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Pathophysiology and Treatment of Hepatitis B and C Infections in Patients With End-Stage Renal Disease

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An in-depth understanding of viral hepatitis is important to the care of patients with end-stage renal disease undergoing hemodialysis. Both hepatitis B and C viruses are acquired through hematogenous spread and can lead to horizontal transmission. Concurrent hepatic and renal injuries have ominous outcomes with significant morbidity. Hepatitis B incidence has decreased through practices including vaccination of nonimmune individuals and isolation of patients with the disease. The pathogenesis of hepatitis B leads to various symptoms and serologic changes with unique temporal associations dictating an acute or chronic presentation. Chronic hepatitis B develops when there is persistence of surface antigen for more than 6 months. Occult hepatitis B is an enigmatic form of the chronic disease where viral DNA is present despite the patient remaining seronegative. Nucleoside analogs are used as a treatment for individuals with hepatitis B who have comorbid CKD; however, the mainstay of infection control relies on immunization. Hepatitis C, an RNA virus, has increased in prevalence. Strict universal precautions with sound infection-control practices are important to prevent seroconversion. Recent therapeutic advances involving the development of direct-acting antiviral agents have broadened treatment options for patients with renal impairment and hepatitis C, offering the potential for a definitive cure. Controversy on the timeliness of treatment for transplant options has also risen with the advent of these newer therapies. We review the epidemiology, pathophysiology, and updates in treatment of these viral entities as they relate to the hemodialysis population.

Key Words: Hepatitis B, Hepatitis C, End-stage renal disease, Dialysis, Direct-acting antiviral agent

Patients with end-stage renal disease (ESRD) who undergo maintenance hemodialysis are at significant risk for contracting a variety of viral infections. Alterations in both the innate and adaptive branches of the immune system coupled with the potential for exposure from infected blood-borne sources associated with an extracorporeal circuit predispose these individuals to infection.[1] Both hepatitis B virus (HBV) and hepatitis C virus (HCV) are of particular interest as they have the potential for transmission via a nosocomial hematogenous spread and can ultimately cause severe liver disease.

EPIDEMIOLOGY OF VIRAL HEPATITIS

An estimated 2 billion people worldwide have been infected with HBV, and an estimated 350 million have chronic, lifelong infections, making it a severe global public health issue.[2,3] The epidemiology of hepatitis B varies by region with increasing prevalence in North Africa, the Middle East, parts of Eastern and Southern Europe, parts of Latin America, and South Asia while high-prevalence areas are seen in Western Africa and South Sudan.[3,4] Between 15% and 40% of those with chronic HBV develop cirrhosis, hepatocellular carcinoma (HCC), or liver failure.[4,5] An analysis of data from the Dialysis Outcomes and Practice Patterns Study showed an HBV prevalence of 0%-6.6% across dialysis facilities in Western Europe, Japan, and the United States.[5,6]

Although the incidence of acute HBV has steadily declined at an estimated rate of 80% in the United States since the late 1980s, the incidence of HCV has increased 20% from 2015 to 2016 based on data from the Centers for Disease Control and Prevention (CDC).[7] The incidence rate of HCV for 2016 was 1.0 case per 100,000 population, an increase from that for 2015 (0.8 cases per 100,000 population). Actual acute cases are estimated to be 13.9 times the number of reported cases in any year due to underreporting/ascertainment. The CDC estimates that 3.5 million people are living with HCV infection in the United States. These numbers are confounded in that many patients are unaware of their HCV status. The number of annual HCV-related deaths continues to rise and exceeded the number of deaths reported for 60 other nationally notifiable infectious diseases combined.[8] The prevalence of HCV in the United States among patients with ESRD is reported as 8%-10% as opposed to 1.6% in the general population. Extrahepatic manifestations/complications of HCV and increased exposure risk of hemodialysis are identified as factors for the increased prevalence.

COMPLICATIONS OF VIRAL HEPATITIS

Viral hepatitis has been implicated as a causative factor in the development of various forms of extrahepatic vasculitis that can lead to both acute kidney injury and chronic kidney disease (CKD). Patients affected with HBV, particularly those with the hepatitis E antigen, have a higher incidence of developing membranous nephropathy.[9] Polyarteritis nodosa, a systemic necrotizing disorder that affects both small- and medium-sized arteries, is associated with chronic HBV.[10] Both HCV and HBV predispose patients to developing membranoproliferative glomerulonephritis. Cryoglobulinemic vasculitis typified by the

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presence of serum proteins that precipitate in cold temperature can be caused by HCV infections. Despite treating the aforementioned underlying disease processes, progression of chronic disease may result, ultimately leading to dialysis dependence.

Morbidity associated with HBV and HCV ranges from fulminant hepatic failure to a chronic carrier state that can perpetuate transmission to others. Cirrhosis can develop in untreated individuals and compound the already immense burden of disease in patients with ESRD, manifesting as encephalopathy, refractory ascites, coagulopathy, and variceal bleeding. One study evaluating 1068 cirrhotic patients with ESRD compared with a control group without renal diseases showed a near doubling in hazard ratio in patients with ESRD. One-year and 3-year mortality rates of 48.5% and 73.1% in the ESRD group were significantly greater than 32.9% and 55.6% in the control group, respectively.[11] In fact, liver cirrhosis has been shown to be an independent risk factor for death in patients, regardless of dialysis modality, as both patients with peritoneal dialysis and hemodialysis were found to have equivalent adverse outcomes after adjustment for this condition.[12]

HBV PATHOGENESIS

HBV belongs to the Hepadnaviridae family and is a noncytopathic enveloped virus with a partially double-stranded circular DNA genome. It can lead to a severe liver disease such as fulminant hepatitis, cirrhosis, or HCC. The pathogenesis of HBV-related liver disease is largely due to the immune-related liver damage that is induced by active viral replication. The small genome encodes for 4 main genes by a series of overlapping reading frames. The polymerase gene is the largest open reading frame and encodes for the multifunctional polymerase protein. The core gene encodes for the core antigen (HBcAg), and the precore gene encodes for the hepatitis B e-antigen (HBeAg), which has a large overlapping sequence with HBcAg.[13] The 3 envelope genes PreS1, PreS2, and S encode for the large, middle, and small envelope proteins, respectively, and the X gene encodes for the accessory X protein.[13] HBV infection is an established cause of acute and chronic hepatitis and cirrhosis. The antibody response to the HBV envelope antigens is a T-cell–dependent process and may explain why patients with advanced CKD are more susceptible to infections.

CLINICAL SUMMARY

- Hepatitis B and C have a significant impact on the care of patients with end-stage renal disease, influencing infection-control practices on a global spectrum.
- Both viruses have unique replication patterns and pathogenesis affecting surveillance practices, prophylaxis, and treatment.
- Advances in antiviral therapy have led to a number of treatment options based on the genotype.

HBV CLASSIFICATION

Genotypic classification of this DNA virus has become the standard of care as variants are produced as a result of differences that occur with the reverse transcriptase responsible for replication. Ten HBV genotypes have been identified with an alphabetic nomenclature referred to as A–J. HBV genotypes are associated with the modes of HBV transmission (vertical vs horizontal) and with the risk of certain outcomes of chronic infection, such as cirrhosis and HCC.[14] Many studies have reported that different genotypes and subgenotypes show different geographical distributions and are related to disease development, clinical progression, response to antiviral treatment, and prognosis.[6]

ACUTE HBV INFECTION

An acute HBV infection may last up to 6 months with or without symptoms. As the blood becomes exposed to HBV, the body mounts a cell-mediated immune response by sending cytotoxic T lymphocytes and natural killer cells to the virus and releases inflammatory cytokines. After an incubation period of several weeks, antiviral antibodies appear, beginning with immunoglobulin M hepatitis B core antibody (HBcAb).[15] A window period exists in which hepatitis B surface antigen (HBsAg) and hepatitis B surface antibody (HBsAb) are not detected. Serologic tests will be positive for total HBcAb and hepatitis Be antibody (HBeAb) during this time period (Fig 1[16]). In addition to the antibody response, a type 1 helper T-lymphocyte response occurs against hepatitis B core, surface, and envelope antigens, which helps to activate cytotoxic T lymphocytes and B-cell responses through a cytokine release.[15] During acute HBV infections, reductions in the HBV DNA load and antigens in serum usually coincide with or precede liver damage, defined by an elevated level of serum alanine aminotransferase (ALT) and T-cell infiltration, which suggests that there is an earlier, noncytopathic mechanism controlling HBV infections.[17] Potential signs and symptoms include abdominal and/or joint pain, dark urine, fever, loss of appetite, fatigue, nausea, and vomiting. More severe symptoms, including changes in hemodynamic status and alteration of mentation, dictate the need for hospitalization as a fulminant hepatic failure can present with encephalopathy, or in extreme cases, cerebral edema.

The CD4+ T-cell response could facilitate the development of neutralizing antibodies to HBsAb and the induction of cytotoxic T-lymphocyte responses.[17] CD8+ T cells contribute to the production of antiviral cytokines and perform cytotoxic activities to eliminate virus-infected hepatocytes, which not only clears HBV-infected cells but also induces immunopathology. Patients with acute HBV usually generate stronger polyclonal T-cell responses against HBV antigens, especially HBV core antigen and HBeAg, than patients with chronic HBV who developed only a monoclonal or even an undetectable T-cell response. The patient's immune response is imperative to determining whether the virus becomes a chronic infection.

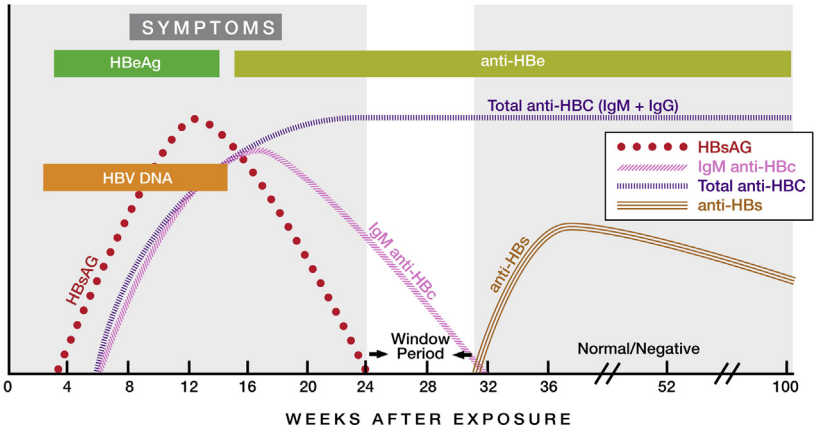

Figure 1. Acute hepatitis B serology. On average, HBsAg can be detected after initial virus exposure. This may precede the onset of symptoms by one to two months. Symptoms typically occur 12 weeks after exposure. HBeAg is a sign of higher infectivity, whereas the presence of anti-HBe denotes lower levels of virus with lower infectivity. The presence of anti-HBs generally indicates recovery. There is a "window period" that occurs when HBsAg has declined before the appearance of anti-HBs where the only serologic marker detectable indicating infection are IgM anti-HBc and total anti-HBc. Note that individual time periods may vary. Abbreviations: anti-HBe, hepatitis B e-antibody; anti-HBs, hepatitis B surface antibody; HBeAg, hepatitis B e-antigen; HBV DNA, hepatitis B virus DNA; HBsAg, hepatitis B surface antigen; IgM anti-HBc, hepatitis B core IgM antibody; total anti-HBc, total hepatitis B core antibody. Figure adapted from CDC (Centers for Disease Control and Prevention) video clip: https://www.cdc.gov/hepatitis/resources/professionals/training/serology/training.htm.

CHRONIC HBV INFECTION

A chronic infection occurs when immunocompromised individuals cannot eradicate and clear infected hepatocytes. Acute HBV progresses to chronic HBV in approximately 40% of affected patients requiring hemodialysis.[2] Chronic HBV infections seem to have diminished CD4+ and CD8+ cellular responses in the peripheral blood.[15] Patients who are chronically infected are defined by primarily having persistent HBsAg for more than 6 months. Associate findings include having intermittent elevations of ALT and aspartate aminotransferase and HBV DNA > 20,000 IU/mL.

Chronic HBV is divided into 4 phases: (1) immune tolerance; (2) immune clearance; (3) inactive carrier; and (4) HBV reactivation.[17] These phases are linked to the degree of HBV replication and the corresponding immune response. Initially in the immune tolerant phase, the HBV DNA viral load is elevated but not the ALT. After many years, when immune tolerance is lost, the immune-clearance or active phase occurs when the immune system attacks infected hepatocytes. This results in elevated ALT levels and fluctuating HBV DNA levels causing liver fibrosis. The inactive carrier phase follows when HBeAg is negative or low or has undetectable HBV DNA levels with a normal ALT and does not involve damage to the liver. The final reactivation phase is spontaneous but can be triggered as a result of immunosuppression. Patients can revert to HBeAg positivity, but most are HBeAg-negative with detectable DNA levels, high ALT, and moderate-to-severe necroinflammation with variable amounts of fibrosis on liver biopsy. A prolonged immune-clearance phase and HBeAg-negative hepatitis, with persistent or recurrent hepatitis flares, will eventually result in advanced liver fibrosis and increased risk of HCC.[18]

HEPATITIS DELTA VIRUS

The hepatitis delta virion (HDV) is the smallest RNA pathogen known to interact with a human host and is the most severe form of viral hepatitis. HBV plays an essential role as a helper virus for HDV because its envelope proteins are necessary for HDV propagation.[19] HDV requires the envelope proteins of HBV for its assembly and release and exclusively occurs in the presence of HBV.[19] Therefore, the release of HDV from the infected hepatocytes can occur only if the cells are coinfected with HBV or when HDV superinfection occurs in individuals already infected with HBV.[19] A study in Sudan demonstrated an increased prevalence of HDV (13.3%) among hepatitis B patients on hemodialysis.[20] Hepatitis D is transmitted through percutaneous or mucosal contact with infectious blood and can be acquired either as a coinfection with HBV or as superinfection in people with HBV infections.[21] A superinfection is the most common form of hepatitis D and leads to a more severe liver disease than chronic hepatitis B infection alone. Up to 90% of superinfected individuals will develop chronic hepatitis D, of which approximately 70% will progress to cirrhosis, compared with 15%-30% of those infected with HBV alone.[22] There is no HDV-specific treatment. The results of pegylated interferon alpha (IFNa) have led to unsatisfactory outcomes in HDV-infected individuals.[19] Preventative measures including hepatitis B immunization, safe injection practices, blood safety, and harm-reduction services with clean needles and syringes are the focus of preventing transmission of HDV.[23]

TREATMENT OF HBV INFECTION

Therapeutic management of HBV in dialysis patients focuses on suppression of HBV replication via antiviral therapy to prevent the development of complications including cirrhosis and HCC.[24] The decision to start antiviral therapy relies on the demonstration of active viral replication. This can be defined by HBeAg or serum HBV DNA detectable by branched DNA or hybrid capture assays, elevated serum ALT concentrations >1.5 times the upper limit of normal, or evidence of moderate-to-severe

chronic hepatitis on liver biopsy.[24] The conventional cutoff level of serum ALT for commencing antiviral therapy may prove too high and inappropriate for dialysis patients, and liver biopsy appears to be the only definitive means to establish the activity of liver disease in dialysis patients. Note that it can be difficult to interpret ALT elevations in patients undergoing dialysis as they can have a low serum ALT level at baseline, and thus an increased ALT level in this population may still remain in the normal range.[24]

Two major groups of antiviral treatments have been licensed for the treatment of chronic HBV infection in many countries. These include IFNa or pegylated IFNa and nucleoside analogs (NAs) or nucleotide analogs. Limited literature exists on IFNa therapy on patients with chronic HBV infection receiving hemodialysis. Exacerbation of IFNa side effects, mostly myelosuppression and malnutrition, hampers its use in clinical practice.[25] The treatment options for patients with CKD are based on NAs (lamivudine, telbivudine, and entecavir) or nucleotide (adefovir, Tenofovir disoproxil fumarate and Tenofovir alafenamide fumarate (TAF) analogs. All NAs need to be dose adjusted in hemodialysis patients due to altered pharmacokinetics, except TAF which is not recommended to use in hemodialysis patients (Table 1).[25] NAs are dialyzable in 50% of cases because they have low molecular weight and relatively lack protein binding. However, due to the high volume of drug distribution (>100 L) and the intermittent nature of hemodialysis, no additional dose after hemodialysis is required.[26] Most NAs are given once weekly after a hemodialysis session. For patients who have chronic HBV and are NA-naive, the first-line treatment recommendation is entecavir, TAF, and Tenofovir disoproxil fumarate. Tenofovir is the NA of choice for patients with resistance to NAs. Long-term entecavir therapy is not as effective in patients with lamivudine resistance.[24,25]

OCCULT HBV INFECTION

Occult HBV infection (OBI) is defined as the presence of HBV DNA in liver tissue and serum of subjects who are seronegative for HBsAg. OBI is important in patients with ESRD undergoing dialysis due to the transmission of viruses through shared-use dialysis machines, frequent blood transfusions, or by reactivation after kidney transplantation.[27] Therapeutic consideration toward isolation remains controversial. Previous reports from studies in dialysis units have indicated that the prevalence of occult HBV ranges from 0% to 58% among patients.[28] Although there have been no studies in the United States, there are data demonstrating unrecognized OBI worldwide. A study in Iranian hemodialysis patients with isolated HBcAb showed that 50% presented with a detectable HBV DNA. This survey showed that OBI was common in hemodialysis patients with isolated HBcAb and could reflect unrecognized OBI in hemodialysis patients. Most of these infections are associated with low viral loads.[29] A study in Palestine of the overall prevalence of OBI among hemodialysis patients found a prevalence of 12.5%. Of the 132 hemodialysis patients tested for HBcAb, 31.8% were found to be positive.[30] Ersoy and colleagues[31] studied the prevalence of OBI in patients on maintenance hemodialysis. Eighty patients who were on dialysis and were previously detected as HBsAg negative were recruited. Sixty-eight patients (85%) tested positive for at least 1 of the serological markers used for hepatitis B, 3 patients (3.75%) for only HBcAb, and 33 patients (41.25%) for only HBsAb.[31] The prevalence of OBI was found to be 1.25%. OBI patients are at risk for progression of liver disease, causing cryptogenic liver disease, acute exacerbation of chronic HBV or fulminant hepatitis, poor response to antiviral treatment, and development of HCC.[24]

PREVENTION OF HBV

Preventing transmission of HBV in dialysis centers has been an important part of infection control in hemodialysis. In an environment where multiple patients receive dialysis concurrently, repeated opportunities exist for person-to-person transmission of infectious agents, directly or indirectly via contaminated devices, equipment and supplies, environmental surfaces, or hands of personnel. Recommendations for the control of hepatitis B in hemodialysis centers were first published in 1977,

Table 1. Dosage Adjustment of Nucleos(t)ide Analogs and Interferon According to Serum CrCl for Hepatitis B[25]

CrCl (mL/min)	Lamivudine	Telbivudine	Adefovir	Entecavir*	TDF	TAF	Pegylated Interferon α-2α
≥50	100 mg/day	600 mg/day	10 mg/day	0.5 mg/day	245 mg/day	25 mg/day	180 μg SQ/week
30-49	First dose, 100 mg; then 50 mg/day	600 mg/day 2	10 mg/day 2	0.25 mg/day	245 mg/day 2	25 mg/day	135 μg SQ/week
15-29	First dose, 35 mg; then 25 mg/day	600 mg/day 3	10 mg/day 3	0.15 mg/day	245 mg/day 2-3	25 mg/day	
5-14	First dose, 35 mg; then 15 mg/day	600 mg/day 3	10 mg/day 3†	0.05 mg/day†	245 mg/week†		
<5	First dose, 35 mg; then 10 mg/day	600 mg/day 4	10 mg/week after HD‡	0.5 mg/week after HD‡	245 mg/week after HD‡		

Abbreviations: CrCl, creatinine clearance; HD, hemodialysis; SQ, subcutaneous; TAF, Tenofovir alafenamide fumarate; TDF, Tenofovir disoproxil fumarate.
*Recommended only for nucleos(t)ide analog-naive patients.
†Recommended only for CrCl ≥ 10 mL/min.
‡Only for patients on HD.
Reprinted from Pipili et al,[25] with permission from the International Society of Nephrology.

and by 1980, their widespread implementation was associated with a significant reduction in incidence of HBV infection among both patients and staff members.[32]

Routine preexposure vaccination should be considered for adults who are at increased risk, such as ESRD patients due to increased risk of percutaneous or mucosal exposure to blood. Three HBV vaccine formulations are available, ENGERIX-B (GlaxoSmithKline, Research Triangle Park, NC), RECOMBIVAX HB (Merck & Co., Inc., Whitehouse Station, NJ), and HEPLISAV-B (Dynavax Technologies Corporation, Berkeley, CA). When ENGERIX-B and RECOMBIVAX HB are used as a 3-dose series in immunocompetent patients, more than 90% of healthy adults and children develop adequate antibody responses. However, patients with renal failure require larger vaccine doses: 40 mcg of RECOMBIVAX HB at 0, 1, and 6 months (3 doses) or 40 mcg of ENGERIX-B at 0, 1, 2, and 6 months (4 doses). HEPLISAV-B is a two-dose series given at least 4 weeks apart in patients aged 18 years and older with all subtypes of hepatitis B. When a vaccine series initiated with one dose of a vaccine from a different manufacturer must be completed with HEPLISAV-B, 3 total hepatitis B vaccine doses should be administered. HEPLISAV-B may be used for revaccination after an initial hepatitis B vaccine series that consisted of doses of HEPLISAV-B or doses from a different manufacturer. Before initiating dialysis, patients' full hepatitis B serologic status should be documented and all susceptible patients should be vaccinated.[32] The CDC recommends an additional HBV vaccination series in the setting of failure to seroconvert after primary vaccine for all hemodialysis patients. Patients who fail to seroconvert after revaccination should be retested for HBsAg. Booster vaccination is recommended when antibody levels decline below 10 mIU/mL.[14]

In addition to vaccination, other infection-control practices have been used to prevent the transmission of hepatitis B. These include segregating HBV-infected patients in a separate treatment room, not assigning the same staff members to care for HBV-infected and susceptible patients, and assigning dedicated dialysis equipment and other supplies to infected patients so that these are not used by susceptible patients. Chlorinated bleach or comparable disinfectant is used in addition to standard precautions to sterilize dialysis devices and equipment due to the fastidious nature of the organism.

HCV CLASSIFICATION

HCV, first identified in 1989, is an RNA, enveloped, single-strand virus in the family Flaviviridae. Seven genotypes have been identified and are further divided into 67 subtypes.[33] Genotype 1 is the one most commonly reported in the United States. It is highly mutagenic and historically prone to treatment failure especially in the era preceding the use of directly acting antiviral (DAA) therapies. Acute presentation may be asymptomatic, and chronic disease rate is high. The incubation period is 14-180 days with an average of 45 days. Among newly infected persons, 20% to 30% develop symptoms of an acute disease, 75% to 85% develop chronic infections, and 15% to 25% spontaneously clear the virus.

HCV TRANSMISSION

Health-care exposures remain important sources of transmission and include the following: (1) receipt of blood products before 1992 (routine screening for HCV implemented in 1992); (2) receipt of clotting factor concentrates before 1987; (3) long-term hemodialysis; (4) needle-stick/sharp-object injuries; and (5) patient-to-patient transmission resulting from poor infection-control practices. Additional risk factors include incarceration, intranasal drug use, and tattoos obtained in unregulated settings.

HCV DIALYSIS–SPECIFIC FACTORS

Extrahepatic manifestations/complications of HCV and increased exposure risk of hemodialysis are identified as factors for increased prevalence. Isolation is not recommended, and dialyzer reuse is not contraindicated. Unlike HBV, no vaccine is currently available, so prevention requires strict attention to infection-control practices. Even a single reported case of acute HCV infection or seroconversion in a hemodialysis patient warrants thorough investigation because it might represent intrafacility transmission.[34] Potential causes include lack of patient-free period between shifts, sharing of hemodialysis machines and multidose vials, breaches in disinfection practices, and breaks in universal precautions.

The CDC's reference document, "Recommendations for Preventing Transmission of Infections Among Chronic Hemodialysis Patients", including the "Recommended Infection Control Practices for Hemodialysis Units at a Glance", are incorporated by referring the ESRD conditions for coverage.[35] The document suggests that HCV transmission within the dialysis environment can be prevented by strict adherence to infection-control precautions and that routine testing for ALT and anti-HCV is essential to monitor transmission. Monthly ALT testing of HCV-negative patients is expected to facilitate timely detection of new infections and aid in determination of when exposure or infection might have occurred. Testing for HCV antibody (HCAb) every 6 months is also recommended to monitor the occurrence of new HCV infections as ALT levels are not always reliable. If unexplained ALT elevations occur, repeat HCAb testing is warranted. If unexplained ALT elevations persist in patients who repeatedly test HCAb negative, testing for HCV RNA should be considered. At present, HCV RNA screening while providing a more sensitive test may not be feasible due to economic limitations. An HCV antigen test is pending Food and Drug Administration approval and may replace antibody testing, should prove helpful in posttreatment monitoring and/or serve as a more economical option to molecular testing.[36] Despite the CDC's testing recommendations, ESRD facilities are currently excused from the recommended testing schedule by exclusion of the HCV screening. It is important to note that the Code of Federal Regulations was published before any HCV treatment–specific renal studies and when use of interferon- and/or ribavirin-supplemented HCV treatment protocols were limited and ineffective. In 2015, the Association for Professionals in Infection Control and Epidemiology recommended removal of the HCV screening

exclusion to the Centers for Medicare and Medicaid Services.[37] A regulatory change to update the Center for Medicare and Medicaid Services ESRD CFC's language regarding hepatitis C testing recommendations would be required to remove the current exclusion and is currently under review by the Center for Medicare and Medicaid Services clinical standards group. HCV seroconversions may require reporting to the local health department as required by state-specific laws or regulations. When a seroconversion occurs, the dialysis unit should review all other patients' routine laboratory test data to identify potential additional cases. Potential sources of infection should be investigated to determine if transmission might have occurred within the dialysis unit, including review of the newly infected patients' recent medical history (eg, blood transfusion and hospitalization), history of high-risk behavior (eg, injecting-drug use and sexual activity), and unit practices and procedures. Genomic and molecular characterization of the HCV isolates in any outbreak should be considered,[38] and increased frequency of testing is recommended.

TREATMENT OF HCV INFECTION

HCV-positive persons should be evaluated for treatment. They should receive education on the routes of transmission to prevent further spread of the disease and should not donate blood. Vaccination against hepatitis A or B, if susceptible, is recommended to prevent compounding hepatic injuries.

Historically, HCV was treated with interferon- and ribavirin-based therapies. Owing to renal elimination, they required significant dose reductions. Cure rates were low, and adverse events were high among ESRD patients. DAAs have greatly reduced the need for these aforementioned medications and impacted the management of HCV by dramatically improving cure rates among CKD stage 4-5 patients. DAAs target viral proteins associated with replication, including NS3-4A protease, NS5A protein, and NS5B polymerase. Treatment algorithms generally rely on medications proven by study to achieve a sustained viral response for the targeted genotype. Patients who have undetectable HCV RNA in the serum, when assessed by a sensitive polymerase chain reaction assay, 12 or more weeks after completing treatment, are deemed to have achieved a sustained viral response. Treatment duration is variable and generally based on the medication selected, genotype, genotype resistance patterns, and whether the patient has cirrhosis or prior HCV treatment experience. The decision to treat algorithms generally includes confirmation of disease with HCV quantification (viral load). Patients with positive HCV antibody but negative HCV RNA have spontaneously cleared the infection, have been successfully treated for HCV, or are a false-positive and do not require treatment. Active infection confirmed by a positive HCV RNA test should be followed by genotyping. Recently "pangenotypic" therapies that can treat all major viral genotypes have been approved by the US Food and Drug Administration.[39] Patients who have failed prior DAA therapies should be referred for reevaluation to ensure an appropriate second-line regimen is selected as advances in retreatment protocols have been reported.[40]

Treatment options with DAAs are dynamic. Any attempt to provide a current treatment table would likely be outdated before publication. The American Association for the Study of Liver Diseases in partnership with the Infectious Diseases Society of America has established an HCV guidance website with recommendations for testing, managing, and treating hepatitis C. It is a highly recommended resource and should be referenced often for current practice and treatment therapies based on individual patient profile.[41] A historical summary of study-supported treatment options for patients with renal impairment is provided in Table 2[39,43-50] to remove doubt of treatment efficacy within the renal population.

Estimation of the degree of liver fibrosis is required for risk stratification, choice of DAA regimen, and follow-up care. Liver biopsy remains the "gold standard," but less invasive screening is becoming more practical. Despite having lower accuracy in assessing liver fibrosis in patients with stage 4-5 CKD than in the general population, newly developed biochemical test panels and elastography (FibroScan; Echosens, Paris, France), an ultrasound-based technology, are sufficiently reliable to evaluate extensive fibrosis/cirrhosis and preferred over biopsy with the exception of patients with an uncertain underlying cause of liver disease. Patients with advanced fibrosis or cirrhosis require screening for esophageal varices and HCC at the time of diagnosis of cirrhosis. HCC screening should continue every 6 months even after HCV is cured in patients with advanced fibrosis or cirrhosis.[51]

In patients with decompensated cirrhosis, the use of protease inhibitor–based DAA therapies (glecaprevir, grazoprevir, paritaprevir, simeprevir, or voxilaprevir) is often contraindicated because of possible hepatic drug accumulation and worsening liver disease. Dialysis patients with decompensated cirrhosis should be evaluated for dual organ transplantation, and treatment decisions regarding DAAs generally require supervised care by a transplant physician and/or hepatologist. Patients who previously received a liver transplant and have HCV reinfection should be evaluated for DAA therapies and may require alternative regimens.

Patients coinfected with human immunodeficiency virus or HBV require referral to an infectious disease or liver specialist. Drug-drug interactions should be considered before treatment. HBsAg-positive patients should be evaluated to determine if they meet criteria for antiviral treatment of HBV, and those who do should begin treatment before starting the HCV therapy. Those who do not meet criteria for HBV therapy should have HBV DNA levels monitored monthly during DAA therapy and for up to 3 months after the therapy because of the risk that HCV treatment may cause reactivation of HBV infection. In patients with isolated HBV core antibody positivity, the risk of HBV reactivation is rare, but any increase in ALT should prompt evaluation of HBsAg and HBV DNA levels.

Table 2. HCV Treatment–Specific Renal Studies

Study/Drug Regimen	Population Specifics	Summary
C-Surfer (Roth et al. 2015[42]), elbasvir-grazoprevir	• ≥18 years old • HCV genotype 1 • eGFR (MDRD) 5-29 mL/min = CKD 4 <15 mL/min = CKD 5 ± dialysis • Treatment naive or experienced • No HBV/HIV coinfection • Compensated cirrhosis allowed	SVR-12 achieved in 99% of patients with CKD stage 4-5 treated for HCV genotype 1 infection • 100% in treatment naive • 95% in treatment experienced Failure to achieve SVR-12 rare and only one relapse reported (genotype 1b) Regimen well tolerated and efficacy consistent across study subpopulations: diabetes, hemodialysis, and genotype 1a and 1b
Expedition-4 (Gane et al 2017[43]), glecaprevir-pibrentasvir	• ≥18 years old • HCV genotype 1-6 • HCV RNA ≥ 1000 IU/mL • eGFR (MDRD) 5-29 mL/min = CKD 4 <15 mL/min = CKD 5 ± dialysis • Treatment naive or experienced (exclusion of genotype 3 in treatment experienced) • No HBV/HIV coinfection • Compensated cirrhosis allowed • Acute kidney injury excluded	SVR-12 achieved in 98% of patients with CKD stage 4-5 treated for HCV infection for all major HCV genotypes; regimen well tolerated with a favorable safety profile
Expedition-5 (Persico et al 2018[44]), glecaprevir-pibrentasvir	• ≥18 years old • HCV genotype 1-6 • HCV RNA ≥ 1000 IU/mL • eGFR (MDRD) 30 to < 45 mL/min = CKD 3b 5-29 mL/min = CKD 4 <15 mL/min = CKD 5 ± dialysis • Treatment naive or experienced (exclusion of DAA except Sofosbuvir in treatment experienced) • No HBV/HIV coinfection • Compensated cirrhosis allowed	Study regimen highly efficacious in achieving SVR-12 in patients with chronic kidney disease stage 3b to 5 with the product-recommended treatment durations based on genotype, cirrhosis status, and prior treatment experience Treatment was well tolerated. Renal function remained unchanged after treatment in the predialysis patients assessed.
Ruby-I (Pockros et al 2016[45]), ombitasvir-paritaprevir-ritonavir and dasabuvir with or without ribavirin	• ≥18 years old • HCV genotype 1 • HCV RNA ≥ 1000 IU/mL • eGFR (MDRD) < 30 mL/min ± dialysis • Treatment naive • No HBV/HIV coinfection • No cirrhosis	SVR-12 in 90% of patients with HCV genotype 1 infection and stage 4 or 5 CKD. The regimen is well tolerated; however, ribavirin use may require a reduction or interruption to manage anemia.
Ruby-I (cohort 2) (Vierling et al 2016[46]), ombitasvir-paritaprevir-ritonavir and dasabuvir with or without ribavirin	• ≥18 years old • HCV genotype 1 • HCV RNA ≥ 1000 IU/mL • eGFR (MDRD) < 30 mL/min ± dialysis • Treatment naive or experienced (interferon + ribavirin • No HBV/HIV coinfection • Compensated cirrhosis allowed	SVR-12 rate of 96% in patients with CKD stages 4 or 5 in cohort 2; the regimen is well tolerated; however, a large proportion on ribavirin required dose modification to manage anemia.
Ruby-II (Gane et al 2016[47]) ribavirin-free ombitasvir-paritaprevir-ritonavir ± dasabuvir	• ≥18 years old • HCV genotype 1a or 4 • HCV RNA ≥ 1000 IU/mL • eGFR (MDRD) 5-29 mL/min = CKD 4 < 15 mL/min = CKD 5 ± HD • Treatment naive • No HBV/HIV coinfection • No cirrhosis	SVR-12 rate of 100% for genotype 1a and 80% for genotype 4 ($n = 5$ one patient terminated study due to transplant in week 2). No virologic failure or relapse; generally well tolerated; data support that ribavirin may not be necessary to treat genotype 1a or 4, but a larger trial is required to confirm.
Magellan-2 (Reau et al 2017,[48] glecaprevir-pibrentasvir	• ≥18 years old • Body mass index ≥ 18 kg/m^2	SVR-12 of 99%; rate surpassed historical standard of care; well tolerated

(*Continued*)

Table 2. HCV Treatment–Specific Renal Studies (*Continued*)

Study/Drug Regimen	Population Specifics	Summary
	• HCV genotype 1-6 • Liver or kidney transplant > 3 months prior with a stable immunosuppression regimen • Treatment naive or experienced with interferon, PEG-interferon or sofosbuvir + ribavirin ± PEG • No HBV/HIV coinfection • No cirrhosis allowed	
HCV-Target (Saxena et al 2016[49]); sofosbuvir (SOF)-containing regimens including SOF/PEG/ribavirin (RBV), SOF/RBV, SOF/simeprevir (SMV) or SOF/SMV/RBV	• ≥18 years old • HCV genotype 1-6 • Longitudinal study comparing baseline eGFR (MDRD) ≤ 45 ($n = 73$) mL/min with >45 mL/min ($n = 1716$) • Treatment with sofosbuvir-containing regimen for HCV • Treatment population, regimens, dosing, duration, or safety management guidelines undefined	SVR-12 of 83% of patients with eGFR ≤ 45 mL/min/1.73 m^2; renal clearance is the major elimination pathway for sofosbuvir; patients had higher rates of anemia, worsening renal dysfunction, and serious adverse events regardless of the use of RBV. Patients with renal impairment require close monitoring with sofosbuvir-containing regimens.
ClinicalTrials.gov NCT02251717 (Colombo et al 2017[50]), ledipasvir-sofosbuvir	• ≥18 years old • HCV genotype 1 or 4 • Kidney transplant ≥ 6 months before • Creatinine clearance ≥ 40 mL/min • Hemoglobin ≥10 g/dL and platelets > 50 K/mm^3 • Treatment naive or experienced • No HBV/HIV coinfection • Compensated cirrhosis allowed	SVR-12 of 100% in study population; no need to extend therapy to 24 weeks; safe and well tolerated; minimal change in eGFR(Cockcroft-Gault) with median change of 0.6 to 3 mL/min during treatment and up to 4 weeks after treatment

Abbreviations: eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; HD, hemodialysis; HIV, human immunodeficiency virus; MDRD, Modification of Diet in Renal Disease; PEG, pegylated interferon; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR-12, sustained viral response in 12 weeks.

Several studies support the safety and efficacy of DAAs after kidney transplant without increasing the risk of acute rejection. Considerable debate has ensued about the timing of DAA therapy in dialysis patients awaiting transplant. Delaying treatment until after kidney transplant allows patients the opportunity to accept an HCV-positive donor kidney and shorten kidney transplant wait time while improving organ allocation.[52] An analysis from 2010 showed that accepting an HCV-positive organ shortened wait times by 310 days in the United States.[53] As reported earlier, cases of acute HCV infection have significantly increased from 2010 to 2016 along with an increase in overdose deaths due to the opioid crisis. Transplant centers that use HCV-positive donor kidneys will likely benefit with even shorter wait times for HCV-positive dialysis recipients. Patients who are listed at transplant centers that do not use HCV-positive kidneys, those with live donors, those who are not candidates for kidney transplant, or those who are not active in a center accepting HCV-positive donor kidneys should be evaluated for treatment. In addition, patients with significant extrahepatic manifestations, those at significant risk of progressive liver disease before transplant, and those with strong personal preference to be treated should be evaluated for treatment with DAAs before transplantation.

SUMMARY

Chronic infection with HBV and HCV in patients with CKD remains a distinct and challenging clinical entity. The special characteristics of this patient group—immunosuppression, polypharmacy, and susceptibility for nosocomial transmission—coupled with complications of progression of liver disease often have long-term implications on patient management, morbidity, and mortality. A primary effort to eradicate these viruses with effective antivirals should be incorporated into nephrology practice collaboratively with representatives from infectious diseases and hepatology departments. HBV immunization is available and should be considered earlier in the course of CKD to affect immunity and avoid nonresponse. Appropriate and timely monitoring and screening coupled with strict universal precautions and viral eradication should translate to lower risk for seroconversions and improved safety of the dialysis process.

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