ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Kidney News

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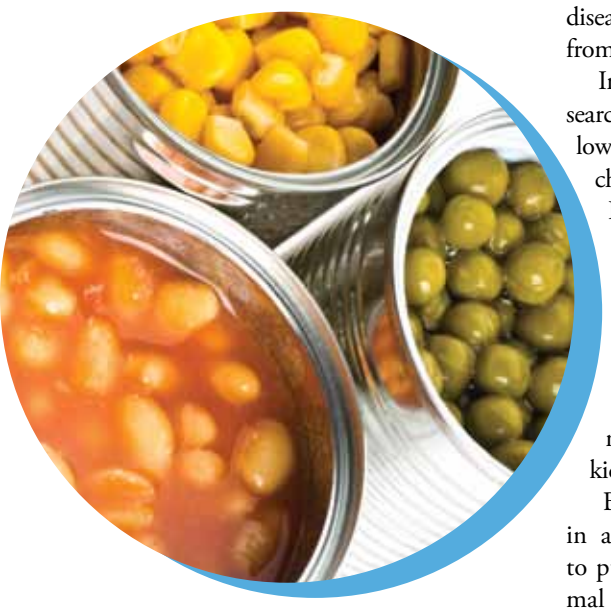
Ongoing Research Links Bisphenol A with Negative Health Effects

By Tracy Hampton



Recent studies add growing evidence to the potential dangers of exposure to bisphenol A (BPA). The estrogen-like chemical may be linked to diabetes in adults and to heart and kidney disease in children. Still, the risks are far from clear.

In some of the most recent work, researchers found a link between BPA and low-grade urinary albumin excretion in children and adolescents (Trasande L, et al. *Kidney Int* 2013 Jan 9. doi: 10.1038/ki.2012.422). The findings suggest that youngsters who are exposed to BPA, which was once used widely in plastic bottles and is still found in aluminum cans and register receipts, may have an increased risk for the development of heart and kidney disease.

BPA may negatively affect health in a variety of other ways, according to published and ongoing studies. Animal research has linked BPA with early sexual maturation, altered behavior, hyperactivity, and effects on prostate and mammary glands. In humans, the chemical has been linked to cardiovascular disease, diabetes, and male sexual dysfunction (Schecter A, et al. *Environ Sci Technol* 2010; 44:9425–9430. doi: 10.1021/es102785d).

BPA, disease, and obesity

The latest study by Trasande et al. involved an analysis of data from 710 children and adolescents who participated in the 2009–2010 National Health and Nutrition Examination Survey, which included measurements of urinary BPA and albumin. Compared with children with the lowest amount of BPA in their urine, children with the highest amount had an albumin-to-creatinine ratio that was 0.91 mg/g higher.

The findings may be particularly worrisome for children with poor kidney function.

"While we excluded children with preexisting kidney disease from our analysis, I am concerned that BPA exposure may have even greater effects on children with kidney disease," said co–lead author Howard

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Ultrasound of Lung Congestion Could Signal ESRD Outcomes

By Eric Seaborg

Pulmonary congestion, even in patients without symptoms of heart failure, could be an important predictor of mortality and cardiovascular risks in hemodialysis patients, a new study shows.

In the multicenter study reported in the *Journal of the American Society of Nephrology*, researchers who used ultrasound (US) to categorize patients' levels of extravascular lung water found that patients with very severe congestion had a four times greater risk of death and a three times greater of cardiac events than patients with mild or no congestion.

"This article is very significant because it points out the relationship between volume overload and mortality and cardiovascular events," said Rajiv Agarwal, MD, professor of medicine at the Indiana University School of Medicine, noting that the study did not address causality. "They are simply describing an association between a finding of lung congestion and important outcomes for the patients."

Led by Carmine Zoccali, MD, of Riuniti Hospitals in Reggio Calabria, Italy, a research team studied 392 Caucasian patients from 11 dialysis units in southern Italy. They classified the subjects according to the New York

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Inside

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ESRD Outcomes

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Heart Association (NYHA) scale for heart failure. Using ultrasound examinations performed prior to dialysis, the researchers categorized patients' lung congestion according to the number of "lung comets" or sonographic B-lines found: mild (5 to 15 B-lines), moderate to severe (15 to 60 B-lines) and very severe (more than 60 B-lines). They followed the patients for a median time of 2.1 years to monitor for the study end points of mortality and cardiac events.

"We found that lung ultrasound adds significant prognostic information for death and cardiovascular event to classic risk factors, the NYHA score, and powerful risk factors in [chronic kidney disease] patients, like hypoalbuminemia, hyperphosphatemia, and inflammation," the researchers wrote in "Pulmonary Congestion Predicts Cardiac Events and Mortality in ESRD." "The degree of lung congestion measured by lung ultrasound was a better predictor of the risk of death and cardiac events than symptoms of heart failure as assessed by the NYHA score and provided additional independent information . . . over and above classic risk factors." Plugging the lung congestion estimates into a prediction model based on these other risk factors improved the model's prediction of cardiac events by 10 percent.

B-lines are "probably" good indicators of pulmonary congestion, said Elke Platz, MD, an assistant professor at Harvard Medical School and lead author of a study in the *European Journal of Heart Failure* that demonstrated that B-lines measured by ultrasound are associated with cardiac and pulmonary pressures measured by invasive means.

"We know that B-lines can be detected in acute decompensated heart failure and in patients with ESRD prior to dialysis," Platz told *ASN Kidney News*. "We also know from other studies that in both of these patient populations, the number of B-lines decreases with removal of fluid. What we don't really know is what generates these B-lines, which are essentially sonographic 'reverberation artifacts'."

Agarwal agreed with the authors' assertion of lung congestion as a proxy for general fluid overload, which the authors called "a common modifiable risk factor for the exceedingly high death risk of patients with kidney failure on dialysis."

But W. Charles O'Neill, MD, professor of medicine and director of ultrasonography in the renal division at Emory University School of Medicine in Atlanta, found the study less persuasive: "It's an interesting finding, but I'm not convinced that it is actually an indicator of interstitial lung water. I think what they are probably looking at is air bubbles within the alveolar fluid, in other words, pulmonary edema, which is in a sense lung water, but it's not interstitial water."

The researchers found very severe congestion in 14 percent of patients, and these patients were at highest risk of mortality and cardiac events. Some 45 percent of patients had moderate to severe congestion, but 71 percent of these patients were asymptomatic or had only slight symptoms of heart failure. Despite their lack of symptoms, they were still at slightly higher risk of mortality and cardiac events compared with patients with mild congestion.

The researchers have previously published studies showing an association of increased lung congestion with problematic symptoms such as increased pulmonary pressure and left atrial volume. They suggest that the use of ultrasound to detect congestion at a preclinical stage could help prevent cardiac events and other problems.

Agarwal said that a reliable measure of fluid accumulation would have great clinical value because it would alert caregivers to the need to reduce fluid volume during dialysis. Fluid accumulation often goes unnoticed despite the possible approaches to measuring it, including relative plasma volume monitoring, physical examination, body impedance analysis, and echocardiographic techniques such as left atrial volume. But Agarwal noted there is no standard reference method, nor have there been studies to show whether any of these methods can improve patient outcomes.

In their paper, Zocalli and colleagues acknowledge that the development of such a biomarker for clinical practice requires significant evidence, including data from clinical trials. But a trial to begin the process, designed and funded by the European Renal Association-European Dialysis Transplantation Association, was launched in September 2012. The LUST study, which stands for Lung Water by Ultrasound-Guided Treatment to Prevent Death and Cardiovascular Complications in High-Risk ESRD Patients with Cardiomyopathy, will test whether a treatment protocol can deliver results. Given this innovation's potential impact on improving patient care, many nephrologists will undoubtedly be eagerly awaiting the results.

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Bisphenol A

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Trachtman, MD, of New York University School of Medicine. "Because their kidneys are already working harder to compensate and have limited functional reserve, they may be more susceptible to the adverse effects of environmental toxins. We clearly need further study of BPA exposure and its effects on the kidney both in healthy children and in children who have preexisting kidney disease."

Trachtman and his colleagues noted that the link they found between BPA and low-grade albuminuria is consistent with previous results found in Chinese adults. They said the link supports efforts to prevent harmful exposure to the chemical.

"While our cross-sectional study cannot definitively confirm that BPA contributes to heart disease or kidney dysfunction in children, together with our previous study of BPA and obesity, this new data adds to already existing concerns about BPA as a contributor to cardiovascular risk in children and adolescents," said co–lead author Leonardo Trasande, MD, MPP, also of New York University School of Medicine.

Trasande is referring to a study published last year in the *Journal of the American Medical Association* that included almost 3000 children and adolescents aged 6 to 19 years (Trasande L, et al. *JAMA* 2012; 308:1113–1121). The study found that 22.3 percent of children and adolescents with the highest levels of BPA in their urine were obese, compared with slightly more than 10 percent of children and adolescents with the lowest levels of BPA. That translates to 2.6 higher odds of obesity in the highest BPA group compared with the lowest BPA group. Previous research has also shown that elevated urinary BPA concentrations are associated with obesity and incident coronary artery disease in adults.

Evidence from animal studies

As these and other studies continue to find correlations between BPA and negative health outcomes or increased risks of disease, studies in animals are generating a wealth of additional, sometimes conflicting, data.

For example, mouse studies by Randy Jirtle, PhD, of the University of Wisconsin-Madison, have revealed that exposure to BPA in the womb results in the *agouti* gene being inappropriately expressed, leading to offspring that have a yellow coat color and that are more susceptible to obesity and type 2 diabetes than are mice with darker fur. The researchers found that BPA did so by affecting the methylation of DNA, an epigenetic change that does not involve alterations in the DNA sequence.

A recent 3-year study using more than 2800 mice did not find that BPA results in more offspring with yellow coat color and a corresponding risk for adult diseases (Rosenfeld CS, et al. *Proc Natl Acad Sci USA* 2013; 110:537–542). Senior author Cheryl Rosenfeld, PhD, of the University of Missouri, noted that her team's findings say nothing about the positive or negative effects of BPA. (Previous studies in her laboratory indicated that developmental exposure to BPA can disrupt adult behaviors and compromise cognitive abilities in mice.)

According to Jirtle, Rosenfeld's group classified offspring into fewer categories of coat color and bred the females multiple times, which could have decreased the sensitivity of the assay and masked the hypomethylating effects of BPA.

"Also, the mechanism by which coat color changes is epigenetics, which they did not measure," Jirtle said. "Coat color isn't the real issue here—it's epigenetics. They said they could not replicate our findings, but they also did not replicate our studies."

The effects of high-dose BPA seen in Jirtle's studies have been reproduced in another study from the laboratory of Dana Dolinoy, PhD, of the University of Michigan School of Public Health, which also found that there seems to be a clear dose–response curve for BPA, with low doses being less effective at hypomethylating, and possibly leading to an opposite, hypermethylating effect (Anderson OS, et al. *Environ Mol Mutagen* 2012; 53:334–342).

Dolinoy and her team are currently investigating environmental epigenetics and gene–environment interactions using animal models, human clinical samples, and human population studies. One recent study of human fetal liver samples showed that there was considerable exposure to BPA during pregnancy (Nahar MS, et al. *J Biochem Mol Toxicol* 2012 Dec 3. doi: 10.1002/jbt.21459) and that BPA in fetuses was in a form not eliminated from the body, unlike previous studies showing that adult humans can metabolize the chemical and rid their bodies of it. The researchers recently found that female mice exposed to BPA through their mother's

diet during gestation and lactation became hyperactive as adults, also exhibiting spontaneous activity and having leaner body mass than mice not exposed to the chemical (Anderson OS, et al. *FASEB J* 2013 Jan 23. [Epub ahead of print]).

Dolinoy's laboratory is conducting ongoing research that builds on epidemiologic and exposure studies in the United States, Mexico, and Egypt. The aim is to characterize perinatal and peripubertal exposure to BPA and to determine how such exposure affects the epigenome.

"There are several things we need to look at in evaluating studies that look at BPA's effects on health, such as timing of exposure, levels of exposure, and toxicant–diet interactions," Dolinoy said. "In combining animal studies with human cohorts and focusing on developmental exposures and later-in-life health risks, such as obesity, we are evaluating epigenetics as the mechanism linking these two disparate periods of life."

Extent of BPA exposure

Experts agree that it is important to continue to study the effects of exposure to BPA and to monitor the extent of exposure to humans and the environment.

A 2010 study investigated the levels of BPA in fresh food, canned food, and food in plastic packaging in the United States (Schecter A, et al. *Environ Sci Technol* 2010; 44:9425–9423). The researchers detected BPA in 63 of 105 samples, including fresh turkey, canned green beans, and canned infant formula. BPA levels were higher in foods with a pH of 5 than in more acidic and alkaline foods.

Another source of BPA exposure lies in the thermal receipts generated at stores and automatic teller machines, for which it is used as a color developer. One study found that the estrogenic properties of thermal paper could be effectively removed through incubation with partially purified laccase from newly isolated ascomycete fungi (Divya LM, et al. *Appl Biochem Biotechnol* 2013 Jan 10. [Epub ahead of print]). Such treatment could potentially lower public exposure to BPA if it is adopted by industry.

With such a widespread presence of BPA, however, it may be difficult to avoid the chemical. Only increased attention and investigation can help reveal the true health effects of BPA and ultimately spur efforts and policies to reduce exposure.

Journal View

Rituximab Benefits Adults with Steroid-Dependent Nephrotic Syndrome

Rituximab is a safe and effective treatment for adult patients with steroid-dependent minimal change disease, reports a study in *Kidney International*.

The study included 17 adults receiving the anti-CD20 monoclonal antibody rituximab for steroid-dependent (15 patients) or frequently relapsing (two patients) minimal change nephrotic syndrome. Patients were treated at two French nephrology departments between 2002 and 2011. Rituximab therapy was started after the patients failed to respond to immunosuppressive darugs. Mean follow-up was 29.5 months.

Eleven patients had no further relapses a mean of 26.7 months after rituximab infusion. Of these, nine patients were able to stop steroids and other immunosuppressive medications during follow-up. The remaining six patients had at least one relapse after a mean of 11.9 months. However, all were able to stop or substantially reduce their use of immunosuppressive drugs during this time (mean follow-up 34.5 months). There were no adverse events associated with rituximab therapy.

Patients with steroid-dependent nephrotic syndrome may need long-term treatment with multiple drugs, placing them at risk for drug toxicity and renal failure. Studies in children with steroid-

dependent nephrotic syndrome have shown that rituximab can reduce steroid dosage and immunosuppressive drug requirements.

This French experience finds that anti-CD20 therapy with rituximab is "efficient and safe" for adult patients with severe steroid-dependent minimal change disease. Randomized trials are needed to confirm the results and to assess the value of preventive rituximab reinfusion after the reappearance of CD19 cells—which often precedes relapse [Munyentwali H, et al: Rituximab is an efficient and safe treatment in adults with steroid-dependent minimal change disease. *Kidney Int* 2013; 83: 511–516].

Mortality Links to eGFR and Albuminuria Are Stronger in Women

Lower eGFR and higher albuminuria carry increased risks of death and renal failure in both sexes, but the magnitude of the associations is greater in women, reports a study in the *British Medical Journal*.

The meta-analysis by the Chronic Kidney Disease Prognosis Consortium used data on more than 2 million members of 46 cohorts. The data included nearly 1.9 million participants from general population cohorts, plus approximately 150,000 participants from high-risk cohorts and 37,000 from CKD cohorts. In addition

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Journal View

Mortality Links

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to deaths or ESRD events, the studies included information on eGFR and urinary albumin-creatinine ratio.

In all eGFR and albumin-creatinine strata, all-cause and cardiovascular mortality were higher in men than women. For both sexes, lower eGFR and higher albumin-creatinine ratio were associated with a higher risk of death.

However, the slope of the associations for mortality was steeper for women. At an eGFR of 45 mL/min/1.73 m^2, adjusted hazard ratios (HRs) for all-cause mortality were 1.32 in women versus 1.22 for men (compared to eGFR of 95). At a urinary albumin-creatinine ratio of 30 mg/g, HRs were 1.69 for women and 1.43 for men (compared to a ratio of 5). The interactions by sex were significant for mortality; there was no such pattern for ESRD.

It has been unclear whether the adverse outcome risks associated with eGFR and albuminuria in CKD are modified by sex. This large meta-analysis confirms that lower eGFR and higher albuminuria increase the risk of death for both sexes.

However, the slopes of the associations with eGFR and albumin-creatinine ratio are steeper for women. Especially given the lower incidence of starting dialysis in women, the researchers write, "Low estimated glomerular filtration rate or albuminuria should be considered at least as potent a risk factor in women as it is in men" [Nitsch D, et al: Associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex: a meta-analysis. *BMJ* 2013; 346: f324].

Meta-Analysis Questions Benefits of Dual RAS Blockade

Dual renin-angiotensin system (RAS) blockade with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers improves some surrogate outcomes, but does not reduce mortality and may increase the risk of renal failure and other adverse outcomes, concludes a report in the *British Medical Journal*.

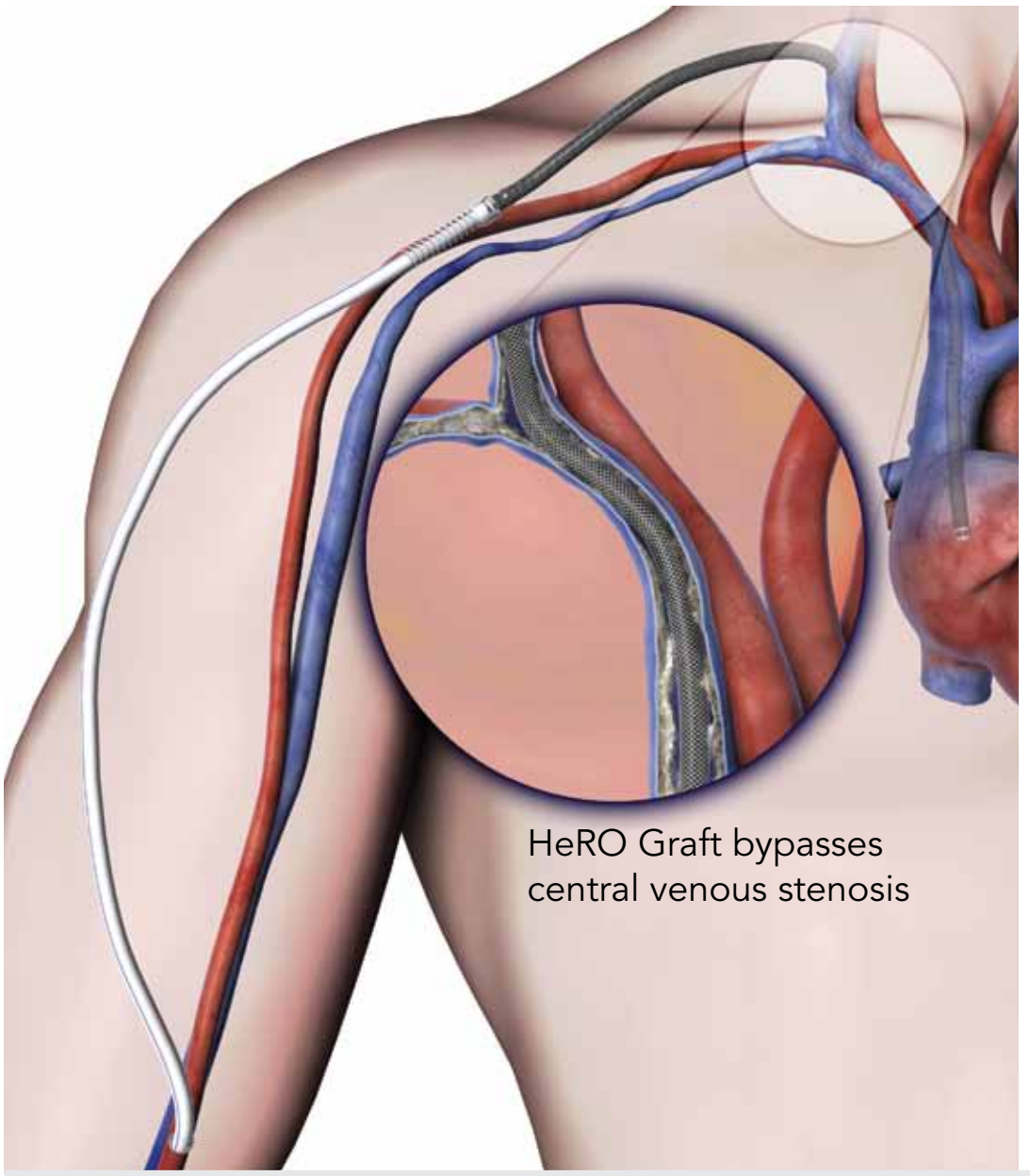
The researchers performed a meta-analysis of data on 68,405 patients from 33 randomized trials of dual versus single RAS blocker therapy. Mortality and adverse events were assessed, with stratification of studies that did and did not include patients with heart failure.

The analysis found no reduction in mortality with dual RAS blockade. All-cause mortality was 15.3 percent with dual therapy and 15.0 percent with monotherapy. Cardiovascular mortality was 14.7 percent and 15.7 percent, respectively. The rate of hospitalization for heart failure was 10.9 percent with dual therapy versus 10.3 percent with monotherapy (risk ratio 0.82). Several adverse events were more frequent with dual RAS blockade, including hyperkalemia and hypotension—risk ratios 1.55 and 1.66, respectively.

Dual blockade was also associated with a higher rate of renal failure: 8.3 percent versus 6.4 percent, (risk ratio 1.41). Most outcomes were similar in study cohorts with and without heart failure. The exceptions were higher all-cause mortality in cohorts without heart failure and a higher risk of kidney failure in those with heart failure.

Despite a lack of long-term safety and efficacy data, dual RAS blockade is widely used in certain groups, including patients with hypertension and diabetes and/or proteinuria. The new meta-analysis questions this practice, showing no reduction in mortality with dual blockade versus monotherapy.

Dual RAS blockade is also associated with higher rates of certain adverse outcomes, including a 41 percent increase in renal failure. The investigators conclude, "The overall risk to benefit ratio argues against the use of dual therapy" [Makani H, et al: Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials. *BMJ* 2013; 346:f360].



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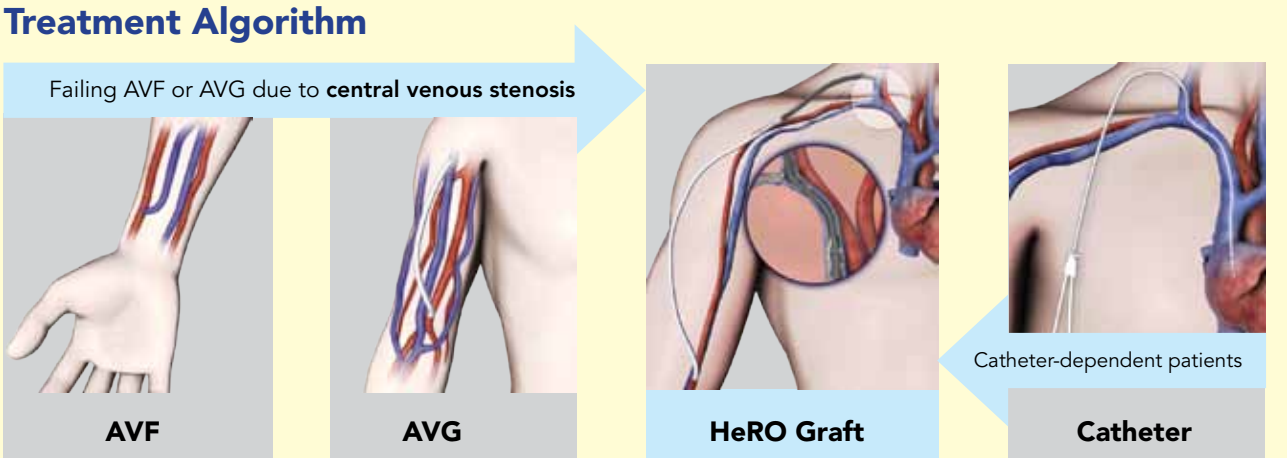

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KDIGO: Whence and Whereto?

By Edgar V. Lerma

In 1995, the National Kidney Foundation spearheaded the development of the first broadly accepted clinical practice guidelines in nephrology, the Kidney Disease Outcomes Quality Initiative (KDOQI).

First published in 1997, these "guidelines" made a significant impact in the quality of care for kidney patients in the United States and across the world.

In 2002, leaders of NKF and KDOQI asked prominent nephrologists from around the world regarding their opinion on the need for a global organization to bring the world's nephrology community more closely together in regard to practice guidelines. This interest in promoting guideline development and implementation subsequently expanded globally and internationally with the establishment of the Kidney Disease: Improving Global Outcomes (KDIGO) in 2003.

The hyperlink below gives a more detailed description of how and why KDIGO was created.

http://www.nature.com/ki/journal/v66/n4/full/4496003a.html

The year 2013 marks the 10th anniversary of KDIGO. In this issue, we invited prominent nephrologists who were part of the team that developed these guidelines to give us the highlights of the currently published Clinical Practice Guidelines.

We also asked two nephrologists, both of whom are actively involved in the clinical and private practice aspects of the specialty, about their insights on the development of these guidelines and their practicality. They give us their interesting perspectives from differing geographic locales.

Edgar V. Lerma, MD, FACP, FASN, is Clinical Professor of Medicine, Section of Nephrology, University of Illinois at Chicago College of Medicine, and is affiliated with Associates in Nephrology, SC Chicago, IL. Dr. Lerma is a member of the ASN Kidney News *editorial advisory board.*

Kidney-Sparing Therapy Requires Assessment of Risk

By John A. Kellum

The authors of the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for acute kidney injury (1) are often asked two important questions: "Who is the guideline for?" and "Is acute kidney injury (AKI) preventable?"

My answer to the first question is that the guideline is for physicians to aid them in the treatment of patients—but which patients and, for that matter, which physicians? These are fair points, and the KDIGO AKI Work Group spent some time debating them. In the end we decided that the guideline was meant for "front-line" physicians, not just for subspecialists. Indeed, when it comes to prevention and early management of AKI, the physicians who matter most are not necessarily the AKI experts but rather physicians primarily responsible for these patients, whether on the wards, in emergency departments, in operating rooms, or in intensive care units (2).

With regard to the second question, the patients most likely to benefit from the KDIGO guideline include patients who have not received diagnoses of AKI. Why? Because some of the best therapies we have for AKI are actually not therapies at all—they are kidney-sparing interventions like avoiding nephrotoxins and optimizing fluids. This introduces the concept of risk assessment for AKI. Patients are at high risk for AKI when they have one or more susceptibilities (e.g., advanced age, chronic kidney disease (CKD), or critical illness), one or more exposures (e.g., sepsis, hemorrhagic shock, or nephrotoxin exposure), or a combination of these. As with all diseases, the risk for AKI is greatest in susceptible populations who have been exposed to various etiologic factors. AKI does not arise without an exposure, even in highly susceptible patients, but it may occur even in those with low susceptibility if the exposure is great. Conversely, even a small exposure may be enough in a highly susceptible patient. For example, a young trauma patient may have been exposed to prolonged hemorrhagic shock, intravenous contrast medium, and resuscitation with hydroxyethyl starch but never manifest AKI. By contrast, an elderly patient with diabetes and CKD may experience AKI with exposure to even "non-severe" pneumonia (3).

The KDIGO guideline discusses several potentially kidney-sparing steps that can be initiated in high-risk patients: 1) discontinue potentially nephrotoxic agents whenever possible (this includes finding alternatives to radiocontrast medium and a variety of drugs that pose some risk for AKI when other viable alternatives exist); 2) ensure volume status and perfusion pressure (this may require echocardiography or various other forms of functional hemodynamic monitoring); and 3) avoid hyperglycemia. The guideline also recommends that high-risk patients receive careful monitoring of serum creatinine and urine output. I would add to these recommendations that consultation with an AKI specialist should be considered for high-risk patients.

Importantly, all of these kidney-sparing steps first require a physician to determine which patients are indeed at high risk. This determination will not be difficult in some cases (multiple susceptibilities and exposures versus no susceptibilities with only limited exposure). However, for many patients significant clinical judgment is required. Unfortunately, there are no proven methods for the precise determination of risk in a specific patient, so it remains a clinical decision. The concept of renal angina (4) is one attempt to identify high risk and several biomarkers are being evaluated as potential aids in this process, but none have yet been approved.

Above all, it is the hope that the KDIGO clinical practice guideline for AKI will prompt all physicians to consider not only the diagnosis of AKI but whether patients exposed to various factors that can cause AKI (especially sepsis) are at high risk for the development of this disorder. Once risk is assessed, kidney-sparing measures can be considered.

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John A. Kellum, MD, FACP, is vice chair of the department of critical care medicine, University of Pittsburgh, and co-chair of the KDIGO Clinical Practice Guideline for Acute Kidney Injury. He has served as a paid consultant to multiple companies involved in developing biomarkers for acute kidney injury, including Abbott, Alere, Astute, and Roche.

Highlights of Kidney Disease: Improving Global Outcomes Clinical Practice Guidelines for Anemia in Chronic Kidney Disease

By Patrick S. Parfrey and John J. V. McMurray

The World Health Organization defines anemia in adults and children older than 15 years as a hemoglobin concentration (Hb) <13.0 g/dL in male individuals and <12.0 g/dL in female individuals. In children aged 1.5 to 5 years anemia is defined as Hb <11 g/dL, in those 5 to 12 years as <11.5 g/dL, and in those 12 to 15 years as <12 g/dL (1).

The Hb falls as GFR falls, but the relationship is nonlinear. In hemodialysis patients, Hb often falls below 8 g/dL if anemia is untreated, whereas in nondialysis patients with chronic kidney disease (CKD) patients, higher Hb levels are usual unless the patients are close to initiating dialysis or have another contributing cause.

The initial investigation of anemia should include a complete blood count, absolute reticulocyte count, serum ferritin and transferrin saturation to diagnose iron deficiency, and serum B12 and folate levels to diagnose rare but treatable vitamin deficiencies. A high index of suspicion for gastrointestinal blood loss in the presence of iron deficiency is advisable.

The three major interventions to treat anemia in patients with CKD include iron, erythropoiesis-stimulating agents (ESAs), and blood transfusions. An individualized approach to anemia therapy was stressed by the KDIGO Work Group, in which the potential benefits of the therapy (avoidance of blood transfusions and improvement of anemia-related symptoms) were balanced against the risk of harm caused by the intervention, rather than a group approach targeting particular ranges of Hb.

Iron

Determination of serum ferritin is the most common test for evaluation of iron storage, and transferrin saturation for the availability of iron to support erythropoiesis. These markers of iron deficiency in CKD have limited sensitivity and specificity to diagnose diminished bone marrow iron stores and to predict the erythropoietic response to iron supplementation (2). No iron intervention trials have been sufficiently powered or long enough in duration to enable assessment of long-term safety, and no studies have addressed the clinical benefit, cost effectiveness, and risk-to-benefit comparison of using different transferrin saturation and ferritin levels as a trigger for iron supplementation.

The KDIGO Work Group sought to make recommendations of iron supplementation that would balance diagnostic sensitivity and specificity of iron status tests with assumptions regarding safety, with the understanding that intravenous iron would be necessary in dialysis patients or in CKD nondialysis patients whose Hb had not increased after a 1- to 3-month trial of oral iron therapy. Consequently, it was suggested that for adult CKD patients with anemia not receiving iron or ESA therapy, or those receiving ESA therapy who were not receiving iron supplementation, a trial of intravenous iron was reasonable if 1) an increase of Hb without starting ESA treatment was desired or a decrease in ESA dose was desired, and 2) transferrin saturation was ≤30 percent and ferritin was ≤500 µg/mL. This advice was predicated on the understanding that the potential increase in Hb would achieve clinical goals, such as transfusion avoidance or improvement in anemia-related symptoms, and the Hb response and clinical response to iron supplementation would determine subsequent use of intravenous iron. In other words, the objective of iron supplementation was not to achieve particular iron status test targets but rather to provide a clinical benefit to the patient.

The previous Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines for iron use in children were not changed because there were no new data since 2005 (3). Consequently, it was recommended that all children with CKD and anemia not receiving iron or ESA therapy be given oral iron (or intravenous iron in hemodialysis patients) when transferrin saturation was ≤20 percent and ferritin was ≤100 µg/mL. In children receiving ESA therapy but not iron supplementation, oral iron (or intravenous iron in hemodialysis patients) was recommended to maintain transferrin saturation >20 percent and ferritin >100 µg/mL.

Erythropoiesis-stimulating agents

Objective evidence to support the treatment of Hb <9 g/dL with ESAs is quite strong because transfusion benefits are substantial and the quality-of-life improvements are clinically important (4). However, the safety of ESAs in treating severe anemia (arbitrarily defined as baseline Hb <10 g/dL) has not been evaluated in large placebo-controlled trials.

Several large randomized control trials of ESA therapy in moderate anemia, where baseline Hb was >10 g/dL, have been reported (5–9). The intervention in these trials was complete correction of anemia with ESAs, compared with partial correction with ESAs in four trials and with placebo in one trial. In the largest trial—the Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT)—correction of anemia did not diminish cardiovascular or renal events, and there was a substantially increased risk of stroke (9). The harm-to-benefit tradeoff was one stroke for five transfusions prevented by the high Hb target. Compared with placebo, darbepoetin conferred a consistent but small improvement in fatigue and overall quality of life for a duration of 97 weeks (10). Analysis of these trials led to the guidance outlined in Table 1.

ESA hyporesponsiveness

Relative resistance to the effects of ESAs is a common problem, and hyporesponsiveness is one of the strongest predictors of cardiovascular and mortality risk (11). This may be the result of a comorbidity that prevented an increase in Hb and caused the adverse outcomes, and hyporesponsiveness was just a marker for this comorbidity. However, the possibility that high ESA doses used

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Table 1. Important KDIGO guidelines for ESA use in CKD

1. For adult CKD ND patients with Hb ≥10.0 g/dL, we suggest that ESA therapy not be initiated. (2D)
2. For adult CKD ND patients with Hb <10.0 g/dL, we suggest that the decision whether to initiate ESA therapy be individualized based on the rate of fall of Hb, prior response to iron therapy, the risk of needing a transfusion, the risks related to ESA therapy, and the presence of symptoms attributable to anemia. (2C)
3. For adult dialysis patients, we suggest that ESA therapy be used to avoid having the Hb fall below 9.0 g/dL by starting ESA therapy when Hb is between 9.0 and 10.0 g/dL. (2B)
4. Individualization of therapy is reasonable because some patients may have improvements in quality of life at higher Hb, and ESA therapy may be started above 10.0 g/dL. (Not Graded)
5. For all pediatric CKD patients, we suggest that the selection of Hb at which ESA therapy is initiated in the individual patient include consideration of potential benefits (e.g., improvement in quality of life, school attendance/performance, and avoidance of transfusion) and potential harms. (2D)
6. In general, we suggest that ESAs not be used to maintain Hb concentration above 11.5 g/dL in adult patients with CKD. (2C)
7. Individualization of therapy will be necessary because some patients may have improvements in quality of life at Hb above 11.5 g/dL and will be prepared to accept the risks. (Not Graded)
8. In all adult patients, we recommend that ESAs not be used to intentionally increase Hb above 13 g/dL. (1A)
9. In all pediatric CKD patients receiving ESA therapy, we suggest that the selected Hb be in the range of 11.0 to 12.0 g/dL. (2D)

Table 2. KDIGO guidelines for red blood cell transfusion use in CKD

1. When managing chronic anemia, we recommend avoiding, when possible, red blood cell transfusions to minimize the general risks related to their use. (1B)
2. In patients eligible for organ transplantation, we specifically recommend avoiding, when possible, red blood cell transfusions to minimize the risk of allosensitization. (1C)
3. When managing chronic anemia, we suggest that the benefits of red blood cell transfusions may outweigh the risks in patients in whom (2C)
   - ESA therapy is ineffective (e.g., hemoglobinopathies, bone marrow failure, ESA resistance)
   - The risks of ESA therapy may outweigh its benefits (e.g., previous or current malignancy, previous stroke)
4. We suggest that the decision to transfuse a CKD patient with nonacute anemia should not be based on any arbitrary Hb threshold but should be determined by the occurrence of symptoms caused by anemia. (2C)

Abbreviations: CKD = chronic kidney disease; ESA = erythropoiesis-stimulating agents; Hb = hemoglobin concentration; KDIGO = Kidney Disease: Improving Global Outcomes; ND = nondialysis.

KDIGO Anemia Guidelines

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in hyporesponsive patients are toxic in themselves cannot be excluded. The definition of initial hyporesponsiveness was derived from the secondary analysis of TREAT (11). Patients were classified by the Work Group as hyporesponsive if they had no increase in Hb from baseline after the first month of treatment with appropriate weight-based dosing, which was conventional in 2011. In such patients, avoidance of repeated ESA dose escalation beyond double the initial weight-based dose was suggested. Acquired ESA hyporesponsiveness may also occur, classified by the Work Group as requiring two increases in ESA doses up to 50 percent beyond the dose at which they had been stable, in an effort to maintain a stable Hb. In such patients, avoidance of repeated ESA dose escalation beyond double the dose at which they had been stable was suggested. The Work Group suggestions for initial and acquired hyporesponsiveness imply that maximal ESA doses should be no greater than four times the initial weight-based appropriate doses.

Red blood cell transfusions

In iron-replete CKD patients with anemia, the choice between ESA and red blood cell transfusion should be individualized, taking into account the balance between benefits and harms for each treatment. Acute reactions to blood transfusions and mistransfusions occur surprisingly frequently; transmission of infection, although now rare, is a major concern; and sensitization to human leukocyte antigen is a concern for patients eligible for organ transplantation. The more important guidelines for transfusion use are presented in Table 2.

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Patrick S. Parfrey, MB, BCh, MD Cork, MRCP, FRCPC, is affiliated with Memorial University Medical School, St. John's, Newfoundland, Canada. John J. V. McMurray, MD, FRCP (Edin), FESC, FACC, is affiliated with the BHF Glasgow Cardiovascular Research Centre, Glasgow, United Kingdom.

Highlights of the KDIGO Bone and Mineral Disorder Guidelines

By Menaka Sarav and Stuart M. Sprague

During the 1980s and 1990s, the focus of dealing with disorders of bone and mineral metabolism was predominantly "bone centric," with parathyroid hormone (PTH) the main culprit and calcium the primary regulator of PTH. The term "renal osteodystrophy" was generally used to encompass these disorders. The focus of therapy was to maintain relatively high serum calcium concentrations in order to suppress PTH, which would presumably result in normal bone. This strategy did result in decreased PTH concentrations with the use of relatively high dialysate calcium baths, calcium-based phosphate binders and calcitriol; however, this practice resulted in hypercalcemia. As a result, non-calcium–containing phosphate binders and less-calcemic vitamin D receptor activators (VDRAs) were developed. During this time, there was also an increased awareness of the importance of phosphate, and more recently a better understanding of the hormonal regulation of phosphate metabolism with the identification of phosphatonins, predominantly fibroblastic growth factor 23 (FGF23). In addition, a greater appreciation of the role of extraskeletal calcification, predominantly vascular, and the prevalence and severity of fractures in the CKD population became apparent.

In 2003, clinical practice guidelines for bone and mineral metabolism were published by the Kidney Disease Outcomes Quality Initiative (KDOQI). The guidelines were largely based on ex-

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pert opinion rather than evidence, and were "phosphorus and PTH centric." Since these guidelines were released significant progress has been made in understanding the roles of VDRAs, the calcimimetic agent cinacalcet, FGF23, and possibly alkaline phosphatase. It has become apparent that mineral disorders of CKD were not solely a problem of bone disease.

In 2006, KDOQI created a consensus group to better define the diseases associated with altered mineral metabolism in CKD, which they termed chronic kidney disease–mineral and bone disorder (CKD-MBD). It is a systemic disorder of mineral and bone metabolism found in patients with CKD manifested by either one or a combination of the following:

- Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism
- Abnormalities in bone turnover, mineralization, volume, linear growth, or strength
- Vascular or soft tissue calcification

It is important to note that this list was not intended to be all encompassing and could expand as our understanding of disordered mineral metabolism evolves. The term renal osteodystrophy should now be limited to pathologic changes of bone morphology related to progressive CKD; and is quantifiable by histomorphometry based on bone biopsy (1). It is characterized by alterations in bone turnover, mineralization, and volume and includes the following qualitative disorders of bone: osteitis fibrosis cystica, adynamic bone disease, osteomalacia, and mixed uremic osteodystrophy (2).

In 2008, Kidney Disease: Improving Global Outcomes (KDIGO) presented a preliminary draft of the guidelines for CKD-MBD for public review. The KDIGO Work Group took a more conservative approach and refrained from making specific guidelines on treatment due to lack of high-quality evidence. This was a dramatic shift from the previous 2003 KDOQI guidelines, which had recommended specific targets for calcium, phosphorus, and PTH. Reviewers of the preliminary draft and the KDIGO board

asked that the Work Group provide recommendations even if these were based largely on expert judgment, as long as the Work Group could achieve consensus.

Consequently, in 2009 KDIGO presented the final clinical practice guidelines for the management of CKD-MBD (3). The major difference between the KDOQI and KDIGO guidelines (Table 1) was that the KDIGO followed more stringent criteria for including studies to grade the evidence.

KDIGO presented two levels of recommendations based on evidence. Level 1 is "we recommend," and implies that most patients should receive the course of action. Level 2 is "we suggest," and implies that the choices are likely debatable. Most of the guidelines (approximately 80 percent) were graded Level 2 due to the lack of evidence and/or good randomized controlled trials, and it was left up to the clinician to make a decision based on the clinical circumstances of the individual patient.

Unfortunately, the publication of these guidelines has resulted in more controversy rather than therapeutic guidance. A meta-analysis published in 2011 of 47 cohort studies concluded that the current guidelines for calcium, phosphorus, and PTH in CKD patients are poor. They were critical of the KDIGO guidelines in that it "promotes therapeutic strategies without sufficient evidence" and that "high-quality evidence is required before specific treatment should be advocated strongly" (4).

A commentary response to this meta-analysis by a member who was on the KDIGO Work Group does not dispute that there was insufficient data, but tries to address "what should a guideline panel do when evidence is inconclusive." It reports that even when there is lack of evidence, most clinicians prefer to have at least an educated opinion from a guideline committee with a transparent rationale provided as a point of reference (5).

Key questions still need to be answered regarding target phosphate and PTH levels and an optimal treatment strategy for achieving phosphate and PTH targets. There is an urgent need for well conducted randomized control trials in the CKD and dialysis population to address these questions. However, in the interim, it seems reasonable to use the KDIGO recommendations as a guideline.

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Highlights

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Menaka Sarav, MD, and Stuart M. Sprague, DO, FACP, FASN, are affiliated with the Division of Nephrology and Hypertension at North Shore University Health System in Evanston, IL.

Table 1. Guidelines for CKD-MBD(6)

	KDIGO 2009 (3)	KDOQI 2003(7)
Monitoring biochemical components	Start at CKD 3. Include Ca, Phos, PTH, ALP	Same but no comment on ALP
Goal Phos	CKD 3–4: normal CKD 5: toward normal	CKD 3–4: normal CKD 5: 3.5 to 5.5
Goal Ca	Normal Suggest to stay away from CaxPhos	CKD 3–4: normal CKD 5: 8.4–9.5 CaxPhos <55
Goal PTH	CKD 3–4: unknown CKD 5: 2 to 9 times upper limit of normal. When PTH above upper limits of normal evaluate correctable factors like Phos, Ca, Vit D	CKD 3: 35–70 pg/mL CKD 4: 70–110 pg/ mL CKD 5:150–300 pg/mL
Goal 25(OH) Vit D	Start at CKD 3. Correct as in general population	CKD 3–4, measure only if PTH is above target. Replace if <30 ng/mL
PTH assay	Clinical labs should report assay method handling and sampling. Recommend 2nd generation assay	Recommendation based on 2nd generation Nichols Allegro assay currently unavailable
Bone-specific ALP	Suggest testing bone-specific ALP in certain individuals and very high or low levels predict underlying bone turnover	No specific suggestions
Bone biopsy	Reasonable in various settings and prior to bisphosphonates in CKD-MBD	Should be considered
BMD	Not recommended routinely in CKD 3–5 with biochemical abnormalities	DEXA should be measured in patients with fracture and osteoporosis risk
Vascular calcification	No recommendation for routine screening	same

Abbreviations: ALP = alkaline phosphatase; Ca = calcium; CaxPhos = product of serum calcium and phosphorus; CKD = chronic kidney disease; DEXA = dual-energy X-ray absorptiometry; KDIGO = Kidney Disease: Improving Global Outcomes; KDOQI = Kidney Disease Outcomes Quality Initiative; MBD = mineral and bone disorder; Phos = phosphorus; PTH = parathyroid hormone; Vit D = vitamin D.

KDIGO Glomerulonephritis Guideline

By Daniel Cattran

Glomerulonephritis (GN)—including both primary and secondary variants in aggregate—remains one of the most common types of kidney disease that progresses to end stage renal disease (ESRD). However, this fact alone seriously underestimates the extent of the problem associated with GN. Many cases of the disease begin early in life and can have a devastating effect both on the individual and their families. The disease process is often slowly progressive and therefore its devastating impact on the individual's physical growth, educational opportunities, quality of life, and eventual societal productivity is rarely taken into account when assessing the impact of these disorders.

The variants of GN included in the Kidney Disease: Improving Global Outcomes (KDIGO) GN guideline are classified as orphan diseases because of their rarity. This—in combination with their long clinical course, punctuated with remissions and relapses, and very large variation in treatment responsiveness—makes tracking them difficult. A recent *Kidney International* editorial, entitled *Glomerular Disease: Why Is There a Dearth of High-quality Clinical Trials*, further delineates these problems (1). The authors proposed that the GN guidelines developed under the auspices of a global nonprofit foundation KDIGO would help by encouraging a uniform classification system of diseases and common clinical end points as well as utilizing an evidence-based review process to establish clinical practice guidelines for glomerulonephritis. These guidelines were published as a *Kidney International* supplement in June 2012 (2).

Clinical practice guidelines (CPGs) have become an important element in clinical practice and can now be found in virtually every branch of medicine. The Institute of Medicine defines CPGs as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances" (3). The potential benefits of CPGs include providing clear recommendations based on currently available evidence, thereby potentially improving the quality of clinical decisions. The advantage of the physician knowing the specific circumstances surrounding the individual patient cannot be underestimated in the final judgment about treatment. Ideally, decisions take into account the physician's experience and acumen as well as the individual patient characteristics and opinion as well as the evidence. The KDIGO GN guideline was purposely developed to have potential global application. This implies that it takes into account not only the different financial situations at the individual level, but also the social and economic realities of the underlying health care system.

The development of the GN guideline was a lengthy process and took several years. The Work Group consisted of both experienced and expert clinicians and an evidence review team trained in the complex field of guideline development. The Work Group formulated recommendations related to a specific question or topic with each set of recommendations followed by a rationale section summarizing the evidence and the reasoning for each recommendation, and explaining why specific wording was chosen. It is critical to understand the grading process in the KDIGO GN guideline. Each recommendation has both an alphabetical and numeric code. The alphabetical code (A, B, C, and D) indicates the quality of the evidence supporting the recommendation or suggestion, whereas the numeric grade (1 or 2) denotes the strength of the evidence. At a practice level, level 1 generally means a recommendation that this course of action should be instituted, whereas level 2 is more compatible with a suggestion that requires that each affected individual needs careful consideration and that different choices may be appropriate for different patients. This provides a range of recommendations from 1A (the highest recommendation) to 2D (the lowest), with the latter usually reflecting the considered opinion of the GN Work Group.

No matter what the grading, the ultimate physician decision always requires consideration in regards to the balance between the risks and benefits of treatment. Ideally, the chosen treatment regimen reduces the total exposure to immunosuppressive therapy yet still results in the minimization of immediate morbidity (e.g., achieving remission of nephrotic syndrome) and prevents disease progression. The total exposure risk, however, must always be balanced against the alternatives (i.e., potential progression to ESRD with its associated shortened life span, and/or a renal transplant with its absolute requirement of continuous immunosuppression). This has modified the physician stance in favor of more intensive and prolonged treatment in the more chronic GN variants—for example, lupus nephritis, vasculitis, focal segmental glomerulosclerosis (FSGS), and even membranous nephropathy—given the alternative. In addition, the recognition that the clinical equivalent of control is often reduction in proteinuria versus cure defined by permanent complete remission of proteinuria has resulted in the concept of "maintenance" therapy in many of these disorders. This paradigm shift in management has translated into the use of more extended (or repeated) treatment regimens with the inevitable cor-

ollary of more toxic drug exposure.

The KDIGO GN guideline is intended to provide the practitioner with information to make an informed decision based on the data available for most of the common glomerular diseases. The important point here is that the CPGs are intended to provide guidance rather than a strict set of rules. The overarching purpose of the recommendations is to assist in decision making and not provide a "cookie-cutter" approach to management. A guideline recommendation/suggestion cannot account for all possible variations of patients, providers, and system factors. Thus, each health care provider needs to assess the appropriateness of a particular recommendation or suggestion within a specific context.

The scope of this GN CPG is limited to the treatment phase of patients already diagnosed with GN. It includes the most common primary histologic variants as well as those associated with systemic disease. It does not cover diagnosis or prevention of GN. The guideline addresses the following forms of GN: steroid-sensitive nephrotic syndrome (SSNS) and steroid resistant nephrotic syndrome (SRNS) in children; minimal change disease and idiopathic FSGS in children and adults; idiopathic membranous nephropathy; idiopathic membranoproliferative GN; GN associated with infections, immunoglobulin A nephropathy, and Henoch-Schonlein purpura nephritis; lupus nephritis; renal vasculitis; and anti–glomerular basement membrane GN.

Treatment approaches are addressed in each chapter and the guideline recommendations are based on systematic reviews of relevant trials. All materials, including evidence tables and evidence profiles, and general management issues not included in the *Kidney International* supplement are available online at http://www.kdigo.org/. Limitations of the evidence are discussed and specific suggestions are provided for future research.

This guideline was written primarily for nephrologists, although the broader health care profession—including other physicians, nurses, pharmacists, and health care professionals who care for patients with GN—will hopefully find it educational and of interest. This guideline was not written directly for patients or caregivers, although certain extracted and well explained elements of the GN guideline would potentially provide useful information.

Prior to specific recommendations on each of the GN types, there is a chapter on the general principles in management of glomerular diseases, including assessment of kidney function, outcome measures, and impact of age, sex, ethnicity, and genetic background—all relevant issues that come into play at the interface between the individual patient and their physician. Management of complications of GN, treatment costs, and other related issues are also touched on in this chapter.

In a recent *Kidney International* article we further explored the critical relationship between GN guideline and their application at a practice level (4). This was done within a case context using specific types of glomerular disease (FSGS, membranous nephropathy, and vasculitis) to underline the relevance of the complex interaction of multiple factors that often impact treatment decisions in GN.

The purpose was to define the strains of as well as the limitations of applying guidelines to individual cases in a way designed to provide guidance to the individual nephrologists when dealing with the complex GN patient. Although the literal application of the guideline is often not possible and sometimes inappropriate, what guidelines do is provide for the reader the direction to take to ensure that the correct diagnosis is made and that the balance between the risks and benefits of specific immunosuppressive is considered. Examining the guideline within a specific case, for instance of FSGS, underlines the importance of separating the primary from the secondary cause of the lesion, and the need to consider the physical characteristics of the individual (e.g., age and body mass index). It goes on to discuss the potential importance of a normal serum albumin in the setting of the high-grade proteinuria. In addition, it touches on variations in histologic features, such as the degree of the foot process effacement prior to deciding on what treatment should the instituted.

In summary, it is important to remember what the KDIGO Guidelines for Glomerulonephritis can and cannot do. They will

- remind us what we know
- remind us what we do not know

and they

- must be applied with clinical judgment
- will help to balance risk and benefit

but they

- will not tell us what to do for every difficult patient in every situation.

Daniel Cattran, MD, FRCPC, is affiliated with the University Health Network, Toronto General Hospital in Toronto, Ontario, Canada.

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KDIGO Clinical Practice Guidelines for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease

By Roy D. Bloom

Hepatitis C virus (HCV) affects approximately 4 million Americans, and can trigger, share risk factors for, or result from CKD. Besides causing glomerulonephritis, HCV is associated with diabetes, a CKD precursor. End stage renal disease (ESRD) is a risk factor for HCV, transmitted via transfusions or transplantation in the era preceding its identification. The estimated HCV prevalence among U.S. CKD patients is 10 percent, several-fold higher than the general population, and is presumed to increase with CKD stage, with demographic variation. While acute infection is often subclinical, chronic HCV infection develops in most patients, leading to cirrhosis, hepatocellular carcinoma, and liver failure. Together with extrahepatic manifestations of glomerulonephritis and diabetes, these complications reduce HCV-positive CKD patient survival.

Standard antiviral therapy, until recently interferon-alpha (IFN) and ribavirin, achieved sustained response rates around 40 percent. Response rates are lower in patients infected with genotype 1, the most common HCV genotype among infected ESRD patients. Drug intolerance in CKD diminishes efficacy and IFN's immunostimulatory properties increase transplant rejection risk.

The impact of HCV across the CKD spectrum, coupled with limited preexisting recommendations, was the impetus for these guidelines. The multinational Work Group comprised general and transplant nephrologists, hepatologists, pathologists, virologists, epidemiologists, and infection control specialists, all with expertise in HCV or its consequences (1).

Statements were graded as strong (high-quality evidence, intervention "should be performed"), moderate (moderate-low quality evidence, intervention "should be considered"), or weak (low or absent quality evidence, consensus-based recommendations, intervention "suggested"). Five topics were covered: 1) detection and evaluation of HCV, 2) treatment of HCV infection, 3) prevention of HCV transmission in hemodialysis units, 4) management of HCV-infected transplant patients, and 5) diagnosis and management of HCV-associated kidney diseases.

Guideline 1: Detection and evaluation of HCV in CKD

The Work Group suggested that viral testing be performed in pre-ESRD settings where HCV is implicated (e.g., glomerulonephritis), or in diabetics where infection predicts faster CKD progression. In ESRD, because liver enzymes correlate poorly with disease severity, and since earlier diagnosis permits timelier treatment opportunity, HCV testing should be mandatory in maintenance hemodialysis and transplant patients. Hemodialysis patient testing should be performed at time of treatment initiation or unit transfer. Given limited sensitivity of third generation serological testing in ESRD patients, high HCV prevalence facilities should consider testing patients once with nucleic acid testing, since some seronegative individuals may actually be viremic. In low-prevalence units, serological testing should suffice. Since incidence rates of new HCV infection in the United States are 3.1 percent, serological retesting of uninfected patients every 6 to 12 months should be considered. In previously uninfected patients with new/unexplained transaminitis, or whose HCV risk has changed because of new exposures, nucleic acid testing should be performed.

Guideline 2: Treatment of HCV infection in CKD patients

Major randomized controlled trials for treating HCV have excluded CKD patients, resulting in low-quality evidence regarding therapies and indications in this population. Since HCV can cause CKD and reduce ESRD patient survival—and given the slight evidence that viral clearance improves outcomes—the Work Group felt a treatment guideline was necessary even if based on expert judgment and extrapolation from non-CKD patients. In formulating recommendations, they recognized that: 1) the natural course of HCV in CKD may differ from non-CKD populations; 2) most studies are retrospective and underpowered; 3) information on viral co-infection, mode of acquisition, liver histology, and post-treatment outcomes is sparse; and 4) many IFN-based stud-

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Guidelines

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ies comprise European populations and lack generalizability.

The Work Group suggested that HCV treatment in CKD patients be based on liver histology, age, comorbidities, life expectancy, and ability to tolerate therapy. Since HCV liver disease progression is typically insidious, death from CKD comorbidities, like cardiovascular disease, is more probable than from viral complications. It was suggested that treatment be considered when potential life-extending benefits of viral clearance outweigh risks of therapy-related harm, for example in HCV-positive transplant candidates.

Accounting for renal elimination of antiviral therapies, the Work Group suggested combined pegylated-IFN/ribavirin for CKD stages 1 and 2, pegylated-IFN monotherapy for CKD stages 3 to 5 given ribavirin-induced anemia risk, and dose-adjusted standard IFN in ESRD given toxicity of supraphar macological exposure. Although standard IFN response rates are higher in dialysis than non-CKD patients, lower tolerance frequently interrupts treatment.

Where sustained response is achieved, it was suggested that HCV RNA monitoring be performed every 6 to 12 months. Regardless, all patients should have an annual hepatology evaluation for HCV-related complications, with more frequent follow-up for cirrhotics.

Guideline 3: Preventing HCV transmission in hemodialysis units

With declining blood transfusion requirements, nosocomial transmission via contaminated supplies and surfaces is the likeliest HCV source in hemodialysis units, usually from infection control breaches. Dialysis units should implement, and ensure adherence to, infection-control procedures that prevent direct or indirect (via contaminants) interpatient transmission of blood-borne pathogens. Since HCV transmission via circulating dialysis fluids has been excluded in virtually all reported outbreaks, and because isolation does not prevent transmission, dedicated equipment use is not recommended. From a facility operations standpoint, it was suggested that sufficient time and supplies are available to optimize infection control, and that regular audits be undertaken.

Guideline 4: Management of HCV-infected patients before and after kidney transplantation

Many HCV-positive transplant candidates have undiagnosed infection or no prior hepatological evaluation. Given its adverse effect on transplant outcomes, HCV testing should be performed in all new candidates and listed patients not previously tested. The regional HCV prevalence should be taken into account in determining the optimal screening test (discussed in Guideline 1). HCV should not be considered a contraindication to kidney transplantation since infected recipients have superior outcomes to their dialysis counterparts. The Work Group suggested that infected candidates be referred to hepatology, undergo pretransplant liver biopsy, and be considered for IFN, with listed patients placed on hold during this evaluation period. Given lengthy transplant wait times, liver rebiopsy every 3 to 5 years was suggested for listed viremic patients. For ESRD patients with compensated cirrhosis, it was suggested that kidney alone only be considered under investigational protocol.

The Work Group recommended that HCV testing should be performed in all donors. Serological screening—the existing benchmark—does not distinguish potentially infectious from immune donors following prior infection. Use of HCV-positive donor kidneys therefore requires evaluating transmission risks against risks of delaying transplantation. It was suggested that HCV-positive donor kidneys not be used in uninfected candidates given increased risk for liver disease and diabetes posttransplant, but that these kidneys be restricted to viremic candidates because 1) waiting times may be reduced, 2) short-term survival is not affected, 3) progressive liver disease is not invariable and, 4) compared to dialysis, these recipients live longer. Absent randomized trials, the Work Group opined that all existing immunosuppression could be used in HCV-positive recipients, with therapy selection determined by risk/benefit assessment. It was finally suggested that recipients undergo annual hepatology evaluation, with IFN used only where the benefit of halting liver disease outweighed rejection risk.

Guideline 5: Diagnosis and management of kidney diseases associated with HCV infection

Type I membranoproliferative glomerulonephritis with cryoglobulinemia, and occasionally other histological lesions, is associated with HCV viremia independently of liver disease. It was therefore suggested that HCV-positive patients be screened annually for kidney disease. In the absence of robust evidence, the Work Group suggested interferon/ribavirin, targeted to achieve sustained viral clearance, be used where HCV is implicated in the glomerulonephritis pathogenesis. For patients with cryoglobulinemic flares, treating the systemic process with plasma exchange and immunosuppression (e.g., steroids, rituximab) prior to antiviral therapy was suggested.

In conclusion, an unexpected guidelines benefit has been the identification of several knowledge gaps. As research recommendations proposed by the Work Group materialize into formalized studies, and as the emerging antiviral therapeutic arsenal expands, we can look forward to robust advances over the next decade in caring for this complicated population.

Roy D. Bloom, MD, is affiliated with the Perelman School of Medicine, University of Pennsylvania, in Philadelphia, PA.

Reference

1. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. *Kidney Int* 2008; 109 (Suppl):S1–S99.

The KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients

By Michelle A. Josephson

The *KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients* was the third Kidney Disease: Improving Global Outcomes (KDIGO) guideline, published in November 2009 as a supplement to the *American Journal of Transplantation*. This guideline addressed a broader set of issues than did the previous two guidelines (for hepatitis C and bone and mineral disease). The guideline was written for clinicians (doctors, nurses, coordinators, and pharmacists) providing care to patients who have received a transplant. It was also aimed at a diverse audience, including those in both the developed and the developing worlds. To limit its scope, the guideline focused on the post–kidney transplantation period and did not delve into issues related to the potential candidates for kidney transplantation, donors (living or deceased), or any other transplanted organ. The guideline also focused on issues that are unique to kidney transplant recipients. The purpose of the guideline was to improve patient care by helping clinicians base their management on available evidence, and it was developed to enable the development of transplantation programs worldwide. Finally, the literature review and analysis provided an opportunity to identify knowledge gaps and define the areas that needed further exploration and research.

The guideline covers a broad range of topics, including immunosuppression (induction therapy, initial and long-term maintenance medications, strategies to reduce drug costs, and immunosuppression monitoring); treatment of acute rejection; treatment of chronic allograft injury; monitoring allograft function; kidney allograft biopsy; recurrent disease; nonadherence (prevention, detection, and treatment); infectious disease issues (vaccination; viral diseases including BK virus, cytomegalovirus, Epstein-Barr virus, and posttransplantation lymphoproliferative disease; herpes simplex 1 and 2; varicella; hepatitis B and C; HIV; urinary tract infections; pneumocystis; and *Candida* infections); diabetes mellitus (screening for and managing new-onset diabetes after transplantation and preexisting diabetes mellitus); hypertension; dyslipidemia; tobacco use; obesity; cardiovascular disease management; malignancies (cancer of the skin and lip, non–skin malignancies, managing cancer with immunosuppression reduction, transplantation bone disease, and hematologic complications); hyperuricemia and gout; pediatric topics (growth and development); sexual function; female and male fertility; lifestyles; and mental health.

Like the other KDIGO management guidelines, this one was developed on the basis of a systematic review of relevant treatment trials. The recommendations were articulated by use of the Grading of Recommendations Assessment, Development, and Evaluation system. This entails having each guideline accompanied by a grade indicating the strength of the recommendation and also an assessment of the quality of the literature on which the recommendation is based. The strength of the recommendation is indicated as Level 1 (indicated as "we recommend"), Level 2 ("we suggest"), or not graded. The quality of the supporting evidence is depicted as A (high-quality evidence), B (moderate-quality evidence), C (low-quality evidence), or D (very-low-quality evidence).

Only 2 percent (4 recommendations) were graded A (having highest-quality evidence), 13.6 percent (27) were graded B (moderate-quality evidence), 38.9 percent (77) were graded C, and 45.5

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KDIGO: A Promise Unfulfilled

By Joel Topf

When Kidney Disease: Improving Global Outcomes (KDIGO) was first announced in 2004, I was confused. We had Kidney Disease Outcomes Quality Initiative (KDOQI), which seemed reasonably successful and had been well integrated into nephrology. I had learned and was teaching the KDOQI chronic kidney disease (CKD) stages. Researchers were using the CKD stages to define populations and create prognostic models. Dialysis providers were adopting the renal osteodystrophy guidelines as treatment targets and directing their nurses, dietitians, and social workers to empower patients to achieve these goals. Additional guidelines seemed superfluous. When I looked into KDIGO, however, I saw something very different from the KDOQI guidelines. KDIGO, in the introduction of the bone guidelines, promised to avoid opinion-based recommendations. They wanted to limit the evidence they considered to randomized controlled trials of 6 months duration with at least 50 patients. They wanted to avoid using nonvalidated intermediate end points or biochemical intermediate end points not validated as surrogates for hard end points. This commitment to evidence and shunning of expert opinion was the "aha moment" where I understood how KDIGO was different from KDOQI. As I understood it, KDIGO was to provide an evidence-based foundation from which individual professional organizations and government agencies could build additional guidelines. The foundation would be an evidence-based framework that could be trusted to be free from bias and based on the best science offered to date.

After my aha moment, I didn't pay further attention to the KDIGO construction process which meant that I was in for a rather rude surprise when the CKD–mineral and bone disorder (CKD-MBD) guidelines were published in 2009. I was familiar with the KDOQI guidelines and had looked behind the veil at the thin data used to support them. This was not a wall of evidence but more of a chain link fence, more holes than steel. I had seen the lack of data so I understood how high the work group had set the bar. There were (and still are) no randomized controlled trials testing various parathyroid hormone (PTH) targets or, for that matter, no calcium, phosphorus, or bicarbonate targets. We had no qualifying data that phosphorus binders, vitamin D or its analogs provided any patient-oriented, nonbiochemical benefits. I naively thought that the guidelines would be little more than a blank piece of paper given the sorry state of randomized controlled trials focused on the questions inherent in CKD-MBD management. So as I read the guidelines I became confused. They were chock full of specifics that I knew could not have been from randomized controlled trials. Reading the introduction cleared up my confusion:

"The public review overwhelmingly agreed with the guideline recommendations. Interestingly, most reviewers requested more specific guidance for the management of CKD–MBD, even if predominantly based on expert judgment, whereas others found the public review draft to be a refreshingly honest appraisal of our current knowledge base in this field…. the KDIGO Board in its Vienna session in December 2008 refined its remit to KDIGO Work Groups. It confirmed its charge to the Work Groups to critically appraise the evidence, but encouraged the Work Groups to issue practical guidance in areas of indeterminate evidence" (1).

I had hoped that an international clinical practice guideline as high profile as KDIGO that published empty guidelines due to a lack of evidence would shame the nephrology stakeholders to do the studies we need to know how to take care of our patients. In the end KDIGO blinked and published guidelines, very much in the same vein as the KDIGO guidelines that came before them. In their defense, KDOQI rated the strength of evidence and the strength of the recommendation for all of the guidelines, but despite their plea that "Only when evidence is sufficiently strong to conclude that additional research is not needed should guidelines be used to mandate specific medical practices with, for example, clinical performance measures" (1).

I am seeing the KDIGO guideline operationalized in my dialysis units. Soon after the CKD-MBD guidelines were published our PTH targets went from 150–300 pg/mL to 150–600 pg/mL, and our phosphorous goals went from less than 5.5 mg/dL to less than 4.5 mg/dL. Both changes represent a shift from KDOQI to KDIGO targets. Nowhere in my experience rounding was it made clear that these were grade level 2C recommendations (suggestions rather than recommendations based on "low" levels of evidence). Guideline grades are too subtle to intrude in any meaningful way in the dialysis unit.

When I take care of my patients I want to provide the best care possible, but for reasons unclear to me, science has not cast its light on the dark halls of nephrology. I hoped that KDIGO would have shown that the emperor wore no clothes, but had they published a blank piece of paper it would have been a one-week story of outrage and editorials but it would have made KDIGO unimportant, irrelevant, and we would not be celebrating its 10th anniversary.

Joel Topf, MD, is an assistant professor at Wayne State University School of Medicine and affiliated with the St. John Hospital and Medical Center in Detroit, MI.

Reference

1. 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 Suppl* 2009; 113:S1–S130.

Clinical Practice Guideline

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percent (90) were graded D. The quality of evidence directly affected the strength of the recommendation. Consequently, of all the graded statements only 25.3 percent of the recommendations were afforded a Level 1 recommendation (we recommend) and the remaining 74.7 percent were assessed as Level 2 recommendations (we suggest). An additional 45 recommendations were not graded.

The KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients was published more than 3 years ago, and the initial work on it started more than 6 years ago. No doubt some of the guideline needs updating. With this in mind, what follows are my pick of some of the helpful recommendations for the "nontransplantation" nephrologist. They focus primarily on long-term management issues. There are many other useful recommendations, but these give a flavor of some of the important topics that are covered by the KDIGO guideline.

Issues related to long-term maintenance immunosuppression medications are covered, and sample recommendations include:

3.2: We suggest that calcineurin inhibitors be continued rather than withdrawn (2B).

3.2: If prednisone is being used beyond the first week after transplantation, we suggest prednisone be continued rather than withdrawn (2C).

Strategies to reduce drug costs are also touched on, and include this important recommendation:

4.4: After switching to a generic medication that is monitored using blood levels, obtain levels and adjust the dose as often as necessary until a stable therapeutic target is achieved (not graded).

Monitoring immunosuppressive medications is also discussed, including the following recommendation:

5.1: We recommend measuring blood levels of calcineurin inhibitors (1B) and suggest measuring at least:

- whenever there is a change in medication or patient status that may affect blood levels (2C);
- whenever there is a decline in kidney function that may indicate nephrotoxicity or rejection (2C).

In terms of chronic allograft injury, the KDIGO guidelines state:

7.1: We recommend kidney allograft biopsy for all patients with declining kidney function of unclear cause, to detect potentially reversible causes (1C).

With regard to monitoring kidney allograft function:

8.3: We recommend measuring serum creatinine (1B) at least

- every 2 weeks for months 4 to 6 (2C).
- monthly for months 7 to 12 (2C).
- every 2 to 3 months thereafter (2C).

There are many other useful recommendations in this comprehensive KDIGO document. The guideline is presented in a practical format. Each area and chapter includes a focused discussion of the background, rationale, and research recommendations that emerge from the recommendations and level of evidence available. The guideline includes references and an appendix that outlines the approach and an analysis of the available papers. In the end, it achieves what was intended—"it addresses issues that are important to the care of [kidney transplant recipients] in both developed and developing countries." As well, it serves as a useful resource for all of us in the transplantation field.

Michelle A. Josephson, MD, is the chair of ASN's Transplant Advisory Group and is affiliated with the department of medicine, section of nephrology, at the University of Chicago. She was a Work Group Member for "KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients."

KDIGO: An International Perspective

By Brian Michael I. Cabral

Kidney disease is truly a global epidemic and the Philippines is no exception, with tens of thousands of Filipinos diagnosed and likely even more left unrecognized. The availability of guidelines to assist in the proper management of these patients is truly invaluable and, in the appropriate situation, allows for the further improvement of patient care as well as the amelioration of certain deficiencies in health care delivery. It brings us one step closer to bridging the gap between one's own personal practice and the implementation of true evidence-based medicine.

The objective of this commentary is not to criticize individual KDIGO recommendations, but to describe the difficulties faced by Filipino nephrologists as we strive for their implementation. The lack of Filipino data and the fact that consensus statements were based primarily on published Western data is a given and a fact I would prefer not to dwell on. It is obvious that local data are urgently needed.

Let me introduce you to a fictional patient named Juan Dela Cruz, a typical Filipino end stage renal disease (ESRD) patient on dialysis with diabetes, hypertension, and dyslipidemia. He has anemia and is receiving erythropoietin, as well as secondary hyperparathyroidism and hyperphosphatemia. Unfortunately, part of what makes him typical is that he only dialyzes twice a week, that his records show a diagnosis of "chronic glomerulonephritis," but he has never had a biopsy performed despite a disproportionate amount of proteinuria along with his past medical history. He often has difficulty with compliance with dialysis, anemia management, and treatment of chronic kidney disease–mineral and bone disorder because at some point, putting food on the table has become more important.

The harsh reality is that due to multiple extraneous circumstances, the KDIGO guidelines have become a veritable wish list for physicians and patients in our part of the world, and merely reminds us of the things that we are unable to provide our patients.

Too many times, I've had to help patients choose between compliance with thrice weekly dialysis and treatment of their ESRD's sequelae. Should we tolerate twice weekly dialysis to have some money left over for erythropoietin, vitamin D analogs, and phosphorus binders? What of the other illnesses and comorbidities? Unfortunately, as "typical" as this situation may be, there are no studies or guidelines available to help address these types of issues.

In some instances, the guidelines may even make it more difficult to care for patients. Although guidelines involving the use of generics, bioequivalents, and biosimilars are clear, they can be misinterpreted, leading some physicians to encourage patients to use more expensive innovator products and to set aside the fact that at some point, financial constraints may lead to their total and complete abandonment of treatment. Far from the intent for which these guidelines were developed, these impoverished patients now become at greater risk for mortality due to their iatrogenic adherence to the guidelines that were paradoxically developed to improve their outcomes.

The segmentation or the breaking down of the guidelines into particular topics, although convenient and ultimately necessary due to the complexity of kidney disease, may have diverted our focus from the fact that many issues often co-exist and are not exclusive of one another in the patient with kidney disease. Due to the financially challenging nature of kidney disease we must in most cases, learn to prioritize, an issue certainly needing a guideline in and of itself, but for which there is none.

KDIGO stands for Kidney Disease: Improving Global Outcomes. Its mission statement is "To improve the care and outcomes of kidney disease patients worldwide through promoting coordination, collaboration and integration of initiatives to develop and implement clinical practice guidelines." However, when we discuss things on a global scale we must be sensitive to the fact that although most of the concepts, complications, and problems associated with kidney disease are universal, much of the world does not have the financial or technological capabilities of its first world counterparts. Therefore our challenge is to establish guidelines that are equally implementable in areas of the world where access to medical resources for, whatever reason, is limited. Only then can we truly say that we are focused on "Improving Global Outcomes."

Brian Michael I. Cabral, MD, is assistant medical director for medical education, and head of the Center for Renal Diseases at St. Luke's Medical Center–Global City, in Taguig City, Philippines.

Policy Update

Budget Cuts May Pinch NIH

By Grant Olan

Congress missed the March 1, 2013, deadline for replacing the $1.2 trillion in federal budget cuts (sequestration) mandated by the Budget Control Act of 2011. As a consequence, federal defense and domestic programs, including the National Institutes of Health (NIH), are facing an across-the-board cut—or "sequester"—of $85 billion in Fiscal Year (FY) 2013. This translates to an approximately 9 percent budget cut for the NIH and other "nonexempt nondefense programs" (nonexempt defense programs will see a cut of approximately 13 percent). Congress deemed a few agencies "exempt," including Medicare (with cuts capped at 2 percent) and the Department of Veterans Affairs (which is completely exempt from cuts). The remaining $1.1 trillion in cuts mandated by the Budget Control Act of 2011 will be implemented between 2014 and 2021.

NIH recently sent letters to current grantees notifying them of these steep cuts. The agency intends to prioritize administrative costs and current obligations over new research. However, all noncompeting continuation awards are currently being funded at a level below that indicated on the most recent notice of award (generally up to 90 percent). Although some awards may possibly be restored to higher levels, they probably will not reach the full FY 2013 commitment level.

According to NIH, "Plans for new grants and contracts may be re-scoped, delayed, or canceled depending on the nature of the work and the availability of resources." The agency also sent a letter to current contractors about cuts that may affect them. NIH Director Francis S. Collins, MD, PhD, instructed each NIH institute and center to put together their own plans for applying the cuts in ways that minimize the scientific impact. The plans will be announced soon. Links to those announcements will be available on the NIH extramural financial operations page at http://grants.nih.gov/grants/financial/index.htm.

Possible ripple effect

The ASN leadership is concerned about the ripple effect these budget cuts will have on the future of research and on investigators and patients. The society has been actively advocating for a balanced approach to deficit reduction instead of indiscriminate cuts to all programs.

NIH Director Francis S. Collins, MD, PhD, instructed each NIH institute and center to put together their own plans for applying the cuts in ways that minimize the scientific impact.

"Medical research is a smart investment. It doesn't make sense to cut a program that creates jobs, saves lives, and drives down health care costs," said John R. Sedor, MD, ASN Research Advocacy Committee Chair. "Congress needs to sustain funding for NIH, which has benefited from longstanding, bipartisan support from presidents and Congress alike."

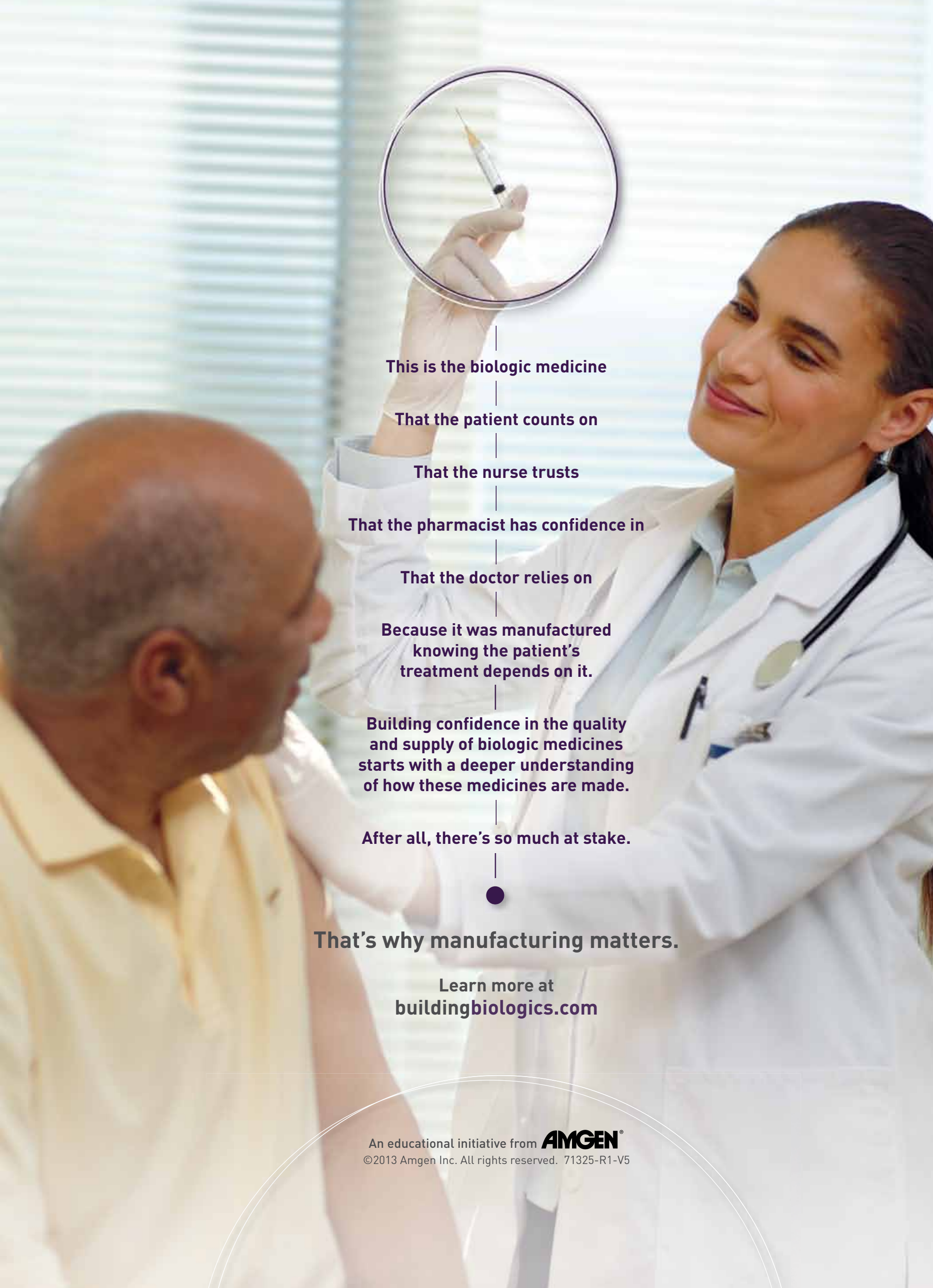
ASN collaborates with a number of coalitions of patient groups and health professional organizations opposed to sequestration. The society has participated in a number of rallies, briefings, and Hill Day meetings with congressional offices. ASN also launched the society's first-ever grassroots campaign last fall. Through calls, emails, and district office meetings with their members of Congress, hundreds of ASN members have answered the call to action.

You can help by sending a letter to the editor and helping build public support for sustained medical research funding. Please visit ASN's website at http://www.asn-online.org/policy/ for a sample letter to the editor you can send to your local newspapers.

The next opportunity to replace sequestration with a rational plan comes in May when Congress must reach a deal to raise the federal debt ceiling, the legal limit of how much debt the United States can assume.

In the meantime, the president will release his 2014 budget recommendations in April. The House and Senate have been working on their 2014 budgets.

Given that—at least for the time being—sequestration does not seem to be going away, ASN is working to ensure that NIH has the most robust baseline budget possible from Congress in 2014. The society is collaborating with the Coalition for Health Funding in support of $65 billion for discretionary public health and health research programs in FY 2014. During the society's third Annual ASN Hill Day on April 25, ASN Council, Board of Advisors, and Public Policy Board members will meet with scores of congressional offices in both the House and Senate to discuss the importance of sustained funding for NIH and innovative kidney research in particular. Last year ASN met with nearly 60 congressional offices, including half a dozen members of Congress who sit on committees with jurisdiction over the society's key issues.



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Industry Spotlight

Renal Cancer Drugs Show Similar Survival Rates

A phase three trial showed that an already approved drug, sorafenib (Nexavar, manufactured by Bayer Pharma), and tivozanib share a similar survival period for patients with advanced renal cell cancer.

Sorafenib, also used for liver cancer, is a treatment for advanced renal cell cancer, and patients use it after earlier treatments with interferon-α or interleukin-2 have failed or if physicians deem these treatments inadequate. Sorafenib is a multikinase inhibitor (a tyrosine kinase inhibitor, an angiogenesis inhibitor, and a vascular endothelial growth factor [VEGF] inhibitor).

Tivozanib, the study drug, is a selective inhibitor of all three VEGF receptors that was designed to block VEGF while minimizing toxicities to other areas. Tivozanib is an oral, once-daily investigational tyrosine kinase inhibitor. Earlier, the TIVO-1 trial showed positive top-line results in advanced renal cell cancer, and the agent is being studied for use against other tumors.

Tivozanib and sorafenib treatment for patients with advanced renal cell carcinoma showed statistically similar overall survival, according to research reported at the Genitourinary Cancers Symposium by Robert J. Motzer, MD, a medical oncologist at Memorial Sloan-Kettering Cancer Center in New York.

At the time of final overall survival analysis, which was 2 years after the last patient was enrolled, 219 subjects had died: 118 (45.4 percent) in the tivozanib arm and 101 (39.3 percent) in the sorafenib arm. The median survival rates were 28.8 months for tivozanib and 29.3 months for sorafenib, which was not a significant difference.

Of the 257 patients taking sorafenib at randomization, more than half, (155, or 60.3 percent) had started taking next-line tivozanib by the time the data were analyzed.

Lead researcher Motzer presented final overall survival data from 1517 patients who were randomized to receive either tivozanib 1.5 mg a day (3 weeks on, 1 week off) or sorafenib 400 mg a day (twice daily, continuously), according to PharmPro.com. In the extension study, patients who experienced progression while taking sorafenib were eligible to receive tivozanib, which researchers said may account for a slightly longer survival time in the patients taking sorafenib.

Some side effects that bother renal cancer patients, including skin toxicity, diarrhea, nausea, and fatigue, were not as common with tivozanib. The lower toxicity and rate of side effects were positive features for a first-line therapy for advanced kidney cancer, Motzer said.

The manufacturers of tivozanib, AVEO Pharmaceuticals in Cambridge, MA, and Astellas Pharma, Inc., in Tokyo, were excited about the news when safety and other data from the study TIVO-1 were announced in 2012. "We are delighted with the outcome of TIVO-1 and to be collaborating with AVEO on tivozanib at this critical juncture," said Steven Ryder, MD, president of Astellas Pharma Global Development. "Tivozanib is an important asset to our strategy of becoming a global category leader in oncology."

NxStage Has Solid 2012

NxStage, a manufacturer of home-based dialysis equipment like the NxStage System One (to date the only portable home system cleared by the U.S. Food and Drug Administration for use in home hemodialysis) and other dialysis products, announced fourth-quarter and year-end results for 2012.

Revenue for 2012 increased 11 percent to a total of $242.1 million, compared with revenue of $217.3 million for 2011. Revenue for the fourth quarter of 2012 increased 14 percent to a record $65.0 million, compared with revenue of $57 million for the fourth quarter of 2011.

NxStage at the same time reported a net loss of $15.2 million (or $0.26 per share) for 2012, compared with a net loss of $21.4 million (or $0.39 per share) in 2011.

NxStage attributed the performance to growth in the home-based dialysis market because of the growing adoption of home hemodialysis with the System One.

NxStage has also enjoyed three recent occurrences that have positioned the company well to do business with members of the European Union (EU). The company obtained CE Mark approval (for doing business in the EU) for its high-flow dialysis capabilities, for its single-needle technology, and for nighttime home hemodialysis with the System One. Although it has been approved for home hemodialysis in the United States, the System One is not currently approved for nocturnal home hemodialysis. NxStage is presently conducting a trial in the United States for this indication.

Separately, NxStage announced plans to transition to a direct sales operation in the United Kingdom, cutting out a distributor relationship. The company anticipates that this action will further strengthen its relationships with local customers and position it to take advantage of new product approvals more rapidly.

"With increasing confidence in our ability to drive continued growth with new direct-to-patient marketing programs, we believe the overall effect of our product execution is that we are better positioned to accelerate adoption of our therapies with much greater potential than in the past," said NxStage chief executive officer Jeffrey Burbank. "With the benefit of these programs largely expected in 2014, we expect top-line 2013 revenue to remain strong and grow at a rate similar with 2012, followed by accelerated success and over 15 percent annual revenue growth in 2014 and beyond, excluding any benefit of service revenue from NxStage-owned centers of excellence."

Brief Summary: Consult full package insert for complete Prescribing Information.

INDICATIONS AND USAGE: Phoslyra® (calcium acetate oral solution 667 mg per 5 mL) is a phosphate binder indicated to reduce serum phosphorus in patients with end stage renal disease (ESRD). Management of elevated serum phosphorus levels usually includes all of the following: reduction in dietary intake of phosphate, removal of phosphate by dialysis, and inhibition of intestinal phosphate absorption with phosphate binders.

DOSAGE AND ADMINISTRATION: The recommended initial dose of Phoslyra for the adult dialysis patient is 10 mL with each meal. Increase the dose gradually to lower serum phosphorus levels to the target range, as long as hypercalcemia does not develop. Titrate the dose every 2 to 3 weeks until an acceptable serum phosphorus level is reached. Most patients require 15–20 mL with each meal.

CONTRAINDICATIONS: Patients with hypercalcemia.

WARNINGS AND PRECAUTIONS:

Hypercalcemia. Patients with end stage renal disease may develop hypercalcemia when treated with calcium, including calcium acetate (Phoslyra). Avoid the concurrent use of calcium supplements, including calcium-based nonprescription antacids, with Phoslyra. An overdose of Phoslyra may lead to progressive hypercalcemia, which may require emergency measures. Therefore, early in the treatment phase during the dosage adjustment period, monitor serum calcium levels twice weekly. Should hypercalcemia develop, reduce the Phoslyra dosage or discontinue the treatment, depending on the severity of hypercalcemia.

More severe hypercalcemia (Ca >12 mg/dL) is associated with confusion, delirium, stupor and coma. Severe hypercalcemia can be treated by acute hemodialysis and discontinuing Phoslyra therapy. Mild hypercalcemia (10.5 to 11.9 mg/dL) may be asymptomatic or manifest as constipation, anorexia, nausea, and vomiting. Mild hypercalcemia is usually controlled by reducing the Phoslyra dose or temporarily discontinuing therapy. Decreasing or discontinuing Vitamin D therapy is recommended as well.

Chronic hypercalcemia may lead to vascular calcification and other soft-tissue calcification. Radiographic evaluation of suspected anatomical regions may be helpful in early detection of soft tissue calcification.

The long-term effect of Phoslyra on the progression of vascular or soft tissue calcification has not been determined.

Hypercalcemia (>11 mg/dL) was reported in 16% of patients in a 3-month study of a solid dose formulation of calcium acetate; all cases resolved upon lowering the dose or discontinuing treatment.

Maintain the serum calcium-phosphorus product (Ca X P) below 55 mg^2/dL^2.

Concomitant Use with Medications. Hypercalcemia may aggravate digitalis toxicity. Phoslyra contains maltitol (1 g per 5 mL) and may induce a laxative effect, especially if taken with other products containing maltitol.

ADVERSE REACTIONS: No clinical trials have been performed with Phoslyra in the intended population. Because the dose and active ingredients of Phoslyra are equivalent to that of the calcium acetate gelcaps or tablets, the scope of the adverse reactions is anticipated to be similar.

Hypercalcemia is discussed elsewhere *[see Warnings and Precautions]*.

Clinical Trial Experience. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In clinical studies, calcium acetate has been generally well tolerated.

The solid dose formulation of calcium acetate was studied in a 3-month, open-label, non-randomized study of 98 enrolled ESRD hemodialysis patients and in a two week double-blind, placebo-controlled, cross-over study with 69 enrolled ESRD hemodialysis patients. Adverse reactions (>2% on treatment) from these trials are presented in Table 1.

Table 1: Adverse Reactions in Patients with End-Stage Renal Disease Undergoing Hemodialysis

	Total adverse reactions reported for calcium acetate n=167	3-mo, open-label study of calcium acetate n=98	Double-blind, placebo-controlled, cross-over study of calcium acetate n=69	
			Calcium acetate	Placebo
Preferred Term	n (%)	n (%)	n (%)	n (%)
Nausea	6 (3.6)	6 (6.1)	0 (0.0)	0 (0.0)
Vomiting	4 (2.4)	4 (4.1)	0 (0.0)	0 (0.0)
Hypercalcemia	21 (12.6)	16 (16.3)	5 (7.2)	0 (0.0)

Calcium acetate oral solution was studied in a randomized, controlled, 3-arm, open label, cross-over, single-dose study comparing calcium acetate oral solution to a solid formulation in healthy volunteers on a controlled diet. Of the observed drug-related adverse reactions, diarrhea (5/38, 13.2%) was more common with the oral solution.

Postmarketing Experience. The following additional adverse reactions have been identified during post-approval of calcium acetate: dizziness, edema, and weakness.

DRUG INTERACTIONS: The drug interaction profile of Phoslyra is characterized by the potential of calcium to bind to drugs with anionic functions (e.g., carboxyl, carbonyl, and hydroxyl groups). Phoslyra may decrease the bioavailability of tetracyclines or fluoroquinolones via this mechanism.

There are no empirical data on avoiding drug interactions between calcium acetate or Phoslyra and most concomitant drugs. When administering an oral medication with Phoslyra where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, administer the drug one hour before or three hours after Phoslyra or calcium acetate. Monitor blood levels of the concomitant drugs that have a narrow therapeutic range. Patients taking anti-arrhythmic medications for the control of arrhythmias and anti-seizure medications for the control of seizure disorders were excluded from the clinical trials with all forms of calcium acetate.

Ciprofloxacin. In a study of 15 healthy subjects, a co-administered single dose of 4 calcium acetate tablets (approximately 2.7 g) decreased the bioavailability of ciprofloxacin by approximately 50%.

USE IN SPECIFIC POPULATIONS

Pregnancy: Category C. Phoslyra contains calcium acetate. Animal reproduction studies have not been conducted with Phoslyra, and there are no adequate and well controlled studies of Phoslyra use in pregnant women. Patients with end stage renal disease may develop hypercalcemia with calcium acetate treatment *[see Warnings and Precautions]*. Maintenance of normal serum calcium levels is important for maternal and fetal well being. Hypercalcemia during pregnancy may increase the risk for maternal and neonatal complications such as stillbirth, preterm delivery, and neonatal hypocalcemia and hypoparathyroidism. Phoslyra treatment, as recommended, is not expected to harm a fetus if maternal calcium levels are properly monitored during and following treatment.

Labor and Delivery. The effects of Phoslyra on labor and delivery are unknown.

Nursing Mothers. Phoslyra contains calcium acetate and is excreted in human milk. Human milk feeding by a mother receiving Phoslyra is not expected to harm an infant, provided maternal serum calcium levels are appropriately monitored.

Pediatric Use. Safety and effectiveness of Phoslyra in pediatric patients have not been established.

Geriatric Use. Clinical studies of calcium acetate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

OVERDOSAGE: Administration of Phoslyra in excess of the appropriate daily dosage may result in hypercalcemia *[see Warnings and Precautions]*.

HOW SUPPLIED/STORAGE AND HANDLING: Phoslyra for oral administration is a clear solution containing 667 mg calcium acetate per 5 mL. Phoslyra is supplied in a 473 mL (16 oz) amber-colored, multiple-dose bottle, packaged with a marked dosing cup. Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. The shelf life is 24 months.

PATIENT COUNSELING INFORMATION: Inform patients to take Phoslyra with meals, adhere to their prescribed diets, and avoid the use of calcium supplements including nonprescription antacids. Inform patients about the symptoms of hypercalcemia *[see Warnings and Precautions and Adverse Reactions]*.

Advise patients who are taking an oral medication where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy to take the drug one hour before or three hours after Phoslyra.

Manufactured for:
Fresenius Medical Care North America
Waltham, MA 02451 1-800-323-5188

Manufactured by:
Lyne Laboratories
Brockton, MA 02301

FRESENIUS MEDICAL CARE

101493-01 Rev. B 08/2012

In patients with ESRD...

Take as is

First and only FDA-approved little LIQUID phosphate binder

- May lessen pill burden
- Potential to reduce optional fluid intake associated with administration of solid PBs
- No water required
- Premixed—No need to reconstitute or dissolve in water
- No refrigeration, even after opening

Phoslyra®

calcium acetate oral solution
667 mg per 5 mL

Clearly different.

INDICATION:

Phoslyra® (calcium acetate oral solution, 667 mg per 5 mL) is a phosphate binder (PB) indicated for the reduction of serum phosphorus in patients with end stage renal disease (ESRD). Phoslyra is administered orally with food.

IMPORTANT SAFETY INFORMATION:

- **Phoslyra is contraindicated in patients with hypercalcemia.**
- **Patients should have serum calcium levels closely monitored and their dose of Phoslyra adjusted or terminated to bring levels to normal.** No other calcium supplements should be given concurrently with Phoslyra.
- Phoslyra may decrease the bioavailability of tetracyclines or fluoroquinolones.
- There are no empirical data on avoiding drug interactions between calcium acetate or Phoslyra and most concomitant drugs. When administering an oral medication with Phoslyra where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, administer the drug 1 hour before or 3 hours after Phoslyra or calcium acetate. Monitor blood levels of the concomitant drugs that have a narrow therapeutic range.
- The most common (>10%) adverse reactions experienced with Phoslyra are hypercalcemia, nausea, and diarrhea.
- Phoslyra may cause diarrhea with nutritional supplements that contain maltitol.

For additional important safety information, please see brief Prescribing Information on this page.

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