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.

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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.

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