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 immunosupulatory properties increase transplant rejection risk. The impact of HCV across the CKD spectrum, coupled with limited existing treatment options, 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.

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 transaminis, 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 treatment outcomes is sparse; and 4) many IFN-based studies...
Kidney Transplant Recipients

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 transplant program guidelines worldwide. Finally, the literature review and analyses 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 postrand transplantation lymphoproliferative disease; herpes simplex 1 and 2; varicella; hepatitis B and C; HIV; urinary tract infections; pneumocystis; and Canandiida infections); diabetes mellitus (screening for and monitoring 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 percent (87) were graded D.

The Work Group suggested interferon/rivabirin, targeted to achieve sustained viral clearance, be used where HCV is implicated in the glomerulonephritis pathogenesis. For patients with cryoglobulins and flares, treating the systemic process with plasma exchange and immunosuppression (e.g., steroids, rituximab) prior to antiviral therapy was suggested. In conclusion, an unexpected guideline 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

Guidelines
Continued from page 19

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 superpharmacological exposure. Although standard IFN response rates are higher in dialysis than non-CKD patients, standard IFN response rates are higher than from viral complications. It was suggested that HCV-positive donor kidneys not be used in uninfected candidates given increased risk for liver disease and diabetes post-transplant, 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 invariably 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 also suggested that recipients undergo annual hepatology evaluation, with IFN used only where the benefit of halting liver disease outweighed rejection risk.

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 transplant program guidelines worldwide. Finally, the literature review and analyses 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 postrand transplantation lymphoproliferative disease; herpes simplex 1 and 2; varicella; hepatitis B and C; HIV; urinary tract infections; pneumocystis; and Canandiida infections); diabetes mellitus (screening for and monitoring 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 percent (87) were graded D.

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 contaminated) 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 hepatologic 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 biopsy 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 post-transplant, 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 invariably 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 also 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 mammalianproliferative 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/rivabirin, 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 guideline 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

Continued on page 22