling ultrasonography and obtaining results can be avoided because the sonogram can be performed and interpreted during the patient visit. Because sonography is critical in the initial evaluation of most patients, using it in the outpatient setting substantially streamlines the evaluation of patients. Ultrasound guidance also substantially shortens the time required for insertion of central venous catheters.

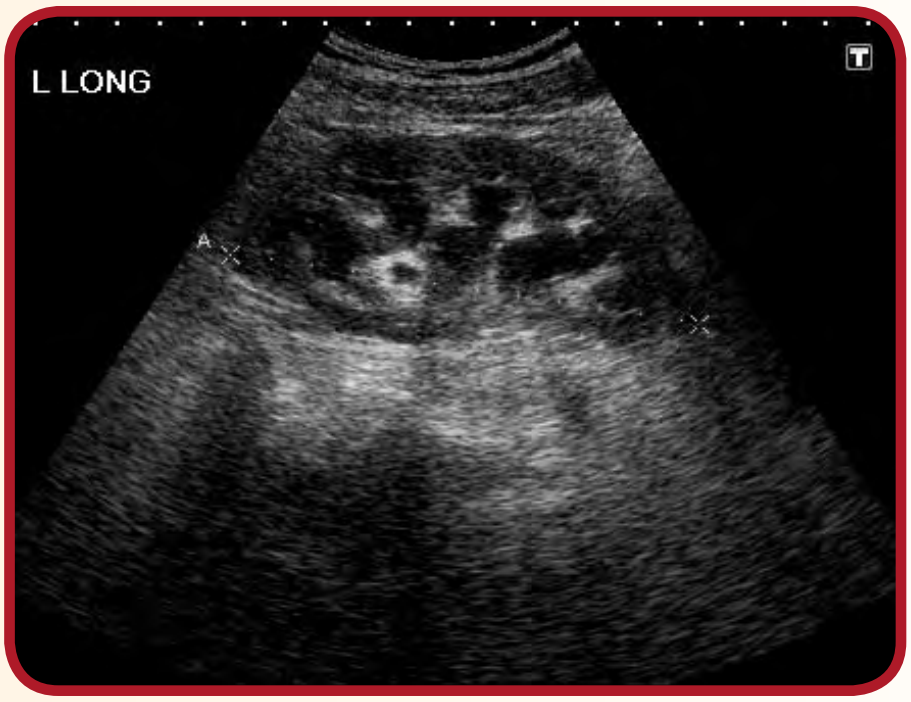
Another advantage that should not be overlooked is the benefit to the practice of nephrology in general. This procedure can expand the domain and increase the diagnostic and procedural capabilities of nephrologists. As evidenced by the interest shown by residents and fellows, ultrasonography can also improve the attractiveness of a career in nephrology.

The growing number of nephrologists who have incorporated ultrasonography into their practices attests to the technique's feasibility. Cost is not an obstacle. The equipment is not expensive and cost can be recovered with as few as two outpatient studies per week. Other concerns include training and credentialing. Our experience in the renal division at Emory University demonstrates that nephrology trainees can become competent sonographers with appropriate training, yet few programs offer such training. This remains a major and puzzling obstacle. For nephrologists seeking training in ultrasonography, the renal division at Emory University offers comprehensive CME-accredited training in the form of a weekend comprehensive course offered several times a year, and a weeklong mini-fellowship that can be scheduled throughout the year. A textbook (1) and other teaching materials are also available. Information can be obtained at the following website (www.medicine.emory.edu/divisions/renal/ultrasound).

The American Society of Diagnostic and Interventional Nephrology (ASDIN) has established training standards for sonography limited to kidneys and bladder as well as a certification program based on these standards. These are available at www.ASDIN.org.

In summary, ultrasonography is an integral part of nephrology that is clearly a feasible procedure for nephrologists. Equipment is not expensive, and training and certification are available. Incorporation of sonography into the practice of nephrology is satisfying for both the patient and the physician and improves patient care. The major obstacle continues to be the lack of exposure to sonography in training programs.

Figure 1. Sonogram of a kidney obstructed by a ureteral stone, showing dilated calyces.



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Molecular Diagnostics in Nephrology

By Abhay Vats

Recent advances in molecular diagnostics are making inroads in how we manage patients with kidney-related disorders. Techniques such as nucleic acid amplification and detection, genomic analysis, proteomics, and metabolomics have enabled development of several molecular diagnostic assays. These developments, in turn, affect the practice of various aspects of nephrology, such as management of acute kidney injury, chronic kidney disease (CKD) and its complications, as well as transplant nephrology.

Many of the ongoing advances in these fields will significantly change the way nephrology is practiced in the near future. Although molecular medicine advances encompass a wide variety of diseases and techniques, two of the major achievements in molecular diagnostics that have affected current clinical practice include 1) the way we approach genetic kidney diseases, and 2) transplant infections.

Genetics and genomics of kidney disease

In the past decade—especially since the sequencing of the entire human genome in 2003—the identification of genes that are mutated in specific disorders has entered an exciting era. Several approaches in the recent past have been used to identify genes associated with a large number of kidney diseases, such as linkage studies, gene expression analysis, and genomewide association studies (1). Combined effects of the genetic makeup of a person (genotype), the environment, and the gene–gene as well as gene–environment interactions are now thought to play a role in the risk of developing several kidney diseases, including CKD, and may also affect the ultimate clinical outcome. Molecular genetic diagnostics has made major contributions to clinical nephrology in the fields of nephrotic syndrome/focal segmental glomerulosclerosis (NS/FSGS), cystic kidney diseases, tubulopathies, and lately CKD.

Nephrotic syndrome

NS is a heterogeneous group of disorders characterized by heavy proteinuria, hypoalbuminemia, edema, and dyslipidemia. In the past decade, studies of familial cases of NS/FSGS have led to the identification of genes encoding proteins important for glomerular structure and function. There are several excellent reviews on various aspects of NS/FSGS genetics (2,3). Genetic tests are available for the targets followed by an asterisk below.

Briefly, structural elements of the slit diaphragm (nephrin*, podocin* and CD2AP) and actin cytoskeleton (α-actinin-4*) have been identified to be important causes of NS/FSGS. The transcription factor WT1*, phospholipase C ε1 (PLCE1), the calcium channel protein TRPC6* (which localizes in membrane lipids complex along with podocin), as well as laminin-β2, a structural component of the glomerular basement membrane, have also been implicated in causing NS/FSGS.

Several novel chromosomal loci have also been linked to various forms of NS/FSGS and/or proteinuria, such as regions of chromosome 9q32, 11q24, and 13q22. The list of genes associated with this phenotype is likely to grow significantly in the years to come (4–6). Some of these genes (nephrin, podocin) cause autosomal recessive disorders with early childhood onset, while others (α-actinin-4*, TRPC6*) are dominantly inherited with generally adult onset of disease, incomplete penetrance, and variable expressivity. It has now been shown that a significant proportion of patients presenting with NS/FSGS in early childhood have an underlying Mendelian genetic disorder involving podocin or nephrin. The genetic component of adult-onset disease is probably not as great as the pediatric-onset disease, but oligogenic and complex inheritance may play a bigger role in some situations (2). For example, certain haplotypes in the MYH9 gene that increase risk of FSGS and glomerular injury/CKD in some adult patients have been recently identified (1).

Cystic diseases of the kidney

Like the NS/FSGS syndromes, cystic diseases of the kidney (CDK) are a heterogeneous group encompassing a large variety of diseases and clinical syndromes. During the past two to three decades, the inheritance patterns of many CDKs have been extensively studied, and several associated genes have been identified. There are now a large number of genes associated with CDKs, with at least nine genes mutated in nephronophthisis (including NPHP1*), 12 in Bardet-Biedl syndrome, at least three in MCKD (including UMOD1*), and at least four in autosomal dominant polycystic kidney disease (including PKD1* and PKD2*) and recessive polycystic kidney disease (including PKHD1*).

This list, as with many other genetic kidney diseases, is destined to expand significantly in the near future. Despite the heterogeneity, all CDKs have one common morphologic feature—cysts in the kidney. Similar to the glomerular structure/function theme for NS/FSGS, most of the genes mutated in CDKs code for proteins that localize to the primary cilium. Several excellent reviews on CDK genetics provide details of various genes involved in these ciliopathies and associated CDK syndromes or diseases (7–9).

Practical considerations for clinical nephrologists

There are currently more than 30 genes associated with CDKs and over 15 genes with NS/FSGS that encompass autosomal dominant and recessive as well as X-linked inheritance. Most of these diseases are monogenic with Mendelian inheritance, but there are examples of oligogenic inheritance, such as three mutations in two genes for both CDKs and NS/FSGS (2,9). The variable expressivity and the broad spectrum of symptoms associated with various kidney diseases suggest that genetic modifiers are important in determining the outcome of a large number of CDKs and possibly NS/FSGS. Finally, new genes are constantly being discovered and mutations in many different genes can produce similar phenotypes, often with substantial overlap of symptoms.

This significant genetic heterogeneity has made molecular diagnostics particularly difficult for practicing nephrologists because the clinical differential diagnosis does not always help in pointing to the right gene to analyze. Nephrologists need to be aware of the various developments in molecular diagnostics and be able to identify appropriate patients as well as tests. Many genetic tests (including those identified in the previous section by *) are now commercially available, and the initial restrictions of insurance reimbursements have gradually been addressed and removed. An NCBI website called GeneTests (http://www.ncbi.nlm.nih.gov/sites/GeneTests/?db=GeneTests) lists the laboratories where the tests for various genes related to kidney diseases can be performed.

Molecular diagnostics and transplant infections

Infectious diseases and their complications are a major contributor to morbidity and mortality associated with long-term outcomes of renal transplantation. Recipients of renal and other solid organ as well as bone marrow transplants are uniquely predisposed to develop infections caused by opportunistic pathogens including a variety of bacteria, viruses, and fungi. The identification and management of viral infectious disease has been aided most significantly from advances in molecular diagnostics, especially related to nucleic acid amplification technologies such as real-time PCR over the last decade (10–12).

Transplant recipients can acquire viral infections from a variety of sources, including the donor, reactivation of latent virus, or from the community. Human herpes viruses, i.e., cytomegalovirus (CMV), Epstein Barr virus (EBV), and HHV6 are some of the most common opportunistic viruses that cause infection after renal and other solid organ transplantation.

The polyoma BK virus is particularly important to nephrologists because it remains latent in renal tubular cells after primary infection. The virus becomes reactivated in kidney transplant recipients causing an opportunistic infection leading to both acute and chronic allograft dysfunction (13). Respiratory viral illnesses due to influenza, respiratory syncytial virus, parainfluenza, and human metapneumovirus may affect all types of transplant recipients, but may be particularly troublesome in the very young and old (12).

Less common viruses affecting transplant recipients include adenoviruses and parvovirus B19. Recent reports of donor-derived infections have attracted a lot of attention both in medical literature as well as the lay media. Although donor-derived infectious diseases appear to complicate less than 1 percent of all transplant procedures, when a transmission occurs, significant morbidity and mortality can result, as has been recently reported for transmission of HIV, hepatitis C virus, and West Nile virus (WNV) from organ donors to recipients. These reports have highlighted the importance and clinical impact of this complication of renal and other solid organ transplantation. Molecular diagnostic assays based on nucleic acid amplification techniques such as PCR, real-time PCR, and others are now available for a large variety of these infections. Many of them (e.g., respiratory pathogens) can be ordered as a panel or a battery of rapid molecular tests.

Among the problems with the emerging field of viral molecular diagnostics are a lack of standardization (except for a few of the viruses, such as HIV and HCV), high cost, and the possibility of false positives (due to contamination) or false negatives (due to viral mutations or testing procedural problems). In addition, health care providers must often wait anywhere from one day to one week to obtain test results, depending on the laboratory used and organism being tested, even though the testing procedure by itself takes less than two to three hours, thus potentially leading to a delay in diagnosis and initiation of appropriate therapy.

Future directions

Several kidney diseases, including CKD, are currently being investigated for the role of genetic—and epigenetic—factors in their causation and outcome (14,15). In the future, the rapidly evolving field of genetics, including genomewide association studies and epigenomics, could identify several genetic determinants (such as mutations, SNPs, or copy number variants) of key renal disorders and transform medical diagnosis and treatment, moving toward "personalized medicine."

Outcomes in the CKD population may therefore be improved by establishing individual genetic or epigenetic profiles, thus enabling physicians to design an individualized therapeutic strategy. Personalized medicine based on a more individualized therapy could be applied in, for example, pharmacotherapy, dialysis therapy, and nutritional and lifestyle modifications. But the vision of individualized treatment based on a patient's genetic makeup and other biological markers needs further work and statistical and clinical validation (1,14).

Another area poised for major advance in the near future is point-of-care diagnostics. Rapid molecular diagnostics based on

novel nucleic acid amplification methods such as Loop-mediated isothermal AMPlification (LAMP) and innovative detection technologies like optical sensing or nucleic acid lateral flow devices (NALF) have gained significant attention in recent years due to advantages of assay speed, potential for point-of-care availability, and low cost (16,17).

Microfluidic systems such as lab-on-a-chip, or BioMEMS offer a great advantage by integrating a large number of assay handling steps into a single device, making the system independent of user intervention and, thereby, less prone to contamination. Miniaturization and integration of assay steps into a lab-on-a-chip type device is being developed for several pathogens, as well as SNPs and mutations, to speed up assay time and make assays available onsite at competitive costs. However, the emerging technologies and approaches still require significant simplification and clinical validation.

Because meaningful assays for infectious diseases need to include a range of pathogens, multiplexed functionality is often required and will need to be implemented in future point-of-care assays (18,19). It is possible in the not too distant future that several of the opportunistic viral infections as well as key mutations or SNPs may be detected with the sensitivity and specificity of PCR or sequencing while the patient is waiting in the outpatient or outlying clinics and at a fraction of the cost current being charged for PCR tests.

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CRRT: Where Are We Now?

By Joseph Sherbotie

Acute kidney injury (AKI) often presents formidable risks to patients in critical care units, particularly those with associated multiorgan failure. Such patients are very likely to die in spite of the best efforts of providers. With this in mind, aggressive management of AKI using hemofiltration and/or dialytic therapy has evolved. Systems appropriate for use in pediatric patients are limited today.

History

Since the serendipitous introduction of continuous arteriovenous hemofiltration (CAVH) as described in 1977, continuous renal replacement therapies (CRRT) have developed steadily, with increasing degrees of complexity. Initial therapies driven by differential arterial and venous pressures have been supplanted by venovenous systems incorporating mechanical pumping of blood through the extracorporeal circuit. Fluid removal control has evolved from makeshift reactionary protocols (e.g., replacing removed fluid retrospectively as a percentage of that removed in the previous hour) to "real time" volumetric and/or gravimetric controlled ultrafiltration. With this complexity have come difficulties related to maintaining patient safety, but this has largely been successful.

AKI is a common problem occurring in ICU patients. Many patients afflicted with AKI in recent times also have multiple organ dysfunction (MOD). Particularly in patients with hemodynamic instability, CRRT has become a preferred method for treating AKI particularly with associated oliguria and volume overload. It has been estimated that some 5 percent of adult patients in ICUs have significant AKI during their stay.

Technology

Capabilities of machines available to perform CRRT in the United States are varied. Most depend at least to some degree on convective clearances, but most also add diffusive measures to increase solute removal. Some machines also provide for therapeutic plasma exchange. Ultrafiltration is usually monitored by one or more scales, though volumetric internal ultrafiltration methods are also available. A general outline of machine capabilities is presented in Table 1.

Improvements in control and accuracy of fluid removal have been particularly beneficial to small adult patients, hemodynamically unstable patients, and children.

Extracorporeal circuit

Unsubstituted cellulose membranes are not used for CRRT. Rather, more biocompatible synthetic membranes or substituted cellulose membranes are used. Because of the popularity of convective clearance in CRRT and desires to remove "middle molecules" (and potentially cytokines), membranes with high ultrafiltration coefficients (high flux) are used in hemofilters and hemodialyzers. Some systems have limited flexibility in terms of circuit size (volume) and membrane, while others are as flexible as chronic hemodialysis systems. A few systems can be used for chronic dialysis treatments, acute hemodialysis treatments, and CRRT. Of note, with increasing intensity of solute removal on a continuous basis, close attention must be paid to removal of important molecules including antimicrobials and vasopressor agents. There may be a risk of undertreatment if "usual" dialysis dosing recommendations are used. We routinely measure drug levels when available, or calculate/estimate relative urea or creatinine clearances on therapy to guide drug dosing

Vascular access

Appropriate vascular access is essential to the successful implementation of CRRT. Generally, double lumen hemodialysis catheters are used. Pediatric patients, particularly infants, present unique challenges. Access must be large enough to permit appropriate blood flows but not be so large as to promote vessel damage, obstruction to venous drainage, or remarkable safety issues during catheter placement.

Shortened CRRT circuit lives (limiting effective treatment of AKI) often are associated with inadequate vascular access. Table 2 provides examples of intravascular catheter sizes and placements for patients of various sizes.

Anticoagulation

Limiting thrombosis within the extracorporeal circuit is essential to proper functioning of CRRT. The mainstay of anticoagulating CRRT circuits has been unfractionated heparin. Alternatives include regional citrate anticoagulation, and saline flushes of the circuit without additional anticoagulation. The latter of these methods may be associated with more frequent clotting of the extracorporeal circuit.

Other choices may include low molecular weight heparin (difficult to safely dose in renal failure), heparinoids, thrombin antagonists, and platelet inhibiting factors. Of the available choices, regional citrate anticoagulation appears to be at least as effective as the heparin standard with demonstrated decreased risk of bleeding since there is no systemic anticoagulation effect. However, there is a risk of clinically important hypocalcemia and of citrate toxicity. These potential complications have largely been overcome by standardized protocols and appropriate adjustments for patients with impaired metabolism of citrate (e.g., liver failure).

Our practice has been to use regional citrate anticoagulation with ACD-A, calcium free dialysate, and calcium infusion to avoid hypocalcemia. Diffusive and convective clearance of citrate has generally been effective at limiting the risk of toxicity. Reports of prolonged hemofilter or dialyzer patency with citrate anticoagulation have not been consistent, though many observe perceived prolongation of circuit life with citrate.

Temperature control

Most modern CRRT systems provide appropriate warming of either blood or dialysate and replacement fluid. This is particularly important in very small patients who would otherwise lose a tremendous amount of body heat radiated from the extracorporeal circuit.

Fluid removal

Control of fluid removal on today's CRRT systems is accurate. Either gravimetric (scales) or volumetric methods are used, most with external collection containers to weigh removed fluid. Still, operator competence at understanding the various machines is critical to patient safety. As

Table 1. CRRT machines available in the United States

	Ultrafiltration	Therapies supported	Pediatric specific
Prisma	Scales	SCUF, CVVH, CVVHD, CVVHDF, TPE	No
Prismaflex	Scales	SCUF, CVVH, CVVHD, CVVHDF, TPE	No
Aquarius	Scales	IHD, IHDF, SCUF, CVVH, CVVHD, CVVHDF	Yes (variable circuit volumes and hemofilter volumes)
Diapact	Scales	IHD, IHDF, SCUF, CVVH, CVVHD, CVVHDF	No
Nx Stage System 1	Volumetric	IHD, SCUF, CVVH, CVVHD	No
Fresenius 2008H/K	Volumetric	IHD, IHDF, SCUF, CVVH, CVVHD, CVVHDF, TPE	Yes (extensive choice of tubing sets and dialyzers)

Abbreviations: SCUF, slow continuous ultrafiltration; CVVH, continuous venovenous hemofiltration; D, dialysis; F, filtration ; TPE, therapeutic plasma exchange; IDH, intermittent hemodialysis.

Table 2. Examples of vascular access for CRRT by patient size. Two single lumen catheters can replace one double lumen catheter if necessary

Patient Weight (KG)	Catheter Size	Site of Insertion
Neonate; to 2.5 to 3 kg	Single lumen 4 or 5 F X 8cm	Internal or external jugular vein, femoral vein, subclavian vein
> 3 kg to 5 kg	Single lumen 5 F; (Double lumen 7F X 10cm)	Internal or external jugular vein, femoral vein, (subclavian vein)
> 5 kg to 8 kg	(Double lumen 7 F X 10cm); Double lumen 8 F X 12cm	Internal or external jugular vein, femoral vein, (subclavian vein)
> 8kg to 15 kg	Double lumen 8 F x 12cm	Internal or external jugular vein, femoral vein, (subclavian vein)
> 15 kg	Double lumen 11.5 F x 15cm; (Double lumen 8 F x 12cm)	Internal or external jugular vein, femoral vein, (subclavian vein)

Abbreviation: F = French.

expected, this is potentially of greater importance in small children (where there is little room for error) or hemodynamically unstable patients.

Fluids

With aggressive continuous therapies, particular attention needs to be paid to dialysate and/or replacement fluid composition. Commonly, serum phosphorus and magnesium levels drop to clinically dangerous low levels. Because of this, both may need to be supplemented in the fluids. Various protocols for this are available. Generally, fluids used should be as physiologic as possible to avoid significant imbalances.

We typically use dialysate concentrates (continous hemodialysis) with sodium phosphate added to the bicarbonate concentrate and magnesium added to the acid concentrate. Previous use of totally custom-made fluids is no longer advised because of the real risk of life-threatening errors, since standardized commercially produced fluids are now available.

Outcomes

No controlled studies have demonstrated clearly improved outcomes comparing CRRT with intermittent dialysis treatments; however, there are no studies clearly demonstrating worse outcomes with continuous therapies. Most comparisons are between CRRT and aggressive daily intermittent hemodialysis.

"Dose" of delivered therapy has been shown to be associated positively with improved outcome, but this has not been consistently demonstrated in relatively large prospective studies. Several studies in both adults and children have suggested that "early" institution of CRRT as related to degree of volume overload is associated with improved survival.

Cost

Costs of CRRT vary widely among centers. On average, CRRT appears to be more expensive than intermittent hemodialysis as currently practiced at most centers. The most costly features appear to be the increased nursing staff needed to care for patients on CRRT and the cost of replacement fluids and dialysate. Choice of treatment (CRRT versus intermittent hemodialysis) has not been consistently associated with ICU stay or subsequent chronic renal failure, quality of life, or functional rehabilitation of treated patients. Such issues clearly contribute to the overall cost or value of therapy.

CRRT is and will likely remain an important modality for treatment of AKI in the ICU in spite of lack of evidence of superior outcomes over intermittent hemodialysis. The ideal dose of therapy has not been consistently identified. It is unclear if even higher doses would have beneficial effects or if additional complications might result.

Continuous therapies are most likely to be beneficial to unstable patients with MOD who may tolerate intermittent hemodialysis poorly. Fluid management is likely to be optimized with CRRT as well. Cost is an issue, but continuous therapies using commonly available materials (e.g., use of hemodialysis machines that mix dialysate on line) are likely to decrease relative expense. Staffing in our pediatric ICU is already "one on one," and CRRT does not typically add to this cost. There is no objective evidence that convective clearance is better than diffusive clearances in spite of the popularity of hemofiltration.

Of importance to optimal patient care is cooperation between the intensivist and renal specialist. Each has unique experiences and skills. It is unlikely that perseverating over outcomes differences between intermittent and continuous therapies will be productive. Centers should use the techniques that suit them and their patients best. CRRT is another valuable tool in the belt of physicians caring for critically ill adults and children.

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ASDIN:
Improving Quality in Dialysis Access Procedures

By Timothy A. Pflederer

The American Society of Diagnostic and Interventional Nephrology (ASDIN) is dedicated to enhancing the quality of care that patients receive related to vascular access, peritoneal dialysis access, and ultrasonography. Established in 2000, the mission of ASDIN is to promote the appropriate application of new and existing procedures in order to improve the care of patients with kidney disease. Membership includes physicians, nurses, technicians, and administrators—all with interest in this specialized field. ASDIN is the representative society for the growing number of interventional nephrologists in America and internationally. The society currently has approximately 600 members.

ASDIN works to accomplish its mission in a number of ways. We are active in promoting research, publication, and the adoption of clinical practice standards related to dialysis access and access procedures. We provide certification of physicians in various procedures and accredit training centers to ensure the highest standards in training for the next generation of interventionalists. We participate in physician and ancillary staff education through an annual meeting and joint meetings with the American Society of Nephrology (ASN) and National Kidney Foundation (NKF). We have been a leading society in establishing best coding practices and a comprehensive coding manual for dialysis and vascular access procedures. Our newest quality initiative is the development of a national dialysis access procedure outcomes benchmarking database.

The ASDIN Procedure Outcomes Registry is an Internet database that collects quality and outcome data related to dialysis vascular access procedures. The goal of this voluntary registry is to promote quality in dialysis vascular access procedures, provide benchmarking opportunity for participants, promulgate useful data, and protect the patient's right to the highest quality, most efficient procedural care. The survey is open to participation by anyone who performs dialysis vascular access procedures; ASDIN membership is not required. Participants may be individual physicians, group physician practices, access centers, or other institutions. More information about this registry is available at the ASDIN website: www.asdin.org under the "Outcomes" tab.

The registry is currently structured to track quality outcomes of catheter and endovascular dialysis access procedures. There are specific data questions in four general areas:

General demographics

1. ESRD population served
2. Number of dialysis facilities served
3. Number of physicians in the practice by specialty
4. Physician credentialing
5. Location of procedures done by physician(s): inpatient hospital, outpatient hospital, freestanding facility
6. Percentage of referring dialysis facilities using surveillance technology

Procedure numbers

1. Number of patient encounters
2. Number of specific procedures performed
3. Number of each CPT code used

Patient characteristics

1. Number of patients at each ASA classification
2. Patient CKD stage
3. Number of each type of anesthesia used: local, moderate sedation, deep sedation with anesthesiologist, general anesthesia

Procedure outcomes

1. Hospitalizations
2. Adverse safety events: patient falls, wrong site surgery, medication errors, moderate sedation complications, infections within 30 days, device malfunctions
3. Procedural complications: type and severity
4. Immediate success rate
5. Functional success rate

Although not comprehensive, these questions represent the core information needed in a dialysis vascular access quality assurance performance improvement (QAPI) program. Participants will easily be able to benchmark their own outcomes with the aggregate quality results across all areas of the survey. Additional survey data questions will be added over time to continue to provide participants with quality improvement resources. Future plans for the ASDIN Procedure Outcomes Registry also include modules directed at quality improvement in peritoneal dialysis access procedures, surgical access procedures, and multicenter research collaboration.

Dialysis access care has improved dramatically over the past 10 years. According to Fistula First Breakthrough Initiative (FFBI) data, prevalent arteriovenous fistula (AVF) rates have increased between 2003 and 2010 from 32 percent to 55 percent. Patients benefit greatly from this trend since those with AVFs experience fewer infections, thrombosis events, and hospitalizations. Indeed, their overall mortality is significantly lower when dialyzing with an AVF.

Also during this time period, there has been a significant shift in the location dialysis access procedures are performed. Procedures continue to shift from the relatively high cost inpatient hospital to lower cost outpatient and freestanding centers. In addition to reducing per procedure cost, this change has allowed patients to have the necessary procedures done more rapidly, which minimizes catheter use.

Over the past few years there has been growing recognition of the specialized skill set involved in performing dialysis vascular access procedures. There are a growing number of surgeons and interventionalists with specific focus on dialysis vascular access. The growth of interventional nephrology has been a key factor in facilitating this trend. Working with other areas of nephrology and the broader medical community, the American Society of Diagnostic and Interventional Nephrology will continue to play an important role in improvements in vascular access, peritoneal dialysis, and ultrasound procedures in the coming years.

Timothy A. Pflederer, is president of the American Society of Diagnostic and Interventional Nephrology.

Journal View

Blood Pressures Are Higher When Measured by Doctors

Clinic blood pressure measurements obtained by physicians are higher than those obtained by staff, reports a study in the *British Medical Journal*.

The researchers analyzed 24-hour ambulatory blood pressure measurements, made using validated devices, from 8575 patients. The patients were seen at 11 Australian hypertension clinics; most were referred for ambulatory blood pressure monitoring. The ambulatory blood pressure results were compared with clinic readings made by trained, nonphysician professional staff. In a smaller cohort of 1593 patients, comparisons were also made to clinic blood pressure readings made by physicians.

The mean seated clinic blood pressure measured by staff was 142/82 mm Hg, compared to a mean of 150/89 mm Hg for physician-measured clinic blood pressures. The physician measurements were significantly higher than the staff measurements, but both sets of clinic measurements were higher than the average 24-hour ambulatory blood pressure of 132/77 mm Hg.

Daytime ambulatory equivalents derived from the clinic measurements made by trained nonphysician staff were 4/3 mm Hg lower than the 140/90 mm Hg threshold, corresponding to the lower limit of grade 1 or mild hypertension. The estimates were 2/2 mm Hg lower than the target clinic value in patients with one associated clinical condition (130/80 mm Hg), and 1/1 mm Hg lower for patients with significant proteinuria who require a target clinic blood pressure of 125/75 mm Hg. The ambulatory values were 1/2 mm Hg lower for women than for men, and 3/1 mm Hg lower for patients aged 65 years or older compared to younger patients.

Guidelines for the treatment of hypertension have become increasingly sophisticated, mainly based on clinic measurements of blood pressure. Similar guidelines are needed to direct the therapeutic response to ambulatory blood pressure measurements.

This large study identifies ambulatory blood pressure thresholds slightly lower than the equivalent clinic-measured values. Clinic measurements made by physicians are higher than those made by trained nonmedical staff, and therefore may lead to inappropriate estimates of ambulatory thresholds. Considering a patient's age and sex may further enhance the accuracy of ambulatory blood pressure treatment targets [Head GA, et al. Definition of ambulatory blood pressure targets for diagnosis and treatment of hypertension in relation to clinic blood pressure: prospective cohort study. *BMJ* 2010; 340:c1104].

Donor Gene Variant Affects Risk of Kidney Transplant Failure

The donor genotype for the gene encoding the tissue fibrosis inhibitor caveolin-1 (CAV1) influences the risk of kidney transplant fibrosis and allograft failure, reports a study in *The Journal of the American Medical Association*.

The researchers performed a candidate gene association and validation study using genomic DNA from a single-center cohort of 758 white kidney transplant donor-recipient pairs. The analysis sought to identify *CAV1* variants associated with increased rates of renal allograft failure. Identified associations were validated in an independent cohort of 697 donors and recipients.

Recipients of kidneys from donors with the AA genotype for the *CAV1* rs4730751 single-nucleotide polymorphism (SNP) had nearly a twofold increase in the risk of allograft failure compared to other *CAV1* genotypes. Predominant interstitial fibrosis was the cause of graft failure in 59 percent of AA kidneys, compared to 26 percent of non-AA kidneys. No other *CAV1* variant affected the risk of allograft failure.

The AA genotype was also associated with an increased risk of transplant failure in the validation cohor. In both cohorts, genotype frequency was similar between donors and recipients, suggesting that the rs4730751 SNP was not associated with an increased risk of end stage renal disease.

Caveolin-1 has been shown to play a role in several different sclerosing diseases. However, few studies have examined its role in renal fibrosis, which is a major contribution to kidney allograft failure.

The AA genotype of the *CAV1* rs4730751 SNP in kidney donors appears to be associated with an increased risk of allograft failure in transplant recipients. This is the first report of a gene variant in organ donors affecting the long-term chances of transplant survival in the recipient. The results have implications not only for kidney transplantation, but also for other renal and nonrenal diseases involving tissue fibrosis [Moore J, et al. Association of caveolin-1 gene polymorphism with kidney transplant fibrosis and allograft failure. *JAMA* 2010; 303:1282–1287].

Industry Spotlight

CKD Learning

The online world, where consumer-friendly health news and information arrive in your inbox or popup with a url, is now more CKD-friendly, too.

DaVita Inc. has launched the online DaVita Phosphorus Challenge. This online program is a learning tool for CKD and dialysis patients. To visit the site, go to www.davita.com/phosphoruschallenge.

The challenge is a 30-day interactive program not only for kidney disease patients, but also for family members, caregivers, and related dialysis and nephrology professionals. The program informs users about phosphorus and its effects on those with CKD, about the need to keep phosphorus levels low, and about the role of phosphorus binders in people with kidney disease.

Program users get emails that are linked to interactive games, quizzes, and other activities geared toward learning.

Transplant Drug News

New drugs to help kidney transplant patients are moving through the pipeline, some faster than others. The U.S. Food and Drug Administration wants more information about belatacept, a drug that seems poised to compete with traditional anti-rejection drugs like cyclosporine. The agency requested the 36-month data from the ongoing phase 3 studies to further evaluate the long-term effects of belatacept.

Manufacturer Bristol-Myers Squibb said that the FDA issued a complete response letter about belatacept use in kidney transplants, according to a press release issued in early May.

Two-year data indicated that belatacept and cyclosporine were similar for measures of patient and graft survival, according to the manufacturer of the newer drug. Belatacept offered more renal benefit in the first year, which was sustained in the second year of the phase 3 BENEFIT trial (Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial).

The FDA approved the Novartis drug everolimus (Zortress) to help prevent organ rejection in adult kidney transplant patients. The transplant drug is to be part of a combination therapy of corticosteroids, cyclosporine, and basiliximab.

Approval of everolimus was based on a 24-month, randomized clinical trial comparing two different doses of everolimus with a regimen of mycophenolic acid in a combination regimen of standard doses of cyclosporine and corticosteroids. Those taking everolimus had 60 percent lower required doses of cyclosporine than those in the mycophenolic acid group. The drug reduced the side effects associated with cyclosporine and preserved kidney function while preventing rejection. The drug was approved as a kidney cancer treatment under the trade name Afinitor.

A new type of drug for kidney transplant patients—bortezomib—debuted results at the American Transplant Congress in May. Bortezomib is marketed as Velcade by Millennium Pharmaceuticals for multiple myeloma and mantle cell lymphoma. It is the first therapeutic proteasome inhibitor to be tested in humans.

In a small study (n = 10), renal function improved in 80 percent of kidney transplant patients, with a sustained improvement in 60 percent of patients for about one year.

The drug was generally well tolerated by most of the patients. While the study showed that bortezomib may decrease DSA (anti-HLS donor-specific antibodies) and prolong the function of the graft, more studies are needed to demonstrate the long-term safety, best dosing strategy, and the best treatment period length, according to Stuart M. Fletcher, MD, of the Cleveland Clinic Foundation, who headed the study.

Another kidney transplant drug is in the news because of a patent dispute: Pfizer filed patent infringement litigation in U.S. District Court against Daiichi Sankyo's Ranbaxy subsidiary regarding Rapamune and also against Watson Pharmaceuticals. Ranbaxy, an Indian company, and Watson both filed FDA applications for generic versions of sirolimus (sold by Pfizer as Rapamune). U.S. sales for Rapamune totaled $210.5 million for the 12 months ending in February 2010, according to IMS Health data.

Policy Update

FDA to Address Challenges of Complex Medical Devices in the Home

Courtesy of NxStage Medical, Inc.

In light of growing use of complex medical devices in the home, the Food and Drug Administration (FDA) announced a new initiative to ensure the safety and safe use of these products. According to an April 2010 FDA white paper, The Medical Device Home Use Initiative will address the unique challenges presented by use of medical devices in the home, rather than clinical, environment. Variation in product usability, caregiver knowledge, and environmental unpredictability all affect the safety of medical devices in the home, and FDA plans to address these factors through five proactive steps (Table 1).

Among the Initiative's action items is the production of guidelines for manufacturers of devices used in the home, which FDA has never before issued. Participating in an FDA workshop convened to help inform the guidelines, ASN staff discussed FDA's working definition of home use, the unique risks of home use that should be factored into design, and approaches to device labeling. FDA will draw upon comments from health care providers, device manufacturers, and patient advocacy groups present at the May workshop as it shapes an initiative implementation plan, to be presented in a forthcoming proposed rule.

Home health care is increasingly common for people with chronic diseases, FDA noted in the white paper—and this is particularly true for the dialysis patient population. While home hemodialysis use peaked in the mid-1980s, in recent years there has been renewed interest, fueled by publication of results from single centers using the therapy as well as new products being introduced for therapy delivery, according to the United States Renal Data Service. In 2007, 2999 prevalent ESRD patients received home hemodialysis—more than a third of whom began ESRD therapy on home hemodialysis between 2005 and 2007.

Home hemodialysis users may benefit significantly from the FDA's new initiative, which aims to improve not only patients' ability to use such devices in the home, but also to enhance caregivers' capacity to do so. This is important given that new ESRD patients treated with home hemodialysis are far more likely to be unable to ambulate or need assistance with daily activities—and therefore rely on another individual to assist them with their dialysis care—than patients treated with in-center hemodialysis.

Moving forward, ASN policy staff will continue to work closely with FDA to implement its five-point action plan, particularly in helping to shape the guidelines for manufacturers of home use devices.

Table 1.

FDA home use initiative actions	Details
1. Guidelines for manufacturers	Currently, FDA does not articulate a clear regulatory pathway outlining the factors medical device manufacturers should consider when designing, testing, and labeling products intended for home use. To establish a more predictable pathway for home use devices, FDA will clarify its expectations for manufacturers of such products in a guidance document recommending steps they should take to receive FDA approval, including usability testing with lay users in a nonclinical setting.
2. Home use labeling repository	Many patients receiving care in their homes use older medical devices, which often come with no labeling or instructions for use. Devices that are labeled typically do not have instructions written for a lay audience and may include complex warnings or contraindications that can confuse patients at home. Recognizing these obstacles to accessing information about the proper use of medical devices in the home, FDA will create an online labeling repository for medical devices for home use, available to the public on the agency's website. Compiling medical device labels in a single online database will facilitate patients' and caregivers' ability to access information about how to safely use their device. As a first step toward this goal, FDA announced a pilot program through which manufacturers may voluntarily submit their labels for FDA to post on its website.
3. Partnership with home health accrediting bodies	Some patients using medical devices receive in-home care from home health practitioners. Given the wide array of medical devices that are used—on or off label—in the home, assuring that these practitioners are adequately trained to use them is challenging. Existing home health accrediting programs typically focus on caregivers' ability to care for patients rather than their medical device usage skills. As such, FDA is partnering with the Joint Commission and the Community Health Accreditation Program to review and strengthen accreditation criteria related to medical device use in the home.
4. Enhanced postmarket oversight	The initiative also contains measures for enhanced postmarket surveillance through HomeNet, a program that collects reports of problems with home-use medical device from home care agencies that is part of FDA's Medical Product Surveillance Network. The white paper notes that HomeNet recently completed a survey to collect information about concerns related to home hemodialysis.
5. Public awareness and education	Expanding upon current activities on outreach and education related to home use of medical devices, the FDA is developing additional educational resources to be made available on a new Home Use Devices Website. FDA is also collaborating with federal and non-governmental organizations, including the Centers for Disease Control and Prevention, to educate the home health community about medical device safety.

ASN Provides Feedback to FDA on Studies of Pharmacokinetics in Renal Patients

The Food and Drug Administration (FDA) recently released proposed recommendations for industry studying pharmacokinetics (PK) in those with renal impairment. The proposed recommendations are intended to assist sponsors planning studies to assess the influence of renal impairment on the pharmacokinetics of investigational drugs. The document outlines recommendations for when such studies should be conducted, their design, and how they should be carried out.

The kidney plays a significant role in processing drugs, and patients with impaired kidney function sometimes excrete drugs more slowly—or less fully—than those with normal kidney function. Consequently, dosage regimens on some drugs that are eliminated primarily through the kidney need to be changed from dosages used for patients with normal renal function, especially those with acute kidney injury.

The primary goal of the FDA-recommended studies is to determine whether a drug's PK is altered in patients with compromised renal function to such an extent that the dosage should be adjusted from the dose(s) established in phase 3 trials during which researchers determine the safety and efficacy of drugs. Frequently, individuals with significantly impaired renal function are excluded from participation in phase 3 trials—though in some cases there may be a sufficient range of renal function to allow an estimation of the effects of decreased renal function from population PK analysis.

Before issuing final recommendations, FDA solicits feedback from the medical community on the proposed document, and ASN recently submitted a comment letter to the agency. Several ASN Advisory Groups—including Acute Kidney Injury, Dialysis, and Chronic Kidney Disease—contributed to the society's review and analysis of FDA's proposal.

The final document, which is expected to be finalized this year, may recommend that sponsors conduct more trials among patients with kidney disease. Because this is a recommendation document, it will remain nonbinding. Nonetheless, the draft document may indicate that FDA is increasing attention to kidney disease and heightening scrutiny of new products in general.

Among the comments ASN submitted to FDA was a suggestion that PK should be rigorously studied in persons with chronic kidney disease who are not on dialysis, as well as in the end stage renal disease and acute kidney injury populations. ASN also suggested that FDA specify that all dialysis PK studies include both intermittent hemodialysis and continuous renal replacement therapy.

The society was also pleased to endorse KDIGO's comment letter on FDA's draft guidance document, which echoed the concerns and suggestions expressed in ASN's letter.

Read ASN's comment letter and learn more about FDA's proposed guidance document on the society's Patient Care Policy page at http://asn-online.org/policy_and_public_affairs/patient-care.aspx.

Workshop on Acute Kidney Injury in Older Adults Unites Nephrologists, Geriatricians, NIH

Bringing together nephrologists, geriatricians, and representatives of the National Institutes of Health (NIH) to discuss research opportunities pertinent to the aging population, the American Society of Nephrology recently participated in the "Workshop on Acute Kidney Injury (AKI) in Older Adults." During the meeting, convened by the Association of Specialty Professors (ASP), participants worked to determine knowledge gaps related to AKI in the geriatric population and to identify research questions, pinpointing windows of opportunity for research.

Organized around six key discussion topics ranging from "Defining AKI in the Older Adult" to "Interaction of AKI with Co-Morbidities" to "Animal Models in AKI," the interactive workshop alternated between lectures and opportunities for conversation among participants. Besides leaders from the National Institutes of Diabetes, Digestive, and Kidney Disease (NIDDK) and the National Institute on Aging (NIA), participants included several ASN members, including President Sharon Anderson, MD, FASN, as well as representatives from ASP and the American Geriatrics Society.

"This workshop is an outstanding opportunity for the renal and geriatrics communities to share knowledge and chart the direction of future research," said Anderson. "As nephrologists, many of us know relatively little about the mechanisms of kidney aging. But looking at the demographics of the United States—particularly the aging baby boomers—it's going to be vital that we pursue research advancing our understanding of and ability to treat kidney disease in the elderly. This workshop is a significant step toward that goal."

This is the second collaborative workshop among ASN, ASP, the geriatrics community and NIH. In 2008, a workshop on Chronic Kidney Disease in Older Adults led to the publication of an article in the *Journal of the American Society of Nephrology (JASN)* on the topic, and since then NIH has issued two funding opportunity announcements on issues discussed during the workshop. ASN anticipates publication of a similar paper on AKI in the aging adult in the near future.

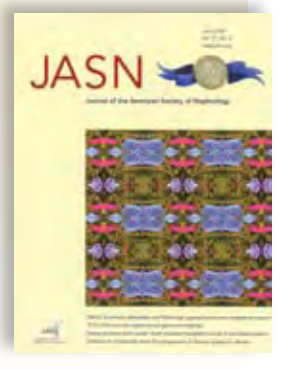
To access the *JASN* paper on Chronic Kidney Disease in Older Adults, please visit the ASN policy website.

ASN News

JASN Anniversary: Celebrating 20 Years of Publication

On July 1, 2010, ASN's *Journal of the American Society of Nephrology (JASN)* officially celebrated its 20th year of publication. Beginning in January of this year, the editors contributed editorials to *JASN* discussing the process of developing content and production procedures, the move to self-management, and more.

As part of ASN's commemoration of this special occasion, ASN's Executive Director Tod Ibrahim sat down with *JASN's* editors to discuss the launch of this important journal. We invite you to view this special conversation on videocast at www.asn-online.org. We also invite you to listen to the podcast produced in honor of *JASN's* anniversary. During this discussion *JASN* Editor-in-Chief Eric Neilson provides an editor's viewpoint on what makes a good paper, how to choose the right journal, and how to review scientific papers submitted for peer review.



JASN is the most highly ranked journal in the field of urology and nephrology. ASN leaders mark this anniversary with great appreciation for the work these editors have done overseeing the peer review process and for the vital contributions all *JASN* authors have made to the scientific literature.

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