Management of Viral Hepatitis in Solid Organ Transplant Recipients

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KEYWORDS

• Hepatitis B virus • Hepatitis C virus • Hepatitis E virus • Liver transplantation
• Kidney transplantation • Thoracic transplantation

KEY POINTS

- Hepatitis B virus (HBV) has declined as an indication for liver transplant in North America, but remains a common indication in Asia. Outcomes following transplant are now excellent in liver and nonliver recipients with chronic HBV infection with modern management strategies including potent antiviral therapy with or without hepatitis B immunoglobulin tailored to patient risk.
- Hepatitis C virus (HCV) remains a leading indication for liver transplant globally. However, direct-acting antiviral therapy can now cure virtually all liver and nonliver transplant candidates and recipients with excellent short-term results, although the optimal timing of therapy remains controversial.
- The use of organs from donors who are either hepatitis B surface antigen or HCV RNA positive has been increasingly described in case series and with modern antiviral therapy seems to be safe in selected cases, although the optimal use of such donors remains to be evaluated.
- Chronic hepatitis E virus infection is an emerging cause of chronic hepatitis and cirrhosis in immunocompromised hosts in the developed world. A high clinical suspicion is needed to make this diagnosis because signs and symptoms may be minimal and serology negative in up to 20%.

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INTRODUCTION

In recent years, strategies for the prevention and treatment of hepatitis B virus (HBV) and hepatitis C virus (HCV) in organ transplant candidates and recipients have evolved rapidly. Although these viral infections no longer threaten transplant outcomes, in either hepatic or nonhepatic transplantation, they continue to be a focus of research. Strategies are needed to optimize cost-effective management that improve survival and quality of life because viral hepatitis remains a leading cause of death globally from liver failure and hepatocellular carcinoma (HCC). Remaining controversies include the ideal timing of HCV antiviral therapy and the use of HCV viremic donors in hepatic and nonhepatic transplantation. Hepatitis E virus (HEV) is an emerging pathogen in organ transplantation, now recognized to be a cause of chronic hepatitis post-transplantation with a significant risk of progression to cirrhosis. This article reviews the current management of HBV, HCV, and HEV in organ transplantation, highlighting remaining priorities for research.

HEPATITIS B VIRUS

Liver Transplant

In 2015, an estimated 257 million people were living with chronic hepatitis B infection globally.[1] Despite a highly effective vaccine and potent antiviral medications for treatment, the global attributable mortality because of HBV increased between 1990 and 2013[2] with most deaths attributable to HCC, followed by liver failure. In the United States, and other Western countries, however, HBV-related liver disease has become an uncommon indication for liver transplant (LT), although it remains a common indication in Asian countries.[3,4] Before the introduction of hepatitis B immunoglobulin (HBIg) and the development of potent nucleos(t)ide analogues (NA) used to prevent HBV recurrence in the graft, early graft loss and mortality were common, but outcomes now for this indication are among the best.[5] Although early data with the use of lamivudine or adefovir in combination with HBIg demonstrated improved early outcomes and lower risk of HBV recurrence, potent NAs with a high barrier to resistance (entecavir [ETV], tenofovir disoproxil fumarate [TDF], or tenofovir alafenamide fumarate [TAF]) are now preferred.

The risk of recurrent HBV after LT is related to the HBV DNA load at the time of transplantation[6] and thus all patients on the LT waiting list with HBV-related liver disease should be treated with a potent NA and a goal of achieving an undetectable HBV DNA. After LT, all patients should receive the combination of HBIg and a potent NA, which reduces the risk of HBV recurrence to less than 5%.[7,8] The NA therapy should continue indefinitely in all; however, in those at low risk for recurrence, HBIg discontinuation is considered, generally after a minimum of 1 to 3 months, although in select patients, potent NA therapy alone, without HBIg has been shown to effectively prevent recurrence.[9,10] Conversely, in those with risk factors for recurrent HBV, including those with detectable HBV DNA at the time of transplant, those with HCC, and those with coinfection with human immunodeficiency virus or hepatitis delta virus, combination HBIg and potent NA therapy should continue indefinitely.

In addition to the potency of NAs, renal function and prior antiviral exposure should be considered in choosing the preferred agent. In those with renal dysfunction, ETV or TAF is preferred. In those with prior lamivudine exposure, TDF or TAF are preferred.[11] Although the risk of recurrence is low with prophylaxis, monitoring is recommended to pick up recurrent disease early and limit the impact on long-term outcomes. HBV recurrence is defined as the reappearance of hepatitis B surface antigen (HBsAg) after LT and quantifiable levels of DNA, although patients on antiviral prophylaxis may

develop HBsAg positivity without detectable DNA, or abnormal biochemistry and histology.[7] The monitoring protocol for HBV recurrence varies among centers, but HBsAg and HBV DNA every 3 months for the first year and every 6 months thereafter is suggested.[12]

The use of liver donors with prior HBV infection, as demonstrated by a negative HBsAg but positive anti–hepatitis B core antibody (anti-HBc), with or without anti–hepatitis B surface antibody (anti-HBs), has been shown to be safe with appropriate prophylaxis in the recipient and is generally accepted as a way to increase the donor pool without compromising outcomes.[7,13] Despite this, there continues to be significant center-to-center variability in the use of anti-HBc-positive liver donors.[14] Recipients of a liver from a donor with past HBV infection (anti-HBc-positive) should receive NA therapy to prevent HBV recurrence, which otherwise occurs in 50% to 80% of cases. Data support the use of lamivudine monotherapy in this setting with a low risk of recurrence of less than 3% and no additional benefit of HBIg.[13,15] Some centers, however, prefer to use potent NA therapy. Most centers also continue NA therapy indefinitely, although in low-risk recipients with prior HBV infection themselves and natural immunity (positive anti-HBc and anti-HBs) NA discontinuation is considered.[13]

There are less data regarding the use of HBsAg-positive donors; however, several case series suggest this is a safe option to expand the donor pool.[13,16] If being considered, donor liver biopsy is required to exclude significant hepatic fibrosis. In most cases, HBsAg-positive liver grafts have been used preferentially for HBsAg-positive recipients and under prophylaxis with HBIg and NA therapy.[16,17] Although recurrence or persistence of HBsAg is common in these cases, reported graft function and survival is excellent. The exception is in hepatitis delta virus coinfected recipients where the use of HBsAg-positive liver grafts should be avoided because of early hepatitis delta virus reinfection and severe liver disease.[18,19]

Nonliver Transplant

The prevalence of HBV in patients with end-stage renal, heart, and lung disease is generally similar to that of the general population of the region. Although response rates are poor, approximating 50%, all nonimmune transplant candidates should be vaccinated against hepatitis B using a high-dose preparation.[20]

Historically, HBsAg-positive kidney transplant recipients had markedly reduced graft and overall survival primarily because of accelerated progression of liver disease.[21] However, with NA therapy, particularly potent agents, such as ETV and TDF,[22,23] outcomes have improved dramatically with survival rates similar to HBsAg-negative recipients.[24,25] As a result, the use of HBIg has been abandoned in this population in most programs.[12,26]

Pretransplant assessment of patients with HBV should be done by a specialist to determine the staging of hepatic fibrosis and need for therapy. In the past staging was done using liver biopsy; however, several noninvasive methods are now validated, including transient elastography, magnetic resonance elastography, shear-wave elastography, and serologic panels. Each one has advantages and disadvantages, although all give comparable classification to liver biopsy, particularly to exclude cirrhosis.[27] Any patients meeting standard criteria for HBV therapy in the general population should be initiated on treatment.[11] HCC surveillance should also be undertaken as recommended in the general population.

Post-transplant treatment in patients with HBV should be started as soon as the immunosuppressive therapy is commenced. The ideal duration of antiviral therapy has not been studied; however, because the risk of reactivation persists lifelong while on immunosuppressive therapy, potent NA therapy is recommended to continue

indefinitely.[12] Although ETV and TDF have both been used successfully to treat HBV post–kidney transplant, many programs prefer to use ETV because of the low, but established risk of renal tubular toxicity with TDF and safety of ETV in renal dysfunction. In those with prior lamivudine exposure, however, TDF is preferred. To date there is no published experience with the use of TAF in kidney transplantation, but this could be considered as an alternative in those with renal dysfunction.

The use of kidneys from donors who are anti-HBc-positive has been shown to be safe, without prophylaxis, in recipients who are immune to HBV (anti-HBs titer >10 IU/mL).[28]

Limited data exist regarding use of HBsAg-positive donors. In a recent study by Chancharoenthana and colleagues,[29] they compare outcomes of kidney HBsAg-negative transplant recipients with anti HBs titer greater than 100 IU/mL from HBsAg-positive donors and HBsAg-negative donors. With a median follow-up of 58.2 months, no significant differences in graft and patient survival were found. In heart transplant, where most available data are from Taiwan and Korea,[30–32] protocols including pretransplant vaccination and post-transplant antiviral therapy with or without HBIg prophylaxis has been shown to be effective in the prevention of HBV transmission from HBsAg-positive donor hearts. In North America, where the prevalence of HBV in donors is also low, organs from HBsAg-positive donors continue to be used selectively weighing the risks and benefits in individual recipients and following strict informed consent (**Table 1**).[13]

HEPATITIS C VIRUS

HCV is estimated to infect 2% to 3% of the global population, corresponding to 150 to 190 million people worldwide.[33] HCV-related end-stage liver disease and HCC remain the leading indications for LT worldwide. Before effective direct-acting antiviral (DAA) therapy, hepatic and nonhepatic transplant recipients with HCV had significantly reduced graft and overall survival compared with HCV-uninfected patients.[21,34] There are now several DAA therapies that are well tolerated and highly effective and can cure more than 90% of those infected, including those post-transplant. As a result, HCV no longer limits access to or outcomes of transplantation and there is growing interest and data to consider HCV viremic organs in HCV-negative recipients.

Liver Transplant

The DAAs currently used for the treatment of chronic HCV infection are effective in patients with advanced cirrhosis and post-LT. The combinations of sofosbuvir and ribavirin, sofosbuvir and ledipasvir, with or without ribavirin, sofosbuvir and daclatasvir,

Table 1
HBV summary

	Treatment of Liver Recipient	Treatment of Nonliver Recipient
Recipient with HBV infection (HBsAg positive)	NA ± HBIg	NA
Donor anti-HBc + ve	NA	Preferred anti-HBs >10 IU/mL If anti-HBs <10 IU/mL, assess donor HBV DNA ± NA
Donor HBsAg + ve	Only HBsAg + ve NA + HBIg	Preferred anti-HBs >100 IU/mL NA ± HBIg

with or without ribavirin, sofosbuvir/velpatasvir and daclatasvir/sofosbuvir have all been shown to improve clinical and biochemical outcomes in those with decompensated liver disease.[35–38] However, whether DAA therapy should be administered in patients awaiting transplantation, or deferred to post-transplant remains controversial.

Data continue to demonstrate that sustained virologic response (SVR) significantly reduces the risk of progressive liver disease, hepatic decompensation, HCC, liver-related mortality, and all-cause mortality.[39] Achieving SVR in patients with cirrhosis may improve the model for end-stage liver disease (MELD) score. Stabilization or improvement in hepatic function may occur in 60% of the patients, whereas about a quarter experience declining liver function and the remainder are unchanged.[40–42] For some, this may result in a lower priority for LT allocation, without improving the poor quality of life associated with complications of end-stage liver disease. This situation has been termed "MELD limbo" or "MELD purgatory."[43,44] In addition, the cure rate in those with decompensated liver disease is significantly lower than those with compensated cirrhosis or post-LT. A recent analysis by Foster and colleagues[45] included 467 patients with Child-Turcotte-Pugh class B/C that received treatment of all HCV genotypes (GTs). Treatment was chosen by clinician and included sofosbuvir with ledipasvir or daclatasvir, and with or without ribavirin. The overall SVR was only 83.5%. Primarily for these reasons, when to treat HCV-infected patients awaiting LT remains controversial. Treatment before LT in this cohort of patients might also limit the donor pool if a listed patient cured of HCV would then no longer be considered for an HCV-viremic donor.[41]

In a recent modeling study by Chhatwal and colleagues[40] long-term outcomes of pre-LT versus post-LT HCV treatment with DAAs for patients with MELD scores between 10 and 40 were simulated using integrated data from United Network for Organ Sharing and the SOLAR 1 and 2 trials. Their findings suggest that at the US national level, treating HCV before LT increased life expectancy if MELD score was less than or equal to 27 but could decrease life expectancy at higher MELD scores. The International Liver Transplantation Society also recently released a consensus statement on HCV management in LT candidates.[42] This suggests that patients awaiting LT with HCV-related cirrhosis who are Child-Turcotte-Pugh B and/or have MELD score less than 20 and who are without refractory portal hypertension be treated with antiviral therapy, whereas those with Child-Turcotte-Pugh C and/or MELD score more than 30 should not undergo antiviral therapy. There are several additional factors that must be considered from an LT program and patient perspective. These include the anticipated wait times in the region, availability of HCV viremic donors, availability of a living donor, and access to DAA therapy.

In patients with HCV-related HCC awaiting LT, decisions regarding the timing of HCV therapy are also complex. Prenner and colleagues[46] studied a total of 421 patients with HCV cirrhosis where 33% had active or a history of HCC. The SVR rate was only 79% in patients with HCC compared with 88% in patients without HCC ($P = .009$). Of the 29 patients with HCC who did not achieve SVR, 93% of these had an active tumor at the time of treatment. DAA therapy in patients with inactive tumor or after removal (resection/LT) had better SVR rates ($P<.001$). These findings suggest that a primary predictor of DAA failure is the presence of active HCC at the time of treatment (odds ratio, 8.5; 95% confidence interval, 3.90–18.49). Presently, The International Liver Transplantation Society consensus statement on HCV management in LT candidates[44] suggests that HCV-infected patients with HCC and either compensated cirrhosis or those with decompensated cirrhosis who are not expected to undergo LT within 3 to 6 months be treated with antiviral therapy. Only in those with HCV-related HCC and decompensated disease who are expected to receive an LT

within 3 to 6 months is deferral of DAA therapy suggested. **Table 2** summarizes the advantages and disadvantages of treating patients with DAAs for HCV-related liver diseases before LT.[43,47,48]

Following LT, cure of HCV results in a significant decrease in morbidity and mortality.[49] Several DAA regimens have been studied in the post-LT population in those with GT1, GT4, GT5, or GT6. The SOLAR-1 study included 223 LT patients with a broad spectrum of fibrosis, including six with fibrosing cholestatic hepatitis, who received sofosbuvir/ledipasvir/ribavirin for 12 or 24 weeks. The overall SVR was 96% to 98% (12 weeks and 24 weeks, respectively) and all with fibrosing cholestatic hepatitis achieved SVR.[50] SOLAR-2 included 168 LT recipients who similarly received sofosbuvir/ledipasvir/ribavirin for 12 or 24 weeks and SVR was comparable in patients without cirrhosis at 94% to 100% (12 weeks and 24 weeks, respectively).[35] The MAGELLAN-2 study included 80 LT recipients and demonstrated glecaprevir/pibrentasvir for 12 weeks to be well tolerated with an SVR of 98%.[51] Real-world cohorts have also demonstrated a high SVR rate with or without the inclusion of ribavirin in combination with ledipasvir/sofosbuvir.[52,53] However, because factors leading clinicians to include ribavirin in the regimen in the observational studies cannot be determined, the addition of ribavirin is still recommended, particularly for patients with unfavorable baseline characteristics, such as cirrhosis or prior treatment experience, by many experts. In those with post-transplant HCV recurrence and GT2 or GT3 infection glecaprevir/pibrentasvir and daclatasvir/sofosbuvir/ribavirin for 12 weeks have been shown to be effective.[51,54,55] There have been no studies published evaluating sofosbuvir/velpatasvir therapy in LT recipients and further data are awaited. Given the limited options for therapy, however, particularly in patients with decompensated cirrhosis, this may be used, based on expert opinion, with or without the addition of ribavirin.

In summary, those with decompensated HCV-cirrhosis where LT is contraindicated or not accessible should receive HCV treatment with the expectation of improved hepatic function in about 60% of cases and resultant longer survival. To optimize outcomes in those who are LT candidates, however, one must consider primarily the severity of the liver disease as measured by MELD and the presence and stage of HCC. In addition, the anticipated wait time at the center, patient treatment history and access to DAA therapy, and availability and local philosophy of HCV viremic donor use (only in HCV viremic recipient or any recipient) remain important factors in the timing of HCV therapy.

Table 2
Advantages and disadvantages of treating patients with decompensated cirrhosis caused by HCV infection before LT

Advantages	Disadvantages
SVR is achieved in >80% of patients	May eliminate the opportunity to have a curative treatment (LT) of liver disease; and place the patient into the "MELD purgatory" situation where quality of life is still poor
Liver function often improves	
May obviate LT (up to 30% of patients)	
Improved liver function may increase options for local regional treatment of HCC and reduce HCC recurrence	Still at risk of progressive liver disease and HCC
Prevent post-LT HCV recurrence	May preclude the use of HCV viremic organs
Fewer drug-drug interactions (compared with treating LT recipients)	Treatment after LT is associated with higher SVR rates compared with treatment in decompensated cirrhosis before LT
	In those who fail therapy, exposure to NS5A inhibitors decreases options when retreating after LT

Nonliver Transplant

The prevalence of hepatitis C in patients with end-stage renal disease (ESRD) varies worldwide, but is higher in those on hemodialysis compared with peritoneal dialysis and in those on dialysis longer. In the United States and Western Europe, it stands at 5% to 10%.[56] Most new infections in ESRD are now caused by the usual risk factors for community acquisition, most notably infection drug use; however, there continue to be cases of health-care acquired HCV in dialysis centers worldwide.[57] With the screening of blood products and the use of erythropoiesis-stimulating agents, the risk of transfusion-related HCV infection in dialysis patients has dramatically declined.

Historically, chronic HCV infection has been associated with a significant decrease in patient and graft survival at 10 years following transplantation.[21] However, even in the era before DAA therapy, there was a clear survival advantage to transplantation versus remaining on dialysis in those with chronic HCV infection. In a recent systematic review and meta-analysis performed by Ingsathit and colleagues,[58] they concluded that patients with chronic HCV who remain on dialysis are at higher risk of death when compared with those who received kidney transplantation (relative risk, 2.19; 95% confidence interval, 1.50–3.20; $P = .004$), comparable with previous meta-analyses.[59,60]

There are now several DAA regimens that have been studied in both ESRD and post–kidney transplant that are safe and effective. In ESRD, elbasvir/grazoprevir for 12 weeks was studied in GT1 HCV-infected patients in the C-SURFER trial and resulted in an SVR of 99%.[61] The pangenotypic combination of glecaprevir/pibrentasvir for 12 weeks, studied in the EXPEDITION-4 trial, demonstrated excellent safety and efficacy in those with ESRD, including those on dialysis resulting in a 100% SVR in 104 patients.[62] As a result, these are the primary recommended treatment options in this population. Published clinical trials to date of sofosbuvir-based regimens have excluded those with estimated glomerular filtration rate less than 30 mL/min and use of these regimens in those with advanced renal disease is not currently recommended. There are, however, accumulating real-world data that suggest sofosbuvir-based regimens are safe and effective[63–65] and clinical trials are ongoing.

Ruling out cirrhosis before HCV therapy and transplantation is important to risk stratify those who would need HCC surveillance and/or endoscopic assessment for varices, and to identify the few that may be better served by combined liver-kidney transplant. The Kidney Disease: Improving Global Outcomes (KDIGO) group, in their most recent guidelines, recommend that patients with chronic kidney disease be assessed for liver fibrosis with noninvasive tests, such as transient elastography or serum markers.[66]

In the post–kidney transplant setting clinical trials in addition to multiple real-world studies have demonstrated excellent efficacy and safety using several DAA regimens. In a phase 2 open label study of 114 kidney transplant recipients with either GT1 or GT4 HCV infection randomized to receive ledipasvir/sofosbuvir for 12 or 24 weeks all patients achieved SVR and treatment was well tolerated.[67] In a Spanish cohort of 103 kidney transplant recipients treated with DAA post-transplant an SVR of 98% was achieved. The most commonly used combinations were sofosbuvir/ledipasvir (n = 59; 57%) and sofosbuvir/daclatasvir (n = 18; 17%), with ribavirin being added in 41%.[68] The combination of glecaprevir/pibrentasvir for 12 weeks in 20 kidney transplant recipients was well tolerated with an SVR of 98%. Several additional cohort studies have reported excellent outcomes following DAA therapy in renal transplant recipients, with SVR comparable with the nontransplant population.[52,69–71]

In thoracic organ transplant candidates, the prevalence of HCV infection has not been studied. The impact of HCV on outcomes of thoracic organ transplant in the pre-DAA is limited in interpretation by the study design. Most are database analysis with a paucity of clinical information and ability to control for confounding factors, and many classify patients' HCV status based solely on serology without data on HCV RNA status.[72–74] Only short-term outcomes following DAA therapy are available to date in case reports and small case series in thoracic transplantation; however, these are encouraging. Three patients post–lung transplant all achieved SVR with sofosbuvir-based regimens, with excellent drug tolerability and no major adverse reactions or immunosuppressive dose adjustment requirements.[75] Similar outcomes were observed in a cohort of 12 chronically HCV-infected heart transplant recipients treated with sofosbuvir combined with either ledipasvir or daclatasvir.[76] In one patient treated post–lung transplant with sofosbuvir/daclatasvir for rapidly progressive fibrosis, cure was also achieved.[77] Although data are limited to date, cure rates with DAA therapy in thoracic organ transplant recipients are anticipated to be excellent and similar to the general population and that observed in liver and kidney transplant recipients.

As in LT, an important unresolved question is the optimal timing of HCV therapy in renal and other nonhepatic transplant candidates. One of the strongest arguments to defer therapy until after transplant is to expand the donor pool for the recipients who would be eligible to receive an allograft from an HCV-viremic donor. However, there are several additional factors that must be considered because HCV viremic patients on dialysis also have an increased risk of death not only compared with transplantation, but also compared with those who are HCV-negative on dialysis. The severity of liver disease and anticipated wait times for transplant are key considerations, and access to DAA therapy. **Table 3** outlines the considerations of HCV therapy before or after kidney transplant. In a medical decision analysis published in abstract form, delayed HCV treatment seemed most cost effective; however, the robustness of this finding is limited by unknown net treatment benefit with DAA on mortality.[78]

For any recipient undergoing DAA therapy post-transplant, drug interactions and the risk of rejection must be considered. Overall there are few significant drug interactions between immunosuppressants and DAAs.[79] Sofosbuvir in combination with daclatasvir, ledipasvir, or velpatasvir is used safely with calcineurin inhibitors and sirolimus. Cyclosporine is contraindicated in combination with HCV protease inhibitors including grazoprevir, simeprevir, and voxilaprevir because of marked elevations in exposure to the protease inhibitor. Coadministration of glecaprevir/pibrentasvir with cyclosporine requires close monitoring because concentrations of glecaprevir/pibrentasvir may increase and this protease inhibitor should be avoided in those requiring a daily dose of cyclosporine of more than 100 mg.

Table 3
Considerations in timing of DAA therapy for HCV viremic kidney transplant candidates

Treat Before Transplant	Defer Treatment Until After Transplant

• Advanced liver disease
• Expected long wait for transplant
  ○ No living donor
  ○ Highly sensitized
  ○ Center average for blood group
• Unwilling to consider HCV viremic donor or not expected to be available rapidly
	• Mild/moderate liver disease (stage F2 or less)
	• Willing to accept HCV viremic kidney
	• Expect possibility of receiving HCV viremic kidney rapidly

Several case reports of acute rejection in patients cured with DAA therapy have emerged. Proposed potential mechanisms for this include improved liver function post-treatment with increased clearance of immunosuppressant agents, reduced calcineurin inhibitor levels attributed to HCV protease inhibitor use, and potential loss of the HCV-immunosuppressive effects that follow HCV cure. Although there is no proof of causation and rejection rates are low,[52] patients should be monitored for rejection during and after therapy.

Hepatitis C Virus Viremic Donors

Three primary factors have led to the international transplant community considering the use of HCV viremic organs for HCV negative recipients: (1) the advancements in HCV DAA therapy and the ability to cure nearly all those infected; (2) the organ shortage and possibility to expand the donor pool; and (3) in North America in particular, the growing number of often young, otherwise excellent, donors with HCV as a consequence of the opioid epidemic.[80] A recently published American Society of Transplantation Consensus suggests that transplantation from HCV viremic donors to negative recipients only be considered in the setting of clinical research at this time.[81] However, emerging data suggest the benefits of accepting an HCV viremic donor likely outweigh this risk of HCV infection in the era of DAA therapy.

In a pilot trial, 10 kidneys from GT1 HCV viremic donors were transplanted into HCV-negative recipients. After documentation of viremia in the recipients, all received elbasvir/grazoprevir for 12 weeks, achieving SVR in 100%.[82] Excellent short-term outcomes have also been seen in liver, lung, and heart recipients, including in cases of unintentional and intentional transplantation of organs from HCV-infected donors.[83–86] Mathematical modeling by Chhatwal and colleagues[87] simulating a trial of HCV-negative patients awaiting LT compared long-term outcomes in those willing to accept HCV-positive livers versus those willing only to accept HCV-negative livers. Patients receiving HCV-positive livers were treated with DAA therapy for 12 weeks. They demonstrated that willingness to accept HCV-negative or viremic livers resulted in an increase in patients' life expectancy when the MELD score was more than 20. Similar modeling in renal transplantation suggests HCV-negative recipients willing to accept HCV viremic kidneys would result in improved survival and be cost effective and under some conditions cost saving.[88]

Although there are practical and financial considerations, most notably ensuring access to DAA therapy for post-transplant treatment, and the need to obtain strict informed consent, the use of HCV viremic donors for HCV-negative recipients is a promising additional advance in expanding the donor pool (**Table 4**).

HEPATITIS E VIRUS

Approximately 3.7 million people worldwide are affected by HEV infection and associated mortality is 70,000 per year.[1] HEV GT1 and GT2 are waterborne and are the cause of infection in developing countries and associated with acute hepatitis and a characteristic high mortality of up to 30% in pregnant women. GT3 and GT4, however, are prevalent in developed countries and are zoonoses with animal reservoirs including pigs, wild boar, and rabbits. HEV infection occurs through drinking contaminated water or consumption of meat from infected animals. Transfusion-transmitted infection plays a minor role as source of infection in the risk group of solid-organ recipients with primary risk factors identified to be consumption of pork or game meat.[89,90] Prevention relies on avoiding raw or undercooked meat. Unlike HEV infection in immunocompetent hosts where infections are self-limited, organ transplant

Table 4
HCV summary

	Treatment of Liver Recipient	Treatment of Nonliver Recipient
Recipient with HCV infection	Timing of DAA (before or after transplant) depends on MELD, CTP class, *portal* HTN, regional anticipated wait list time, availability of living donor, availability of HCV viremic donor, access to DAA, and HCC.	Timing of DAA (before or after transplant) depends on severity of liver disease, regional anticipated wait list time, availability of living donor (kidney only), availability of HCV viremic donor, access to DAA.
Donor with HCV viremia	Previously HCV viremic recipients only. Currently HCV –ve acceptable with DAA after transplant.	

Abbreviations: CTP, Child-Turcotte-Pugh; HTN, hypertension.

recipients develop chronic infection in approximately 60% of cases and this leads to progressive fibrosis and cirrhosis in up to 10%.[91,92]

The diagnosis of HEV infection in immunosuppressed hosts is missed because of the absence of typical clinical signs and symptoms. Clinicians must have a high index of suspicion for infection and should consider HEV in transplant recipients with raised liver enzymes of any degree, although typically alanine aminotransferase levels are between 100 and 200 U/L.[93] The diagnose of HEV infection is by HEV RNA in serum or stool, because HEV antibodies may be absent in up to 20%, and the persistence of at least 6 months defines chronic disease.[89] Clearance of infection occurs spontaneously in more than 30% of cases. Where possible, a reduction in immunosuppression should be considered.

In transplant patients who develop persistent infection, ribavirin has been shown to be effective in the treatment of GT3 chronic HEV infection. A retrospective multicenter study demonstrated ribavirin monotherapy, given for a median of 3 months, to achieve a sustained virologic rate of ~90%.[94] Patients without detectable HEV RNA in the serum, but with persistent HEV RNA detected in the feces at the end of therapy, have a significantly higher risk of relapse,[95] whereas rapid decrease in serum HEV RNA within the first week of ribavirin therapy has been identified as a positive predictive factor for SVR.[96]

Up to 40% of transplant recipients with persistent HEV relapse after 3 months of treatment with ribavirin.[95,96] Most patients who relapse respond to a longer course of treatment with ribavirin, even in those harboring the G1634R mutation that is detected post-treatment.[97] The optimal duration and dose of ribavirin has not yet been determined. Retreating with a longer course of ribavirin in patients that relapse, however, should be considered and continued until two HEV RNA are negative in blood or stool with at least 1 month apart.[94]

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