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.

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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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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.

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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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