New Biomarkers Offer Hope for Identifying Acute Kidney Injury Risk
By Eric Seaborg

A relatively new pair of biomarkers may give a valuable early signal of acute kidney injury (AKI), according to two papers, including a study that selected the pair from a competition with more than 300 potential candidates.

Only further research will determine their actual clinical utility, but the findings reflect an intense effort to bring some AKI biomarkers to market—with some experts expecting a test to be available in the U.S. sometime this year.

At least two assays are available in Europe, and researchers eagerly await data on their effectiveness.

AKI is very common among hospitalized patients and leads to increased mortality, with mortality rates ranging from 30 percent to 70 percent, and even higher among those requiring dialysis.

But the condition continues to vex clinicians because a lack of overt symptoms makes diagnosis difficult before the loss of organ function. Serum creatinine and urine output remain the leading AKI indicators, but they signal that damage may already be occurring.

Even the terminology illustrates the intensified interest in improving care and understanding of this condition. The term AKI replaced acute renal failure in recent years to recognize that the kidney undergoes a spectrum of impairment—and biomarkers could help identify the earliest stages.

“This is an effort to stratify patients to identify those who are at the highest risk, separating them from the patients that have a more baseline risk, so treatment resources can be deployed most effectively,” said John Kellum, MD, professor of critical care medicine at the University of Pittsburgh and corresponding author for both studies. “There is quite a lot of information on what you should do to try to mitigate the risk of acute kidney injury in patients, but it all begins with identifying patients at high risk.”

Kellum and colleagues published a paper last year in Critical Care describing a two-pronged discovery and validation study. The researchers started with more than 1000 potential markers that they narrowed down to about 340 candidates for closer study. They then conducted a continued on page 2

Studies Indicate that Biopsies Do Not Determine Suitability of Organs for Transplantation

Deceased-donor kidneys retrieved for transplantation are increasingly being discarded, and the most common reason given for discarding the kidneys is biopsy results. Two new studies published in the Clinical Journal of the American Society of Nephrology suggest that procurement biopsies are not predictive of posttransplant outcomes and may only serve to dissuade the use of kidneys that are otherwise suitable for transplant. The findings suggest that other methods are needed when weighing whether to transplant a deceased-donor kidney.

Biopsy-reported acute kidney injury and allograft outcomes

Given ever-increasing numbers of patients with end stage renal disease, the medical community has pushed to expand the deceased-donor organ supply. Unfortunately, a clear and consistent balance between organ acceptance and discard after procurement has been difficult to achieve given a lack of precise tools to assess donor kidney quality and prognosis.

“Kidney researchers are investigating newer, non-invasive tools to assess kidney tissue injury, but we need to fully

Continued on page 3
New Biomarkers

Continued from page 1

multicenter study of these 340 markers in more than 500 adults, including patients with sepsis, shock, major surgery, and trauma. This study found that the most effective test was for a combination of two markers, insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases-2 (TIMP-2).

Kellum told Kidney News that these two markers were somewhat of a surprise, but on further examination they made sense. Although they are involved in a variety of different pathways, they share one characteristic—they both induce G1 cell cycle arrest, which is considered a key and very early mechanism in AKI.

“[Cell cycle arrest] is one of the ways that epithelial cells attempt to protect themselves when they are under stress, and the two biomarkers together cover virtually every conceivable stress that an epithelial cell in the kidney might be exposed to,” Kellum said. In a second phase of this Critical Care study, the researchers enrolled 750 adults with critical illness and compared TIMP-2 and IGFBP7 with other known markers, including neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, kidney injury marker-1 (KIM-1), interleukin-18 (IL-18), and liver fatty acid-binding protein (L-FABP).

The primary endpoint was the development within 12 hours of sample collection of stage 2 or 3 AKI using Kidney Disease: Improving Global Outcomes (KDIGO) criteria. The TIMP-2/IGFBP-7 combination achieved an area under the receiver-operating characteristics curve (AUC) score of 0.80, whereas none of the other markers achieved an AUC value greater than 0.72.

A follow-up prospective, multicenter validation study of an immunoassay for the two markers, just published online in the American Journal of Respiratory and Critical Care Medicine, involved 420 critically ill patients. The study tested the ability of urinary TIMP-2/IGFBP7 at a predetermined cutoff to predict the development of moderate to severe AKI within 12 hours of sample collection. Three independent nephrologists judged whether the patients developed AKI. Patients whose levels exceeded the cutoff had seven times the risk of progressing to AKI compared with patients whose levels were below the cutoff. But in terms of specificity and absolute risk, only about 25 percent of those with levels above the cutoff progressed to AKI within 12 hours, compared with 4 percent of the patients with levels below the cutoff.

The study was funded by AstraMed (San Diego, CA) to gain performance data to submit to the U.S. Food and Drug Administration (FDA) on the company’s NephroCheck immunoassay. Whether the FDA will approve the test, and how long any decision might take, are of course open questions. The FDA accepted data in 2011 from BioPorto on a test for what is probably the most-studied AKI marker—NGAL—with apparently no word yet on any decision. Both the NGAL and the TIMP-2/IGFBP-7 tests are available as easily run immunoassays in Europe, and data on both are just beginning to trickle in.

Whatever the outcome of these applications, most specialists anticipate that ultimately a panel of biomarkers is likely to be more helpful than a single marker or test, according to Sarah Faubel, MD, associate professor of medicine at the University of Colorado, Denver, and chair of the American Society of Nephrology’s AKI Advisory Group.

Faubel said that although the studies by Kellum and colleagues were well-thought-out and examined an important and heterogeneous population, she was not ready to declare the new markers better than or likely to displace the other contenders. But they are likely to provide another potential tool.

She noted that the study was based on measuring the markers at a single point, within 15 hours of ICU admission, so “the question is, how does this integrate with other time points during the course of AKI, and how does it integrate with other biomarkers . . . [which could] perhaps identify different phases of AKI.”

Ravindra Mehta, MD, professor of clinical medicine in the division of nephrology at the University of California, San Diego, said that AKI markers fall into two categories, markers of normal function and markers of damage. The TIMP-2/IGFBP7 combination falls into the damage category, and they do seem to stand out in comparison to other markers with their ability to predict the progression to AKI. But he noted that a lot more experience is required before they are likely to be useful in a clinical sense, and whether they will perform outside the study, in clinical practice, is a question only time will answer.

Researchers and clinicians continue to advance the field of AKI, reaching consensus on defining the condition and establishing best practices for patient care. The best practices recognize the importance of early diagnosis and intervention, which in turn make biomarkers potentially so valuable. As these studies indicate, this quest continues to move forward. “The general anticipation in the community is that sometime in 2014 we will have access to some biomarker,” Mehta said.
Biopsies
Continued from page 1

understand the utility and limitations of our current gold-standard, invasive as-
sessment tool—kidney biopsy,” said Isaac Hall, MD, MS, of Yale University and the
Veterans Affairs Medical Center. He and Chirag Parikh, MD, PhD, led a team that
looked for associations between biopsy-reported acute kidney injury at the time of
organ procurement with subsequent kidney transplant outcomes.

“We were hoping to expand our knowledge about these associations and explain inconsistent findings in the medi-
cal literature by performing the largest multicenter study of its kind to date,” Hall
said.

Between March 2010 and April 2012, the researchers biopsied 651 kidneys (tak-
en from 360 donors through four organ procurement organizations) that were lat-	er transplanted into recipients. The team found that biopsy-reported kidney in-
jury was modestly associated with a delay in organ function in the first week after
transplantation, but only for a subgroup of donor kidneys already known to be at
high risk for this early outcome. The in-
vestigators also found that donor kidney
biopsies frequently underreported acute
kidney injury with substantial variability.

“Biopsies are listed as the primary rea-
sons for discarding deceased-donor kid-
neys; however, as they currently relate to
reported acute kidney injury, they provide
little utility for determining the overall
risk of delayed organ function or even
premature organ failure,” Parikh said.

The authors noted that additional
studies are needed to determine how bi-
opsey should affect patterns of organ ac-
ceptance or rejection and whether newer
methods might be better.

Biopsies of discarded kidneys vs. matched transplanted
kidneys

In another study, Bertram Kasikie, MD, of the Scientific Registry of Transplant
Recipients and Hennepin County (MN) Medical Center, and his colleagues com-
pared the results of biopsies from kidneys that were discarded with the results of bi-
opsey from comparable kidneys that were

The researchers compared biopsies of both kidneys from the same donor, when
one kidney was transplanted and the oth-
er was discarded. The analysis included bi-
opsey reports from 83 kidneys discarded in
2010 due to biopsy findings, 83 contralat-
eral transplanted kidneys from the same
donor, and 83 deceased donors randomly
matched to cases by donor risk profile.

“We found that there was a large de-
gree of overlap between the results of biopsies between kidneys discarded and
kidneys transplanted, which raised the question of whether these biopsies can
predict outcomes accurately enough to use in the decision to discard or transplant
a kidney,” Kasikie said. Also, a compar-
ison of two biopsies from the same kidney

often demonstrated significant differences.

The researchers also found that the
quality of the biopsies used in acceptance
decisions was low. The percentage of glo-
meruli that were scarred was most often
used to decide whether kidneys were dis-
carded or transplanted; however, this value
was highly variable, even in biopsies from the
same kidney.

Graft survival at 1 year was 80 percent
for kidneys contralateral to discarded kid-
neys. This compares with graft survival of
92 percent among all deceased-donor
transplants in the Scientific Registry of
Transplant Recipients. Therefore, many
patients may have benefited from kidneys
that were discarded. “If the discarded kid-
neys had been transplanted with the same
graft survival as the transplanted kidneys
from the opposite side, many patients may
have benefited,” Kasikie said. The results
question whether routine procurement
biopsies result in discarding kidneys that
could be acceptable for many of the pa-
ients who die waiting for a kidney trans-
plant.

“A reasonable conclusion from this and
other studies is that the widespread prac-
tice of routinely obtaining biopsies to aid
in deciding to accept or reject a kidney
for transplantation should be abandoned,
as has been successfully done in Europe,”
Kasikie said. “If abandoning this practice
is not acceptable in the U.S., then perhaps
additional studies could be designed to
more precisely determine the benefits and
harm of procurement biopsies.”

“Both of these studies highlight the
limitations of using biopsy results as the
sole criterion for turning down donor kid-
neys,” stated Sayeed Khan Malek, MD, of
Brigham and Women’s Hospital in an edi-
torial accompanying the two articles. He
also expressed concern that because of the intense scrutiny and regulatory oversight
of posttransplant outcomes, some low per-
forming centers adopt a risk-averse strat-
agy and refuse donor kidneys presumed
to be of high risk owing to poor biopsy
findings.

Malek noted that when biopsy findings
are consistent with the clinical evaluation
of the donor, they are useful in determin-
ing a kidney’s suitability for transplantation.
“However, biopsy findings when
considered in isolation are of limited value
and should be interpreted with caution
when making the decision to turn down
a potentially transplantable kidney,” he
wrote.
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- **Vascular Calcification:** Studies of the mechanisms, diagnostics, epidemiology, and clinical trials relating to vascular calcification. (1902)

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Please note that ALL abstract authors (including co-authors) must have current disclosures on file with ASN at time of submission.
Good Responses to Eculizumab in STEC-HUS

Patients in a French outbreak of hemolytic uremic syndrome (HUS) caused by Shiga toxin-secreting Escherichia coli (STEC) O104:H4 responded well to treatment with the anti-C5 monoclonal antibody eculizumab, according to a report in Nephrology Dialysis Transplantation. The 2011 outbreak was caused by contaminated organic fenugreek sprouts served at a community meal with 169 participants. Of 24 patients with STEC gastroenteritis, 9 experienced HUS, with hemolytic anemia, low platelet count, and renal complications. The patients included one child; HUS developed a median of 6 days after the initial symptoms of gastroenteritis.

Laboratory findings included a median platelet count of 26 g/L, hemoglobin 6.6 g/dL, lactate dehydrogenase 1520 IU/L, and creatinine 152 μmol/L. All HUS patients also had hepatic complications; the pancreas was involved in five patients, the brain in three, and the heart in three. Two patients were given dialysis and one received mechanical ventilation.

In the first three patients, plasma exchange failed to increase platelet count. These and all subsequent patients were treated with eculizumab, starting up to 4 days after the development of HUS. Anti-C5 therapy led to good outcomes in all patients, with rapid improvement in laboratory abnormalities. Renal function recovered gradually. There were no serious renal sequelae and no serious adverse effects of eculizumab.

Early eculizumab therapy yielded good outcomes in this limited outbreak of HUS caused by STEC O104:H4. Although no firm conclusions can be drawn about the efficacy of eculizumab, platelet count increased within 3 days after treatment and normalized within 7 days. All patients regained normal kidney function by 10 weeks’ follow-up [Delmas Y, et al. Outbreak of Escherichia coli O104:H4 haemolytic uremic syndrome in France: outcome with ecu- lizumab. Nephrol Dial Transpl 2014; 29:565–572].

High Rates of Excess Antibiotic Dosage Common in Elderly CKD Patients

Incorrect doses of antibiotics are “exceedingly common” in the outpatient care of older adults with chronic kidney disease (CKD), reports the American Journal of Kidney Diseases.

The researchers analyzed data on antibiotic prescriptions in southwestern Ontario, Canada. The analysis included 1464 patients aged 66 years or older with stage 4 or 5 CKD who were prescribed eight common oral antibiotics in January 2003, 2005, 2007, and 2009. Ambulatory laboratories in Ontario began reporting estimated GFR (eGFR) in 2006. The rates of excess dosing of antibiotics requiring dose adjustment in CKD were analyzed, with comparison of periods before and after eGFR reporting.

Overall, 66.3 percent of prescriptions were for doses higher than guideline-based recommendations. The rate of excessive antibiotic dosing was similar before and after the introduction of laboratory eGFR reporting; 64 and 68 per 100 antibiotic prescriptions, respectively. The study identified 169 prescriptions for nitrofurantoin, which is contraindicated in patients with CKD.

Two-thirds of oral antibiotic prescriptions for older adults with CKD may be at too high a dosage for the patient’s level of kidney function, the results suggest. The introduction of eGFR reporting by laboratories appears to have little or no effect on the rate of excess dosing. More research is needed to identify and address the patient, physician, and system factors responsible for this gap in care for CKD patients.
Patient Preparation Linked to Improved Survival in ESRD

A community kidney disease screening and education program improves patient preparation for ESRD, thus leading to increased survival, suggests a report in *Kidney International*.

The study included 595 adult patients who experienced ESRD after attending the National Kidney Foundation’s Kidney Early Evaluation Program (KEEP), a free, community-based program to identify patients at increased risk of kidney disease and to encourage follow-up care. These patients were matched for demographic and clinical characteristics with non-KEEP patients. The researchers hypothesized that KEEP patients would be better prepared for ESRD and that this would be associated with lower ESRD mortality.

Several aspects of ESRD preparation were better in the KEEP group. Significant differences (KEEP group versus non-KEEP group) included receiving a nephrologist’s care before the development of ESRD, 76.0 versus 69.3 percent; peritoneal dialysis, 10.3 versus 6.4 percent; preemptive waitlisting for transplantation, 24.2 versus 17.1 percent; and transplantation, 9.7 versus 6.4 percent. The rates of permanent vascular access were similar between groups: 23.4 versus 20.1 percent.

A median of 1.6 years after the onset of ESRD, there were 175 deaths in the KEEP group versus 1037 in the comparison group: hazard ratio 0.80. The association between KEEP participation and survival remained significant in a propensity score model but became nonsignificant after adjustment for indicators of ESRD preparation.

Suboptimal preparation for ESRD may contribute to high mortality in a patient’s first year of dialysis and to excess costs of ESRD care. This study finds that KEEP participants are better prepared for ESRD and that indicators of preparation are associated with better survival during dialysis. The results “highlight opportunities to improve pre-ESRD care by reaching patients outside of the traditional health-care setting,” the researchers write [Kurella Tamura M, et al. Educational programs improve the preparation for dialysis and survival of patients with chronic kidney disease. *Kidney Int* 2014; 85:686–692].

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**Warfarin Benefits Patients with Atrial Fibrillation and CKD**

Across the range of kidney function levels, warfarin therapy improves survival and reduces adverse events in patients with atrial fibrillation, reports a study in the *Journal of the American Medical Association*.

The researchers identified 24,317 Swedish patients with atrial fibrillation and a history of acute myocardial infarction. On the basis of serum creatinine levels, 51.7 percent of patients had CKD: estimated GFR (eGFR) less than 60 mL/min/1.73 m². At discharge, 21.8 percent of patients had a prescription for warfarin. Outcomes associated with warfarin therapy were analyzed for groups at different levels of kidney function.

At 1 year, rates of a composite outcome of death, myocardial infarction, or stroke were significantly lower among patients receiving warfarin. Adjusted hazard ratios among warfarin-treated patients were 0.73 at an eGFR of greater than 60 mL/min/1.73 m², 0.73 between 30 and 60 mL/min/1.73 m², 0.84 between 15 and 30 mL/min/1.73 m², and 0.57 at less than 15 mL/min/1.73 m². Continued on page 9

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Warfarin

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15 mL/min/1.73 m². Across kidney function groups, there was no warfarin-related increase in bleeding risk.

Warfarin therapy was also associated with a reduction in the combined rate of the primary composite outcome and the bleeding outcome. The adjusted hazard ratios were 0.76 at an eGFR of greater than 60 mL/min/1.73 m², 0.75 between 30 and 60 mL/min/1.73 m², 0.82 between 15 and 30 mL/min/1.73 m², and 0.55 at 15 mL/min/1.73 m² or less.

An increasing number of patients have concomitant CKD and atrial fibrillation. There are conflicting data on the benefits and safety of warfarin for patients with CKD; trials of anticoagulation therapy have excluded patients with reduced kidney function.

In this large Swedish cohort study, warfarin reduced the risk of death, myocardial infarction, or ischemic stroke in patients with concomitant atrial fibrillation and CKD without increasing bleeding risk. Benefits were noted at all levels of eGFR. Reduced kidney function is not a reason to deny warfarin therapy in patients with atrial fibrillation and established cardiovascular disease, the authors suggest [Carrero JJ, et al. Warfarin, kidney dysfunction, and outcomes following acute myocardial infarction in patients with atrial fibrillation. JAMA 2014; 311:919–928].

Small Increase in ESRD Risk for Living Kidney Donors

Living kidney donors have a small but significant increase in the risk of ESRD compared with similarly healthy nondonors, reports the Journal of the American Medical Association.

The study included all 96,217 adult living kidney donors in the United States between 1994 and 2011, identified from the Organ Procurement and Transplantation Network. They were matched with 20,024 healthy nondonors who were free of contraindications to kidney donation, drawn from the Third National Health and Nutrition Examination Survey. Through linkage to data from the Centers for Medicare & Medicaid Services, the researchers compared the cumulative incidence and lifetime risk of ESRD for living donors versus nondonor control individuals.

There were 99 cases of ESRD in living kidney donors at a mean follow-up time of 8.6 years, compared with 36 cases in nondonors at 10.7 years. The estimated 15-year ESRD risk was 30.8 per 10,000 person-years in the living donors versus 3.9 per 10,000 person-years in the nondonor control individuals.

The increase in ESRD risk among living kidney donors was significant for both black donors, 74.7 versus 23.9 per 10,000 person-years; and white donors, 22.7 versus 0.0 per 10,000 person-years. The lifetime risk of ESRD was approximately 90 per 10,000 living donors. This was substantially higher than the 14 per 10,000 rate in healthy nondonor control individuals, but it was lower than the general population rate of 326 per 10,000 unscreened nondonors.

Previous studies have reported no increase in ESRD risk after living kidney donation. However, these studies have used control individuals from the general population, who are at higher inherent risk of ESRD than rigorously screened donors.

The new study shows a small but significant increase in long-term ESRD risk among living kidney donors compared with similarly healthy nondonor control individuals. The researchers note that the risk of ESRD after living donation is still much lower than in the unscreened general population. They conclude, “These findings may help inform discussions with persons considering live kidney donation” [Muzzaale AD, et al. Risk of end-stage renal disease following live kidney donation. JAMA 2014; 311:579–586].

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What the President’s 2015 Budget Means for Kidney Research

By Grant Olan

President Barack Obama’s 2015 budget, released Tuesday, March 4, came and went without much notice outside the Washington, DC, beltway. The president’s annual budget, usually released in February, is an important public statement of what he believes national funding priorities should be and is generally used as a starting point for budget negotiations in Congress. However, it is unlikely Congress will adopt many of the president’s recommendations owing to the late date of the report’s release and that 2014 is an election year.

Let’s look at the numbers. For 2015, the president is recommending $30.4 billion for the National Institutes of Health (NIH), a slight increase of 0.7 percent over 2014. Of that amount, the president is recommending $1.743 billion for the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), a 0.05 percent decrease from 2014. The Agency for Healthcare Research and Quality (AHRQ) budget would also shrink. The president proposed $439.7 million for AHRQ, a decrease of 5.2 percent. The Department of Veterans Affairs (VA) medical research program would increase by 0.6 percent to $588.9 million.

“ASN is glad to see the president’s budget requests for NIH and VA research in 2015 heads in the right direction,” said John R. Sedor, MD, FASN, ASN secretary-treasurer and Research Advocacy Committee chair. “But at the same time we shouldn’t be cutting the National Institute of Diabetes and Digestive and Kidney Disease’s budget. More than 20 million Americans have kidney disease, costing Medicare, and ultimately taxpayers, nearly $77 billion every year for their care. Of that amount, less than 1 percent is invested in kidney research. We need more kidney research dollars for better preventions and therapies, not less.”

The president’s budget also includes $55.4 billion to support a new initiative—called the Opportunity, Growth, and Security Initiative—to boost funding in several areas, including infrastructure and research. Although it would provide another $970 million to NIH on top of the 0.7 percent increase in 2015, Congress would need to increase the federal budget caps for 2015 above the current spending limit levels.

That seems unlikely given that Congress already recently raised the budget caps for 2014 and 2015 to restore some of the funding cuts during those 2 years. As part of its deficit reduction efforts in 2011, Congress passed budget caps for fiscal years 2014 to 2021. ASN is an active member of several coalitions, including the Coalition for Health Funding, dedicated to raising awareness about the impact of those cuts and successfully helped secure the Bipartisan Budget Act that raised the spending caps in 2014 and 2015.

ASN is also implementing an aggressive new research advocacy plan to raise awareness about kidney disease and increase support for more kidney research. One of the society’s research advocacy priorities is a Government Accountability Office report to assess whether current federal investments in kidney research are adequate, and to identify the best strategies for reducing the burden of kidney disease. ASN is confident the report will help bolster another top ASN priority, asking Congress for an additional $1.5 billion ($150 million over 10 years) for kidney research funding.

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Abbreviations: AHRQ = Agency for Healthcare Research and Quality; NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases; NIH = National Institutes of Health; VA = Department of Veterans Affairs.
By Mark Lukaszewski

On January 6, 2014, the Centers for Medicare & Medicaid Services (CMS) Medicare Program proposed excluding immunosuppressive drugs from the six protected drug classes covered under Medicare Part D plans. Although ASN understands the impetus to control health care spending in hard economic times, any cost-cutting approach that also jeopardizes patient safety is not acceptable. In 2013 alone 16,893 patients received a kidney transplant and approximately 121,000 patients were waiting for a kidney, according to the United Network for Organ Sharing, ASN was concerned that the CMS proposed rule as written could put transplant recipients at risk for adverse side effects as a result of restrictions to immunosuppressive drugs.

Protecting access to immunosuppressive drugs

Because patient tolerance for immunosuppressive medications varies widely it is common practice for physicians to try a combination of therapies, knowing that the first drug administered often needs to be adjusted or substituted altogether. Therefore, to provide optimal treatment for transplant patients physicians need all U.S. Food and Drug Administration–approved immunosuppressive drugs at their disposal.

Congress understood that patients with complex conditions need access to a wide variety of medications, which is why Section 176 of the Medicare Improvements for Patients and Providers Act (MIPPA) was enacted in 2008. It established protection for immunosuppressive medications and five other classes of drugs—anticonvulsants, antineoplastics, antiretrovirals, antipsychotics, and antidepressants.

Since that time, there have been no scientifically justifiable reasons to eliminate protections for immunosuppressive drugs under Medicare Part D. This is why ASN was so determined to work with Congress, in conjunction with its comments to CMS, to ensure the choice of immunosuppressive treatments is made by physicians and their patients and not dictated by CMS.

Good news for Part D

Through hard work, along with the overwhelming support of the health care community and powerful letters from Congress, CMS fully understood that the proposed rule would negatively impact transplant patients’ access to appropriate care and could affect overall patient safety.

On March 10, 2014, CMS Administrator Marilyn Tavenner sent a letter to Congress announcing that the “proposals to lift the protected class definition on three drug classes, to set standards on Medicare Part D plans’ requirements to participate in preferred pharmacy networks, to reduce the number of Part D plans a sponsor may offer, and clarifications to the non-interference provisions” would not be finalized at this time. CMS recognized that patients who require these types of therapies need a comprehensive set of options because of the unique sensitivities each patient can have for individual therapies.

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New Drug Performs in Chronic Kidney Disease Clinical Trial

La Jolla Pharmaceutical Company announced on March 10 that its lead experimental drug, which treats chronic kidney disease, met its primary goal of improving kidney function as measured by blood filtering through the kidneys.

The results from the phase 2a study lent the company’s shares a 40 percent bump in trading upon the announcement, which reported results with two tested doses of the drug, known now as GCS-100.

The lower dose was more favorable than the higher. The lower amount of drug showed an increase in the rate of blood filtering, whereas the higher dose did not. The lower dose also reduced the levels of galectin-3, a protein associated with tissue scarring, which causes organ damage.

The higher dose did not show a statistically significant increase in either the rate of blood filtering or the decrease of galectin-3 levels in comparison with placebo. The researchers speculated that a higher dose of the drug might stop the production of galectin-3 so much and so effectively that the body might start producing the protein again, in a feedback loop effect.

The doses were well tolerated, with no adverse effects in the lower-dose group; side effects in the higher-dose group were not related to the drug, the company reported.

Reuters wrote that analysts were bullish on the results. “Even with a modest penetration, we estimate the drug could have more than $2 billion in peak sales in 2024, and that is a conservative estimate,” said Ling Wang of Chardan Capital Markets.

Before the company announced the results, Wedbush analyst Liana Moussatos gave an “outperform rating.” StreetInsider reported.

“GCS-100 is the lead drug candidate which reduces elevated galectin-3 associated with chronic kidney disease and nonalcoholic steatohepatitis (NASH)—both large market opportunities for which the standard-of-care can cause life-threatening side effects and/or has no approved therapies,” Moussatos said.

DaVita settles after federal investigation

DaVita, the second largest provider of dialysis services in the United States, has agreed to a framework for “a global resolution with government officials for both the 2010 and the 2011 U.S. Attorney Physician Relationship Investigations,” the company shared in its most recent financial report.

The company announced that the settlement will include the payment of approximately $389 million, an amount previously announced and put into reserve.

“We have agreed to unwind a limited subset of joint ventures that were created through partial divestment to nephrologists, and agreed not to enter into this type of partial divestiture joint venture with nephrologists in the future,” the statement read.

DaVita HealthCare Partners said it would pay to settle criminal and civil antikickback investigations.

Its joint ventures with kidney doctors involved 28 dialysis clinics.

The Denver Post reported that Kent Thiry, DaVita’s chief executive officer, said the exact settlement is being finalized.

The Post noted that Garry Menzel, DaVita’s chief financial officer, said the company “most likely” will buy out or sell 11 joint ventures it reached with kidney doctors at “fair market value.”

Overall, DaVita had a good year in 2013 and showed an improvement over year 2012 income earnings. Income for the quarter ended December 31, 2013, and the adjusted income for the year ended December 31, 2013, from continuing operations attributable to DaVita HealthCare Partners, Inc., were $212.3 million and $817.6 million, respectively.

Adjusted income from continuing operations attributable to DaVita HealthCare Partners, Inc., for the quarter and year ended December 31, 2012, was $173.8 million and $612.6 million, and that adjusted income excluded the loss contingency reserve and a different adjustment.

New rules proposed for use of off-label drugs and devices

The U.S. Food and Drug Administration (FDA) is revising, for the first time since 2009, its draft guidance on how to present and publish information about off-label use of a drug or device.

The FDA is recommending practices for drug or medical device manufacturers and their representatives to follow when distributing to health care professionals or health care entities “scientific and medical publications that discuss unapproved new uses of approved drugs or approved or cleared medical devices,” the FDA said in an advance copy of its Federal Register notice.

Bloomberg News reported that the guidance is that generally such publications are required to appear in journals, scientific or medical reference texts, and clinical practice guidelines. The draft guidance contains separate but related recommendations for those three types of publications.

The draft guidance recommends that the information have a “prominently displayed and permanently affixed statement that some of the uses for the drugs and/or devices being distributed might not have FDA approval or clearance.”

According to MedPage Today, a medical news website for health care professionals, the new rules would mean that information about off-label use must be peer reviewed; be published by an organization that has an editorial board that includes an independent expert; be distributed with approved labeling; be distributed separately from promotional information; include opposing views—when available—regarding the unapproved use; present a reprint that is unabridged.

The draft guidance on off-label use is open for public comment until May 2, 2014. Submit electronic comments to http://www.regulations.gov. Written comments may be submitted to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.
Technical Issues in Dialysis

By Alex R. Constantinescu, for the American Society of Nephrology Practicing Nephrologists Advisory Group

What are some of the most important challenges facing nephrologists in prescribing dialysis therapy for their patients?

Ever since dialysis therapy has proved to be lifesaving, we have been challenged to decrease the mortality and increase the safety of the procedure (1). Advances in technology have led to increasingly complex equipment, resulting in a steep learning curve for both clinicians and patients alike. Clinicians must evaluate whether the dialysis prescription is actually translating into adequate treatments, and constantly adjust the dose to meet the goals of the Kidney Disease Outcome Quality Initiative (2,3). In addition, we need to be assured that the assessment of dialysis outcomes is based on reliable data and adequate sampling of blood and solutions (4). Patients have to be proficient in certain basic skills for home therapies, both peritoneal dialysis (PD) and hemodialysis (HD), and they must be reassured that backup support is available around the clock at all times (5,6).

What are the most common technical issues encountered during dialysis therapy?

Despite efforts to minimize the risks and complications, we face many technical issues, some of which are difficult to overcome. Technical issues may be related first to patient characteristics and then, in short order, access problems, dialysis solutions, drug administration, equipment and operator problems, and other issues not yet well defined (Table 1).

Table 1. Common technical issues in dialysis

<table>
<thead>
<tr>
<th>Technical issues related to</th>
<th>Hemodialysis</th>
<th>Peritoneal dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anatomic variations, illness, or comorbidities</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Access, tubing, or both</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Poor needle placement, inadequate needle gauge, dislodgement</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Catheter occlusion, malfunction, migration, kinking, disconnection</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Solutions</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Inappropriate mixing, delivery, or contamination</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Mismatch with membrane characteristics, or contamination</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Medications: drug delivery system, clearance, other</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Equipment</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Incorrect dialyzer or blood tubing, blood pump problems, dialyzer rupture, dialyzer reaction, air embolism, ultrafiltration problems (controller inaccuracies)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Machine-pump issues: low fill, low drain</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Mechanical, electrical, or hardware/software failure, nuisance alarms, limitations of protective systems, other</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Operator issues</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Incorrect programming, incorrect collection or processing of sample, blood leak from ruptured dialyzer, clotted dialyzer</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Error in delivery of prescribed dose</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

How important is choosing a dialysis modality in minimizing the risk of complications?

Choosing a dialysis modality is one of our most challenging first steps (7,8). We are reminded time and again that each patient is unique, especially with respect to vascular anatomy (an important determining factor in longevity of HD access). Not only is vessel caliber a major issue in HD (a real challenge in the smallest of our patients), but also comorbid conditions (i.e., obesity, diabetes, vasculitides) can create technical difficulties from the start. The same holds true for PD in patients with prior abdominal surgical procedures, malnutrition, obesity, or extreme prematurity in infants, to name a few. For patients contemplating home dialysis therapies, those with back pain, arthritis, or amputation may not be able to cannulate vessels, perform connections, or open packages or medication bottles. In essence, they may not be capable of performing their own treatment.

How can dialysis solutions affect the outcome of dialysis therapy?

Regarding solutions, the composition is constantly optimized to ensure minimal disruption of the metabolic homeostasis, maximal removal of uremic toxins, and ultrafiltration capabilities. Nevertheless, temperature of the dialysate, conductivity, osmotic pressure, buffer capacity, and electrolyte and dextrose concentrations in both HD and PD solutions are a few of the factors that can affect the success of the dialysis treatment in the short or long term.

Given that drug metabolism is affected by dialysis, what can be done to improve the safety of drug treatment in patients receiving dialysis?

Drug administration can be challenging with regard to bioavailability and clearance, especially with respect to the mode of delivery in patients with limited access. Many new drugs have yet to be studied in the dialysis population (with regard to age, body size, dialysis modality, dialyzer size, and clearance) to ensure their safety and their maximal therapeutic effects. Elimination of medication errors and avoidance of patient complications must remain a central focus of our practice (9).
What are the most common equipment and operator issues encountered during dialysis therapy?

Programming the treatments into the automated cycler (for PD) or the HD or continuous renal replacement therapy machines has to be made by specialized personnel, requires training, and is still subject to the human factor and to mechanical, electrical, or hardware-software failures. In addition, water treatment systems—reverse osmosis and carbon tanks being the most common—need to be installed when some home HD therapies are desired, and backup plans are needed to anticipate power failure or mechanical failure. Troubleshooting and backup plans are essential in bridging these difficult situations. Architectural alterations and infrastructure setup need to be evaluated and agreed upon before the initiation of home HD. A few attached references deal with these issues in detail (6,7,10).

What are the most common technical issues encountered during dialysis therapy based on the modality chosen?

Table 1 depicts a few important technical issues in both HD and PD. These issues have a significant impact on the adequacy of the dialysis dose prescribed, and the problems shown in Table 1 need to be rectified to improve outcomes. The more we learn about the complexity of our patients, the more we realize that there are newer obstacles to overcome. Research and innovations will continue to help pave the way to safer patient care.

Alex R. Constantinescu, MD, is medical director of the Pediatric Nephrology and Hypertension Program at Joe DiMaggio Children’s Hospital in Hollywood, FL.

References
ASN Releases Benchmarks for Home Dialysis Training

By Kurtis Pivot

The American Society of Nephrology (ASN) has developed the first benchmarks for training nephrology fellows in home dialysis modalities. The need for these guidelines was identified at the 2012 National Summit on Home Dialysis Policy, where stakeholders recognized inadequate training as a key barrier to utilization of home-centered therapies. These competencies will serve as a roadmap for nephrology training programs to prepare fellows to care for the growing number of patients selecting the home treatment setting.

A gradual shift to the home setting

In 2011, the most recent year for which data was available, 9.6 percent of patients (37,219) with end stage renal disease (ESRD) in the United States chose to dialyze at home. The majority (85 percent) used peritoneal dialysis (PD) (either continuous ambulatory PD or continuous cycling PD) and the remaining 15 percent utilized home hemodialysis. Regardless of modality, the percentage of patients opting for in-home treatment has gradually increased over the past 5 years by 26 percent.

“The Centers for Medicare & Medicaid Services (CMS) has long tried to incentivize a greater use of home dialysis,” said Rajnish Mehrotra, MD, FASN, of the University of Washington School of Medicine. “It is an clinically effective as in-center hemodialysis, offers patients more control over their lives and schedules, and is significantly less expensive (more for PD than for home hemodialysis).

With the implementation of the expanded bundle (the ESRD prospective payment system [PPS]), CMS expanded financial incentives for home dialysis by offering identical payments to providers of dialysis services for patients treated either in-center or at home, he said. “This spurred a rapid growth in programs for patient and physician education and is changing patterns of care delivery, with more late-referred patients being considered for—and offered—PD than ever before.”

Yet several factors could potentially deter patients from opting for home dialysis. “For many patients isolation is not an incentive to choose a home dialysis setting because they live in close proximity to an in-center facility,” said Nancy Day Adams, MD, of the University of Connecticut School of Medicine. “Patients must have other reasons to determine and encourage their motivations.” Financial circumstances may also be a disincentive for in-home treatment.

Finally, patients may not have access to providers familiar with home dialysis. Adams noted that practicing nephrologists who did not experience much home dialysis during their fellowship may not feel confident in handling some situations that can arise in this setting. Participants at the Home Dialysis Summit also determined that inadequate training of nephrology fellows in home dialysis delivery inhibited greater home dialysis use in the United States. The summit, organized by the Alliance for Home Dialysis, brought patient groups, health professional societies, academic medical centers, government, and dialysis organizations together to collaborate on ways to improve utilization of home dialysis and develop a framework for the optimal training of patients with ESRD.

And although fellows may be exposed to PD during their training, fewer gain experience with home hemodialysis. A recent survey of 135 nephrology trainees found 60 percent reported that they had little or no training in home hemodialysis and more than 40 percent reported that they had some training in PD but did not feel they were competent (1). “This is in part because most programs neither have access to sufficient patients to ensure adequate training nor are they able to assign enough training time to ensure this competency,” said Mehrotra.

Identifying competencies for in-home treatment

Mehrotra, who attended the summit, noted “ASN took up the challenge and decided to develop standards for training of fellows to ensure competency in the care of home dialysis patients as a resource for training program directors.” A workgroup composed of members of the ASN Dialysis Advisory Group (DAG) (chaired by Mehrotra), Training Program Directors (TPD) Executive Committee (chaired by Adams), together with home dialysis experts and fellows in training, drafted a list of benchmarks designed to give nephrology trainees a competency-based background in home dialysis methods. After a full review by the DAG and TPD and Education Committees, the final benchmarks were presented to ASN Council in October 2013.

The benchmarks are comprehensive and contain two important components (see box for a sample of the competencies).

First, they identify areas for training under each of the six core competencies identified to be important by the Accreditation Council for Graduate Medical Education (ACGME) (medical knowledge, patient care, system-based practice, professionalism, practice-based learning and improvement, and interpersonal and communication skills) for both PD and home hemodialysis. Second, they offer suggestions on how best to structure the clinical training of fellows to ensure sufficient experience in the care of such patients to achieve clinical competency in delivering that care. Both these components are equally important and meant to be a resource for training program directors. The benchmarks also fit within the competency-based milestones being implemented in nephrology and 20 other medical subspecialties beginning this July. “While ACGME Milestones are general in patient care and medical knowledge, these benchmarks address the medical knowledge aspects of home dialysis modalities and the actual care of patients on home dialysis,” said Adams.

However, as the authors point out, the new standards outline the optimal training in PD and home hemodialysis and several of the goals are aspirational. With an increasing number of patients on home therapies, and as more programs introduce more home programs, it will be easier for all fellows to get adequate experience, Adams noted.

“Even in a robust home program it can be difficult to incorporate the fellow into the practical patient interactions. Home patients are independent, which is why they chose home dialysis, and a lack of flexibility in the fellow’s training schedule can make follow-up evaluations with these patients hard to integrate,” said Adams. The practical experience with home dialysis patients is important to preparing fellows for unsupervised practice, she said. “They can do all the reading they can and may have a lot of medical knowledge, but if they haven’t seen patients they won’t be ready.”

To view the complete list of home dialysis training benchmarks, please visit: http://www.asn-online.org/education/training/tdp/PD_and_HHD_benchmarks.pdf.

Selected ASN Home Dialysis Benchmarks

Fellows must demonstrate knowledge and competency in the following areas:

Peritoneal Dialysis

- Medical Knowledge
- The structure and function of the peritoneal membrane, including ultrafiltration, reabsorption, and solute transport characteristics
- Patient Care
- Providing education and support to advanced CKD patients about various dialysis modalities, including PD

Home Hemodialysis

- Medical Knowledge
- The different hemodialysis platforms available for HHD, how the platforms differ and their implications for HHD prescription (such as frequency and duration of a treatment)
- Patient Care
- Diagnostic and laboratory testing in the evaluation and management of HHD patients

Home Dialysis (Combined Competencies)

- System-Based Practice
- Participate in the application of treatment algorithms and protocols for management of common clinical issues in the care of home dialysis patients
- Practice-Based Learning and Improvement
- Utilize support tools to improve patient care (such as dialysis adequacy and volume management), access guidelines, and gain pharmacologic information at the point of care
- Professionalism
- Exhibit sensitivity to patient preferences and adjust dialysis prescription to fit the patient’s lifestyle
- Interpersonal and Communication Skills
- Discuss with the patient lifestyle needs and expectations from home dialysis in order to ensure adherence and satisfaction with modality

CKD = chronic kidney disease; HHD = home hemodialysis; PD = peritoneal dialysis.
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AVF

AVG

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References:

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